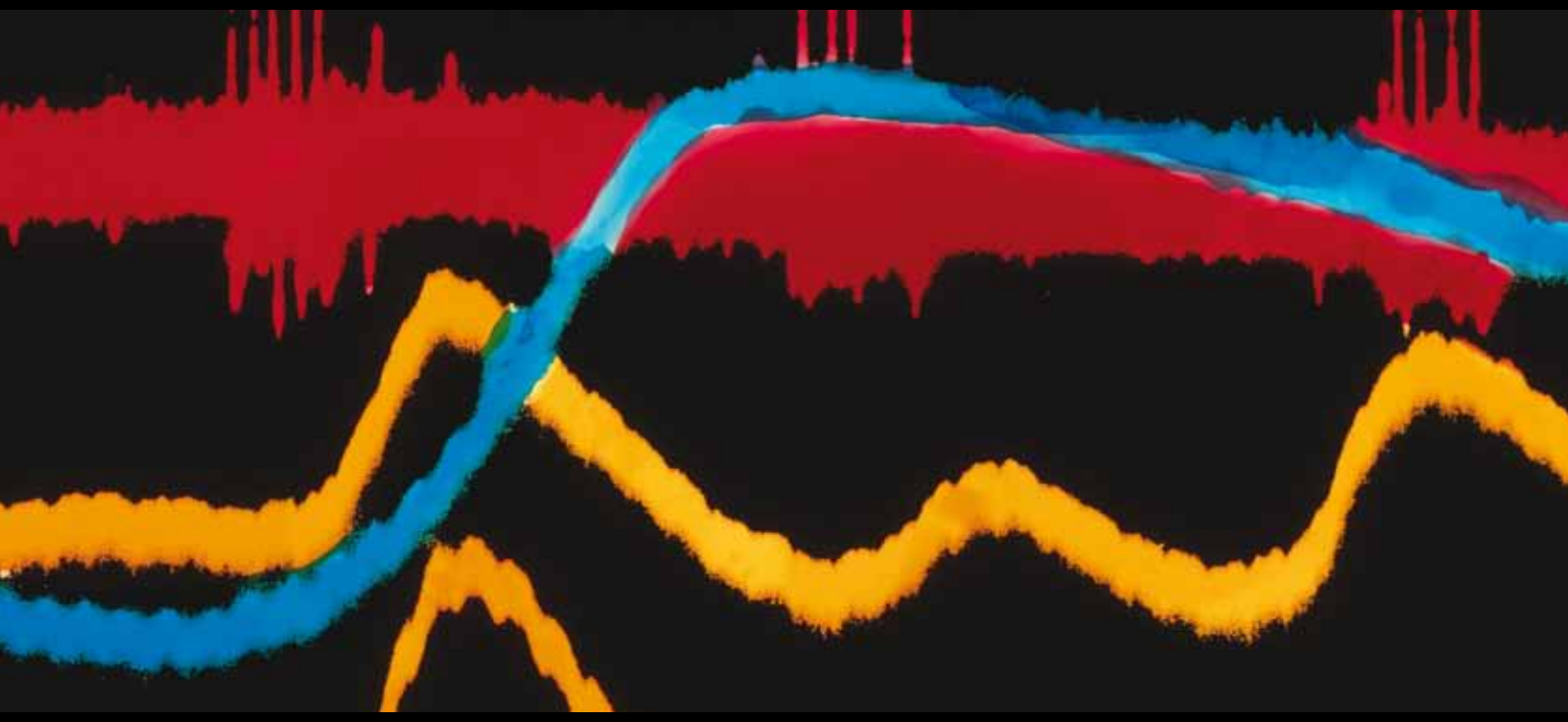
Sleep Apnea

Guest Editors: Manos Alchanatis, James MacFarlane, and Sofia Schiza



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Editorial Board

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Editorial
Sleep Apnea

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The obstructive sleep apnea syndrome (OSAS), a form of periodic breathing, is highly prevalent disorder that affects at least 4% of adult male population and 2% of females and is associated with repetitive episodes of complete (apnea) or partial (hypopnea) occlusion of upper airway during sleep. These episodes result, among others, in loud snoring and in daytime symptoms such as excessive sleepiness, morning headache, irritability, cognitive impairment and lead to reduced quality of life. Varying degrees of transient oxygen desaturation follow the upper airway occlusion, and it is a common pathway for the development of several cardiovascular complications. Central Sleep Apnea (CSA) is another form of periodic breathing characterized by lack of respiratory effort during sleep and frequently coexists with OSA. One major underlying mechanism of CSA is unstable ventilatory drive during sleep. Treatment options for sleep apnea include continuous positive airway pressure (CPAP), oral appliances, and weight loss.

In this special issue on sleep-related breathing disorders a number of distinguished scientists report on the following: the association between the duration of sleep and cardiovascular and metabolic comorbidities of patients with OSAS, the influence of age on clinical characteristics and polysomnographic findings of patients with OSAS in Greek population, the effect of weight loss by behavioural, pharmacological, or surgical approaches in the management of OSAS, the mechanisms that may trigger cognitive decline in OSA patients, the evaluation of two different mandibular advance appliances and the application of sclerosant agents for treatment of snoring, the presence of Cheyne-Stokes respiration (CSR), a form of central sleep apnea, in patients with radiologically-proven first-ever lacunar stroke, the implication of age in the pathogenetic link between sleep apnea and plasma homocysteine levels.

All the above help us to better understand some mechanisms involved in pathogenesis, consequences, and treatment of sleep apnea syndrome and snoring, and clearly this special issue is a great contributor to our knowledge.

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Clinical Study

Cheyne-Stokes Respiration in Patients with First-Ever Lacunar Stroke

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The aim of this single-center prospective study was to assess the presence of Cheyne-Stokes respiration (CSR) and CSR-related variables in 68 consecutive patients with radiologically proven first-ever lacunar stroke undergoing a respiratory sleep study using a portable respiratory polygraph within the first 48 hours of stroke onset. CSR was diagnosed in 14 patients (20.6%). Patients with CSR as compared with those without CSR showed a significantly higher mean (standard deviation, SD) apnea-hypopnea index (AHI) (34.9 (21.7) versus 18.5 (14.4), $P = 0.001$) and central apnea index (13.1 (13.8) versus 1.8 (3.4), $P = 0.0001$) as well as higher scores of the Barthel index and the Canadian Neurological scale as a measure of stroke severity, and longer hospital stay. CSR was present in one of each five patients with lacunar stroke. The presence of CSR was associated with a trend towards a higher functional stroke severity and worse prognosis.

1. Introduction

Central sleep apnea and Cheyne-Stokes respiration are frequently observed during sleep in patients with stroke affecting large areas of the cerebral parenchyma [1–5] and in patients with congestive heart failure and low ventricular ejection fraction [6–10].

In a previous study carried out in a nonselected sample of patients with cerebral infarction, Parra et al. [11] reported the presence of Cheyne-Stokes respiration in 26% of patients, a percentage higher than 6% of observed in the study of Bassetti and Aldrichet [12]. To date, Cheyne-Stokes respiration in stroke patients has been related to a worse prognosis probably because this abnormal breathing pattern is found in more extensive cerebral lesions and is also more common in hemorrhagic strokes than in ischemic infarctions [11, 13]. However, the traditional relationship between nocturnal Cheyne-Stokes respiration and large cerebral lesions is a matter of controversy given that Cheyne-Stokes respiration has been occasionally described in patients with transient ischemic attack (TIA) [11]. Lacunar infarctions are very homogeneous cerebral lesions regarding infarct size (maximal diameter of the lesion <20 mm), topography (affecting subcortical structures or the pons), and clinical features (limited neurological deficit and favorable neurological recovery on hospital discharge). In this respect, patients with lacunar stroke may constitute an intermediate group of stroke severity between TIA and extensive cardioembolic or atherothrombotic infarctions.

Given that the presence of Cheyne-Stokes respiration in patients with lacunar infarction has not been previously

examined, a prospective study was designed. The objective of the study was to determine the frequency of Cheyne-Stokes respiration patients with first-ever lacunar infarction and to identify variables associated with this breathing pattern in this population.

2. Patients and Methods

The study population included 68 consecutive patients admitted to the Service of Neurology of Hospital Universitari Sagrat Cor in Barcelona (Spain) because of a first episode of a lacunar stroke. Lacunar infarcts were defined [14] as (a) sudden or gradual onset of a focal neurological deficit lasting >24 hours of the type described in the common lacunar syndromes (pure motor hemiparesis, pure sensory stroke, sensorimotor stroke, ataxic hemiparesis, dysarthria-clumsy hand, and atypical lacunar syndromes); (b) computed tomography (CT) scans or brain magnetic resonance imaging (MRI) was either normal or demonstrated only small, localized brain lesions with diameters <20 mm that seemed appropriate for the neurological deficits; (c) absence of cortical ischemia, cervical carotid, and/or vertebrobasilar stenosis (>50% diameter), or a major source for cardioembolic stroke. Patients with clinical symptoms of congestive heart failure or major cardiopathies were excluded from the study as were patients with a left ventricular ejection fraction ≤40% in the echocardiographic study. All eligible lacunar stroke patients underwent transthoracic echocardiography at the time of hospitalization, showing an ejection fraction >40%.

In all cases, a respiratory sleep study was performed in the hospital ward during the first 48 hours after admission using a portable respiratory recording device (Hypno TT Digital Recorder) that has been previously validated using full polysomnography and used in stroke patients [11]. This portable device measures respiratory nasal flow (flow nasal sensory), chest wall movements (impedance), heart rate and thoracic impedance (ECG electrodes), arterial oxygen saturation (SaO_2, finger pulse oximetry), and body position (position sensor). Sleep-related breathing disorders were classified as obstructive or central apnea. Central apneas were defined as a cessation of airflow for ≥10 s in the absence of any thoracic motion. A hypopnea was considered when a discernible reduction in airflow or thoracic motion that lasted >10 s and was associated with a cyclical dip in SaO_2 of >3%. The Cheyne-Stokes respiration pattern was defined as a periodic breathing with central apnea in a crescendo/decrescendo pattern of >10% of the time spent in bed [2] (Figure 1). The apnea-hypopnea index (AHI) was calculated taking into account the time spent in bed with the respiratory recording device (lights out was considered the beginning of the recording and was usually initiated between 11:00 and 12:00 PM and terminated between 6:00 and 7:00 AM). Manual scoring of these variables was performed in all cases. An experienced scorer, who was blind to the clinical neurological data, performed the scoring. The percentage of nighttime with SaO_2 of <90% (CT90) was obtained automatically.

In all patients the following variables were recorded: age; sex; height; weight; body mass index (BMI); clinical features related to sleep-related breathing disorders, including snoring, observed apnea, and daytime sleepiness assessed by means of the Epworth sleepiness scale [15]; results of respiratory sleep studies; neurological and outcome data according to the standardized protocol of the Hospital of Sagrat Cor stroke registry. Definition of cardiovascular risk factors were those used by our group in previous studies [14, 16, 17]. All patients were admitted to the hospital within 48 hours of the onset of symptoms. Brain neuroimaging studies were performed within the first week of hospital admission. Patients with negative results in the first CT scan usually performed at the emergency department had a second CT examination during their stay in the hospital or were studied by MRI. Other investigations performed at the discretion of the attending physician included angio-MRI, echo Doppler of the supra-aortic trunks, arterial digital subtraction angiography, B mode echocardiography, and lumbar puncture.

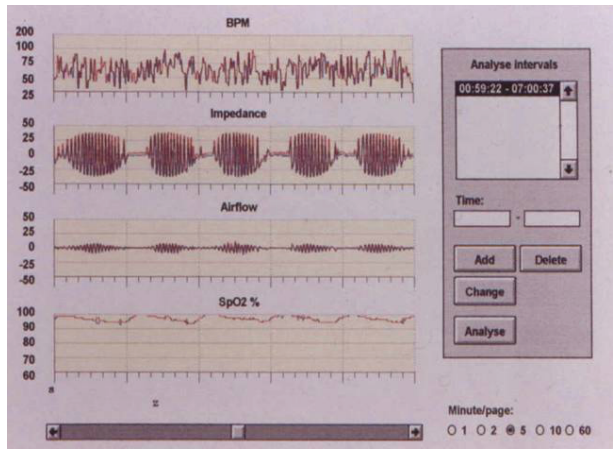

Figure 1: Cheyne-Stokes breathing in a patient with lacunar stroke. Central apnea with a crescendo/decrescendo pattern.

The Barthel index [18] was measured to assess performance in basic activities of daily living, total scores range from 0 (complete dependence) to 100 (complete independence). A Barthel index score of more than 75 indicated a good prognosis (absence of functional impairment or minimal functional disability at hospital discharge) [18]. The Canadian Neurological scale [19] was used to assess stroke severity; total score range from 0 (maximum impairment) to 10 (no impairment). The outcome was said to be good when the score was >7. Moreover, the modified Rankin scale [20] was used to assess clinical outcome at hospital discharge. We defined a good outcome as a modified Rankin scale ≥2.

Prior to conducting the study, approval was obtained from the Ethical Committee on Clinical Research of the hospital. Written informed consent to undergo respiratory sleep studies was obtained from all patients.

2.1. Statistical Analysis. Univariate analysis for the different cardiovascular risk factors, clinical features, lacunar syndromes, respiratory data, topography of lacunar infarction, and scores of the Barthel index, Canadian Neurological scale, and modified Rankin scale in relation to the presence or absence of Cheyne-Stokes respiration was assessed with

the analysis of variance (ANOVA) and the chi-square (χ^2) test with Yates or Bonferroni's correction when necessary. Statistical significance was set at $P < 0.05$.

3. Results

A total of 68 consecutive patients with lacunar infarction that was proven radiologically (CT and/or MRI) were included in the study. There were 31 men and 37 women, with a mean (standard deviation, SD) age of 73.2 (9.6) years and mean BMI of 26.3 (3.6) kg/m^2.

Fourteen patients (20.6%) had Cheyne-Stokes respiration. There were 9 men and 5 women, with a mean age of 76.7 (6.8) years (range 39–89 years) and a mean BMI of 26.3 (4.3) kg/m^2. The main cardiovascular risk factors were hypertension in 78.6% of the cases, diabetes mellitus in 28.6%, dyslipidemia in 28.6%, cigarette smoking in 28.6%, and peripheral artery disease in 7.1%. No case of decompensated congestive heart failure was recorded. Pure motor stroke was diagnosed in 6 patients, sensorimotor stroke in 3, dysarthria-clumsy hand plus ataxic hemiparesis in 3, and atypical lacunar syndrome in 2. Atypical lacunar syndromes included dysarthria associated with central facial palsy in 1 patient and isolated dysarthria in 1. The most frequent topographies of lacunes were the internal capsule and the pons in 35.7% of the patients each, the centrum semiovale in 21.4%, and the thalamus in 7.1%.

The mean (SD) score of the Epworth sleepiness scale was 3.3 (2.6) and the mean AHI 34.9 (21.7). The AHI was <10 in 1 patient, ≥10 in 13 patients, ≥20 in 12 patients, and ≥30 in 7 patients. A central apnea index >5 was observed in all 14 patients with Cheyne-Stokes respiration. The mean CT90 (percentage of time below 90% saturation) was 8.4 (11.3). The comparison between patients with ($n = 14$) and without ($n = 54$) Cheyne-Stokes respiration is shown in Table 1. Both groups were similar in relation to demographic data, clinical features, distribution of lacunar syndromes, and topography of lacunes. However, patients with Cheyne-Stokes respiration as compared with patients without sleep-disordered breathing showed significantly higher mean values of AHI (34.9 (21.7) versus 18.5 (14.4), $P = 0.001$) and central apnea index (13.1 (13.8) versus 1.8 (3.4), $P = 0.0001$). On the other hand, there was a trend towards higher functional impairment and worse prognosis in patients with Cheyne-Stokes respiration as noted by a lower percentage of patients with a score >75 of Barthel index (44.5% versus 68%, $P = 0.397$) and a score >7 of the Canadian Neurological scale (44.4% versus 75%, $P = 0.21$). Mean scores of the Barthel index, the Canadian Neurological scale, and the modified Rankin scale were similar in both groups (Table 2).

Mean scores of the Barthel index were 58.3 (32.5) for patients with Cheyne-Stokes respiration and 75.8 (27.9) for patients with normal breathing pattern ($P = 0.130$); the corresponding figures for the Canadian Neurological scale and the modified Rankin scale were 6.9 (1.9) versus 7.9 (2.1) ($P = 0.131$) and 2.4 (1.3) versus 2.2 (1.1), respectively.

None of the patients died within the first 30 days after stroke onset. The mean length of hospital stay was 14.9 (11.1) days in patients with Cheyne-Stokes respiration and 11.5 (5.6) in patients without Cheyne-Stokes respiration ($P = 0.184$).

4. Discussion

Cheyne-Stokes respiration has been usually described in patients with congestive heart failure [6–10] and in patients with extensive cerebral infarctions and poor outcome (3–5). Cheyne-Stokes respiration was also found to be associated with hypocapnia and poorer ejection fraction in a group of stroke patients (undifferentiated location) [7]. The present study also demonstrates that Cheyne-Stokes respiration is present in 20.6% of lacunar stroke patients with small size cerebral infarcts (<20 mm). None of the patients had history of congestive heart failure or presented an ejection fraction <40% of the echocardiogram. Accordingly, Cheyne-Stokes respiration in patients with lacunar stroke can be reasonably considered secondary to the acute lacunar infarction.

Sleep-related breathing disorders have been increasingly recognized as a risk factor for stroke and, on the other hand, acute stroke may be the cause of either central apneas or Cheyne-Stokes respiration. In the study of Parra et al. [11] of sleep-related breathing disorders in stroke patients, it was shown that during the stable phase of stroke, there was a decrease of respiratory events mostly of central apneas, whereas obstructive events remain unaltered. Also, acute stroke may cause destabilization of the upper airways or according to the cerebral area affected, motor weakness of the muscles of the upper respiratory tract favouring obstructive apneas or hypopneas.

One question to be solved in these types of studies is the cutoff value for central apnea and Cheyne-Stokes respiration that may have clinical, functional, or prognostic impact. Most authors have considered a central apnea index >5 as the minimum number of central apneas per hour that might have some clinical repercussion, although this cutoff value is still undefined [8]. Moreover, central hypopneas are not included in this index given the difficulty in distinguishing obstructive hypopneas from central hypopneas in polysomnographic studies [21]. In relation to Cheyne-Stokes respiration, 10% was the minimum time that may have some clinical relevance rather than whether or not Cheyne-Stokes respiration was observed. In the present study, lacunar stroke patients with Cheyne-Stokes respiration showed a significantly higher mean AHI value than patients with a normal breathing pattern despite the fact that differences in BMI between both groups were not found. The central apnea index was also significantly higher among patients with Cheyne-Stokes respiration but without affecting daytime sleepiness, although with a lower nocturnal SaO_2 probably at the expense of obstructive phenomena.

It should be noted that significant differences in demographic data, cardiovascular risk factors, and clinical features between patients with and without Cheyne-Stokes respiration were not documented. The pons and the internal capsule were the most common topographies in both study groups. Up to the present time, a relationship between Cheyne-Stokes respiration and a particular cerebral topography could not have been established [13]. Although pure motor

Table 1: Clinical characteristics of 68 patients with lacunar stroke according to the presence of Cheyne-Stokes respiration.

Variables	Cheyne-Stokes respiration		*P* value
	Present, $n = 14$	Absent, $n = 54$	
Sex, men/women	9/5	28/26	0.405
Age, years, mean (SD)	76.7 (6.8)	72.3 (10.0)	0.101
Body mass index, BMI, kg/m^2, mean (SD)	26.3 (4.6)	26.2 (3.2)	0.788
Respiratory data, mean (SD)			
AHI	34.9 (21.7)	18.5 (14.4)	0.001
Central apnea index	13.1 (13.8)	1.8 (3.4)	0.000
Obstructive events	21.8 (12.7)	16.7 (13.9)	0.390
Epworth sleepiness scale	3.3 (2.6)	5.4 (3.4)	0.064
CT90(%)	8.4 (11.3)	2.5 (5.2)	0.110
Vascular risk factors			
Hypertension	11 (78.6)	34 (63)	0.271
Diabetes mellitus	4 (28.6)	22 (40.7)	0.404
Previous TIA	3 (21.4)	4 (7.4)	0.124
Atrial fibrillation	1 (7.1)	6 (11.1)	0.633
Ischemic heart disease	0	2 (3.7)	0.465
Peripheral artery disease	1 (7.1)	4 (7.4)	0.973
Chronic obstructive pulmonary disease	1 (7.1)	2 (3.7)	0.577
Dyslipidemia	4 (28.6)	8 (14.8)	0.618
Smoking	4 (28.6)	8 (14.8)	0.229
Alcohol abuse	0	3 (5.6)	0.367
Salient clinical features			
Sudden onset	6 (42.9)	31 (57.4)	0.330
Headache	2 (14.3)	7 (13)	0.896
Motor deficit	11 (78.6)	37 (68.5)	0.462
Sensory deficit	4 (28.6)	20 (37)	0.555
Speech disturbances	7 (50)	35 (64.8)	0.309
Lacunar syndrome			0.163
Pure motor hemiparesis	6 (42.9)	24 (44.4)	0.915
Pure sensory stroke	0	12 (12.2)	0.121
Sensorimotor stroke	3 (21.4)	3 (5.6)	0.181
Ataxic hemiparesis + dysarthria clumsy hand	3 (21.4)	9 (16.7)	0.982
Atypical syndrome	2 (14.3)	6 (11.1)	1.0
Topography of lacunes			
Internal capsule	5 (37.5)	21 (38.9)	0.828
Centrum semiovale	3 (21.4)	4 (7.4)	0.124
Basal ganglia	0	6 (11.1)	0.191
Thalamus	1 (7.1)	11 (20.4)	0.247
Pons	5 (35.7)	14 (25.9)	0.467

Data as numbers and percentages in parenthesis unless otherwise stated.

Table 2: Outcome results in 68 patients with lacunar stroke according to the presence of Cheyne-Stokes respiration.

Variables	Cheyne-Stokes respiration		*P* value
	Present, $n = 14$	Absent, $n = 54$	
Barthel index	58.3 (32.5)	75.8 (27.9)	0.130
Canadian Neurological scale	6.9 (1.9)	7.9 (2.1)	0.131
Modified Rankin scale	2.4 (1.3)	2.2 (1.1)	0.131
In-hospital mortality	0	0	
Length of hospital stay	14.9 (11.1)	11.5 (5.6)	0.184

Data as mean (standard deviation, SD).

hemiparesis was the most frequent lacunar syndrome, a relationship between type of lacunar syndrome and presence of Cheyne-Stokes respiration was not found. However, none of the patients with pure sensory stroke had Cheyne-Stokes respiration as compared with 12.2% among patients without Cheyne-Stokes respiration, a fact that may suggest a higher probability of Cheyne-Stokes respiration in lacunar syndromes with motor dysfunction due to a lesion of the pyramidal tract. This observation can also be related to a higher mean AHI in the group of patients with Cheyne-Stokes respiration mainly related to obstructive sleep apneas prior to the stroke, but also to obstructive phenomena caused by destabilization of the upper airways or to involvement of pyramidal-related musculature that without affecting swallowing (none of the patients required placement of a nasogastric tube) may cause a higher instability of the upper respiratory tract during the night.

The small sample size is the main limitation of the study. Although the number of patients was insufficient to assess the impact of Cheyne-Stokes respiration on the early outcome of lacunar stroke (a stroke subtype with mild neurological impairment [22]), a trend towards a more severe stroke and worse prognosis in patients with Cheyne-Stokes respiration was found. Different studies have shown a less favourable immediate and long-term clinical course and worse quality of life in stroke patients with sleep-related breathing disorders [20–26], although some authors have suggested that sleep-related breathing disorders would most affect the time of stroke recovery [27]. In our study, the mean scores of the Barthel index, the Canadian Neurological scale, and the modified Rankin scale between patients with and without Cheyne-Stokes respiration were similar, but further studies with a larger sample size and sufficient statistical power are needed to assess the impact of Cheyne-Stokes respiration in lacunar infarction. The use of a portable respiratory recording device instead of a full-night polysomnography may be considered a limitation of the study. However, this procedure has been previously validated using full polysomnography and has been used in stroke patients [11].

In summary, Cheyne-Stokes respiration was documented in 20.6% of patients with lacunar stroke. The presence of Cheyne-Stokes respiration appeared to be related to a trend towards a higher functional stroke severity and worse prognosis. Our findings warrant further investigation in a larger study population.

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Research Article

Short-Term Change in Occlusal Function after Using Mandibular Advancement Appliance for Snoring: A Pilot Study

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The main aim was to evaluate the influence on occlusal contact area (OCA), maximum bite force (MBF), center of occlusal load (COL), and tooth pain after the nocturnal use of different mandibular advance appliances (MAAs) for snoring. Subjects were consisted of ten adult volunteers with mild snoring in Hiroshima University Hospital. Recordings of occlusal function were performed six times for two hours, that is, immediately and 5, 15, 30, 60, and 120 minutes after the nocturnal use of MAA. The subjects continuously scored their pain intensity on a 10 cm visual analogue scale (VAS) when MBF was measured. Comparing two MAAs, OCA and MBF were significantly larger in two-piece MAA than in one-piece MAA five minutes after removing the appliance. Significant difference in COL and VAS score compared to baseline disappeared more quickly with two-piece MAA than with one-piece MAA. In conclusion, it is shown that two-piece MAA could be superior to the one-piece one in terms of the degree side effect on occlusal function.

1. Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of upper airway obstruction that occur during sleep, usually associated with a reduction in blood oxygen saturation [1]. Excessive daytime sleepiness caused by nocturnal sleep fragmentation interferes with daytime activities, being a common complaint of patients with OSA. OSA is also associated with increased morbidity and mortality from cardiovascular, metabolic, and cognitive alterations in adults [2–7].

Mandibular advancement appliances (MAAs), aiming to enlarge the upper airway by repositioning the mandible forward, are known to be useful as a lifelong treatment tool for primary snoring and mild-to-moderate OSA [8–11]. MAAs are sometimes more preferable for moderate-to-severe OSA when the nasal continuous positive airway pressure (nCPAP) therapy is not indicated, although MAA therapy was less effective than nCPAP [12, 13].

Recently, several studies have focused on the side effects of MAAs related to temporomandibular joint (TMJ) discomfort and the masticatory muscles stiffness with difficulty in chewing immediately after the nocturnal use of MAAs [14–16]. George [17] reported that most OSA patients, after the use of MAA for a whole night, experience that the bite does not feel right upon awakening, but that it normalizes after breakfast. Ringqvist et al. [18] also demonstrated that some patients had problems in biting in the regular habitual intercuspal position during the first hour or so after using MAA for a whole night. The adverse event might be small and transient, but it happens repeatedly every morning.

To date, numerous MAAs are available and distributed in the market for the treatment of snoring and OSA [19]. MAAs can be classified roughly into two different types. One is one-piece type and the other is two-piece one. Especially, the latter is expected to improve jaw and muscle discomfort during MAA therapy. However, side effects of two-piece

type MAA on masticatory system have not been investigated objectively and comparatively.

In the present study, a controlled randomized study was designed to test a hypothesis that the influence on occlusal function and tooth pain would be less in two-piece MAA than in one-piece ones. The primary aim was to compare the difference in mandibular movement of two-type MAAs when one-piece and two-piece MAAs are similarly used. Secondary aim was to evaluate the influence on occlusal contact, bite force, and tooth pain after the nocturnal use.

2. Materials and Methods

2.1. Subjects. Subjects were consisted of five males and five females (mean age: 26.2 ± 5.8 years) selected from the volunteers who have mild snoring in Department of Orthodontics, Hiroshima University Hospital. The inclusion criteria for the subjects were as follows: (1) normal horizontal and vertical skeletal relationships, (2) no malocclusions and periodontal disease, (3) no complaints of TMJ disorders, and (4) no history of snoring treatment.

Informed consent was obtained from each subject prior to the experiment. The Ethics Committee of Hiroshima University approved the secondary use of data in this study.

2.2. Measurement of Mandibular Movement with Different MAAs. Both one-piece (Figure 1) and two-piece (Figures 2(a) and 2(b)) MAAs were constructed of 0.75 mm thick acrylic resin that provides full occlusal coverage of teeth. Two-piece MAA is made of resin and an orthodontic wire, 0175″ multistranded round wire, attached on the buccal sides of the lower splint. The amount of initial mandibular advancement achieved by both MAAs was defined as two-thirds of maximum mandibular forward repositioning with a 3-4 mm vertical opening in the anterior teeth. The mean advanced mandibular position was very similar, 6.2 ± 0.9 mm and 6.4 ± 1.0 mm with one-piece and two-piece MAAs, respectively. The appliance was adjusted to maximize comfort by relieving all uncomfortable pressure points on the teeth and gums.

Prior to the initiation of one-night clinical study, the difference in the maximum mandibular movement between using both MAAs was investigated horizontally in the anteroposterior (P-A) and right-left (R-L) directions by means of an optoelectric jaw-tracking system with six degrees of freedom. This system consists of a head frame, face bow, light-emitting diodes (LEDs), two CCD cameras, and a personal computer (Gnathohexagraph system II, Onosokki Co., Yokohama, Japan) [20, 21]. Each subject was in supine position on the floor with a head frame and a face bow, each with 3 LEDs. These devices were attached firmly to the head and the dental clutch, which was bonded to the labial surface of the lower splints. Two CCD cameras were placed approximately 1.2 meters away from subjects, as illustrated in Figure 3.

Each subject was requested to perform maximum voluntary movements with MAA three times, all the way to reposition the jaw forward and backward, and side to side.

Figure 1: One-piece MAA.

We calculated the maximum displacement of the mandible from the path of LEDs recorded by CCD cameras.

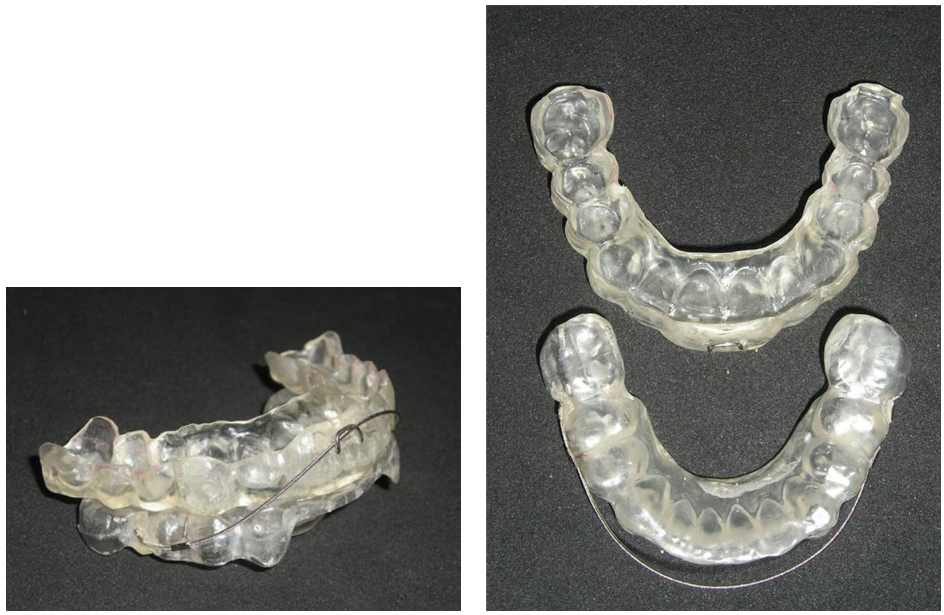
2.3. Clinical Recording and Analytical Procedure. The subjects were randomized to use either one-piece or two-piece MAA for six or more hours for a whole night and crossed over to the other MAA after one-week washout period. Recordings of occlusal function were performed six times for two hours, that is, immediately and 5, 15, 30, 60, and 120 minutes after the nocturnal use of MAA. The sequence of recordings and evaluations is illustrated in Figure 4.

2.4. Evaluation of Occlusal Function. An occlusal diagnostic system, Dental Prescale Occluzer, (Fuji Film Co., Tokyo, Japan) was used to evaluate occlusal contact area (OCA), maximum bite force (MBF), and center of occlusal load (COL) (Figures 5(a) and 5(b)) [22–26]. Dental Prescale is a 98 μm thick horseshoe-shaped sheet wrapped with polyfilm. The microcapsules in the sheet break and release a color-forming material at various occlusal pressures. Each subject was instructed to bite a pressure-sensitive sheet in the habitual intercuspal position with maximum clenching for 3 seconds by one of the investigators (GW). Then, an image scanner (FPD-703, Fuji Film Co.) was used to determine OCA, MBF, and COL. Both OCA and MBF were quantified with an occlusal force diagram according to the degree of coloring. In order to evaluate changes in COL, the anteroposterior distance from the baseline point is measured (Figure 6).

2.5. Visual Analogue Scale for Tooth Pain. The volunteers continuously scored their pain intensity on a 10 cm visual analogue scale (VAS) when MBF was measured. The upper extreme was marked "most pain imaginable," and the lower extreme was marked "no pain" (Figure 7).

VAS scores were calculated as tooth pain in accordance with previously described methods [27, 28].

2.6. Statistics. The arithmetic mean and standard deviation (SD) were calculated for each variable. No significant differences were found between sexes. Recordings from men and women were therefore pooled and analyzed together.



(a) (b)

Figure 2: (a) Two-piece MAA (lateral view), (b) upper and lower plates.

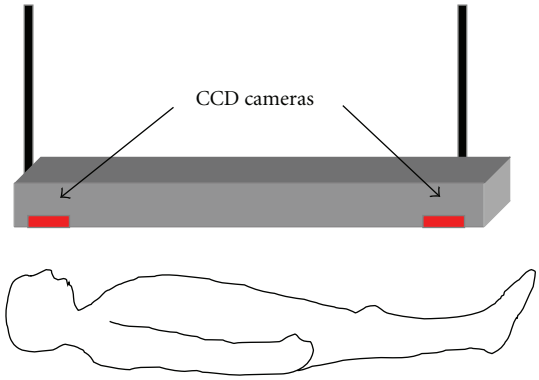


Figure 3: Schematic illustration to show the recording jaw movement by means of Gnathohexagraph.

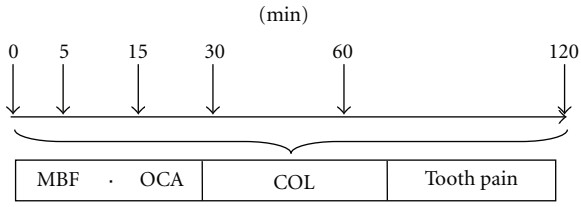


Figure 4: Schematic illustration to show the time course.

Statistical significance of the differences in the measured values between the MAAs was performed with Mann-Whitney U test. Among six performances, the data were statistically analyzed using analysis of variances (ANOVA) and the subsequent pairwise comparisons.

P values less than 0.05 were considered significant.

3. Results

3.1. Maximum Mandibular Movement with MAA. Table 1 shows the comparison of maximum mandibular movement when two-type MAAs were used. Two-piece MAA showed a greatly significant R-L movement, approximately 11 mm in the transverse direction, during voluntary lateral jaw movement.

With respect to the P-A direction, significant differences were found between two MAAs during maximum jaw opening and lateral movement. However, mean displacement of the mandible using two-piece MAA was below 2 mm.

3.2. Evaluation of Occlusal Function and Tooth Pain. Changes in OCA and MBF after nocturnal use of two MAAs are shown in Figures 8(a) and 8(b), respectively. OCA is increased gradually from approximately 2.5 to 16 mm^2 during 120-minute measurement. MBF exhibited similar changes to OCA and showed an increase gradually from approximately 100 to 800 N through the experiment. Thirty and fifteen minutes after initiating the measurements, OCA and MBF were found significantly smaller than those of the baseline in one-piece and two-piece MAAs, respectively. After 30 minutes, significances in OCA and MBF disappeared, although both two parameters still showed almost 80% of baseline after 120 minutes.

Comparing two MAAs, OCA and MBF were significantly larger in two-piece MAA than in one-piece five minutes after removing the appliance.

Mean COL after using MAA for a whole night is located approximately 20 mm anterior (around the canines or first premolars) to the baseline COL (Figure 9). Then, it is getting closer to the baseline point (around the first molars) shifting backward through the morning.

(a) (b)

Figure 5: (a) A pressure-sensitive sheet (dental prescale), (b) an occlusal diagnostic system (dental prescale occluzer).

Table 1: The distance of mandibular movement with different MAAs during maximum voluntary effort.

		One-piece MAA	Two-piece MAA	
Right-left direction	Shift to the right	0.64 ± 0.41	11.1 ± 2.49	**
	Shift to the left	0.79 ± 0.67	11.4 ± 1.83	**
Anteroposterior direction	Maximum jaw opening	0.51 ± 0.38	1.71 ± 0.79	NS
	Lateral jaw movement	0.32 ± 0.08	1.00 ± 0.66	NS

Unit: mm, $^{**}P < 0.01$, NS: not significance.

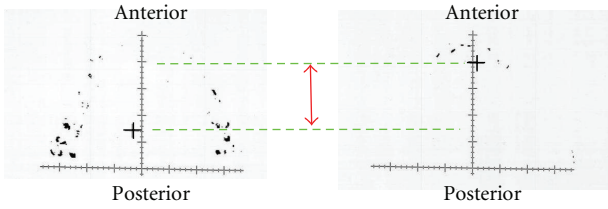


Figure 6: A cross represents the COL in the upper dentition during maximum clenching.

(No pain) (The most severe pain I ever felt)

Figure 7: Visual analogue scale for tooth pain.

Significant difference in COL compared to baseline disappeared more quickly with two-piece MAA than with one-piece MAA, after 5 and 30 minutes, respectively.

Comparing two MAAs, COL was significantly larger in one-piece MAA than in two-piece five minutes after removing the appliance. Although COL returned to the baseline 120 minutes after the use of two-piece MAA, COL with one-piece MAA was still 3 mm backward from the baseline.

Figure 10 shows changes in VAS for tooth pain with two MAAs. Mean VAS score immediately after removing MAA was between 5 and 6. Significant difference in VAS score compared to baseline disappeared more quickly with two-piece MAA than with one-piece MAA, after 15 and 30 minutes, respectively.

Comparing two MAAs, VAS score was higher in one-piece MAA than in two-piece MAA until 30 minutes, and significance was found 30 minutes after removing the appliance. After one hour, mean VAS decreased to below 1, and for two hours during the experiment, VAS score became the same as the baseline, that means 0 (no pain).

4. Discussion

This study is the first prospective randomized crossover study to compare influence of two-type MAAs masticatory system. Two-piece MAA showed a significantly greater jaw movement in the transverse direction. However, with respect to the P-A direction, mean displacement of the mandible was below 2 mm during any jaw movement in the laboratory-based results. Furthermore, two-piece MAA which allows mandibular movement in various directions showed significantly less influence on occlusal function and tooth pain than one-piece MAA.

Currently, more than 50 different devices are distributed in the market for dentists in USA and Canada [29], where one-piece MAA has been used most frequently because it is cheaper and easier to fabricate than two-piece, adjustable appliances. However, two-piece type has become popular because of the merit to decrease orofacial discomfort.

In the present study, all subjects with either MAA got considerable improvement of snoring based on the information from their bedpartners. Thus, the efficacy of two different MAAs was clinically similar. Different MAAs have been designed and evaluated in previous studies. Ferguson et al. [30] reported two prospective randomized crossover studies to compare the efficacy, side effects, and preference of both

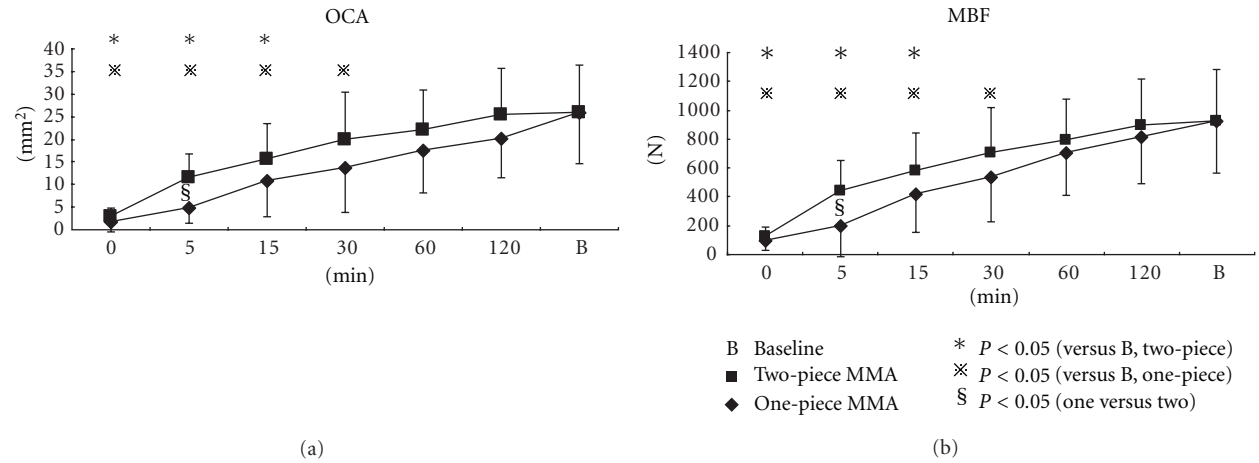


Figure 8: (a) Changes in occlusal contact area after nocturnal use of different MAAs, (b) changes in maximum bite force after nocturnal use of different MAAs.

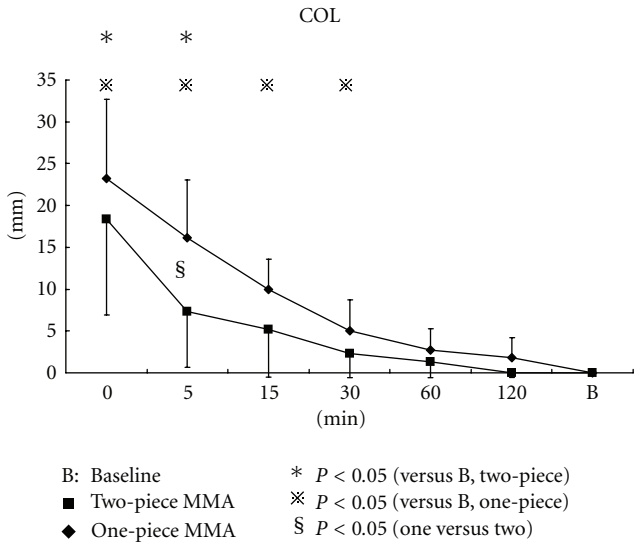


Figure 9: Changes in center of occlusal load after nocturnal use of different MAAs.

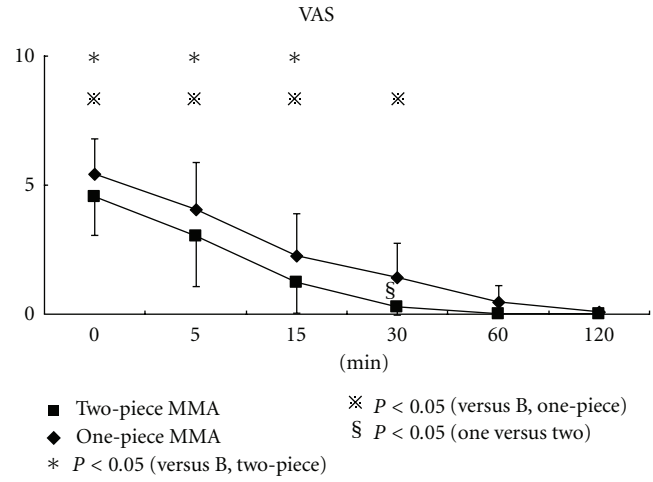


Figure 10: Changes in tooth pain after nocturnal use of different MAAs.

rigid and nonrigid MAAs relative to nCPAP. Both MAAs were effective in reducing symptoms, and the long-term preference was overwhelmingly in favor of MAA therapy, superior to nCPAP. Treatment success rate was 48% and 61%, and compliance failure rate was 24% and 4% with nonadjustable and adjustable MAAs, respectively in their different studies. In addition, another study [16], directly compared a one-piece appliance with a two-piece one. Fritsch et al. showed no significant difference, but one-piece, monoblock MAA was comparatively favored by patients because it produces negligible side effects.

As far as we know, no clinical randomized and controlled study has confirmed objectively the superiority of two-piece MAA over one-piece one in terms of the influences on masticatory system. In this study, mean OCA and MBF were significantly small, approximately 20% of baseline immediately after the nocturnal use of both the types of MAAs, then getting increased gradually during two hours. Significant differences from the baseline were found until half an hour passed.

Otsuka et al. [31] found that mean OCA and MBF of OSA patients during MAA therapy were significantly smaller in the morning than at night. They also demonstrated a decrease in the occlusal function by 40% when morning and night data were compared. Ueda et al. [32] also reported the similar findings in consecutive 3-day data in OSA patients.

Both OCA and MBF were significantly decreased in the morning. The finding may be explained in part by the side effects of MAA in use such as joint edema, stiffness of masticatory muscles, or altered occlusal function [30, 33]. In addition, the most likely explanation for the reduction in occlusal function immediately after the nocturnal use of MAA is that

the mandible is repositioned anteriorly by MAA and does not return to the original normal position, which means the condyle cannot attain its normal position during maximum clenching. One important result of this study was that COL with two-piece MAA returned the baseline point significantly quickly. COL data in this study support our speculation because significant forward COL means less occlusal contact in the molar region and close contact in the anterior region, due to MAA-induced forward position of the mandible.

The recovery of OCA and MBF was observed up to 120 minutes after removal of MAA, although occlusal function could not reach the baseline level yet for all the subjects. The fact that a few subjects presented reduced occlusal function by 50% below the baseline with one-piece MAA even two hours after the removal should not be neglected.

When the mandible is repositioned forward rigidly even several hours per night, a major concern has been that it may generate a special strain upon the orofacial structures, causing adverse effects on the TMJ and masticatory muscles. Masticatory system including the mouth, pharynx, and TMJ is involved cooperatively in many vital physiological activities, such as breathing, swallowing saliva, and yawning during sleep. Miyamoto et al. [34] investigated mandibular posture during sleep in seven healthy adults and OSA patients. Their results showed that vertical mandibular posture is more downward during sleep in OSA patients than in controls, and mandibular opening progressively increases from 0 to more than 10 mm during apnoeic episodes. In our previous study, Shikata et al. [35] found that the amount and duration of vertical mandibular displacement were significantly increased (approximate 10 mm) by experimentally induced nasal respiratory obstruction in awake healthy subjects. From these studies, the nature of mandibular displacement with breathing disorder can be often observed at around 10 mm mouth opening; therefore, we believe that it is more favorable not to fix the mandible rigidly in terms of the jaw reflex and masticatory stiffness even during sleep.

Another explanation for the superiority of two-piece MAA may be that the compliance of using MAA relate to the balance between the benefits and side effects [36]. de Almeida et al. [37] demonstrated 35.9% of the 251 OSA patients stopped MAA treatment after a mean of 5.7 years and 72% of those did so during the first year of treatment. In their speculation, major reasons that patients discontinued MAA treatment were major side effects and poor treatment effects on snoring and OSA symptoms. With these considerations, it is of a great importance to diminish side effects of MAA and to enhance the treatment effects for snoring and OSA to be satisfied by patients.

VAS is used extensively as a subjective estimation for pain. That is quite simple and easy for subjects. As a result of VAS examination, the recover of tooth pain was a little different from occlusal function mentioned above. After two hours, tooth pain during biting the pressure-sensitive sheet disappeared totally on VAS. This may be due to that the threshold of human sensation has some range. In addition, tooth pain might be easy to be influenced easily by individual's feeling under psychological situation.

The present study has several potential limitations. Subjects in this one-night study were young volunteers with mild snoring, not diagnosed OSA patients. Further investigation in this area is required, especially for typical middle-aged OSA patients who have disadvantage of periodontium undergoing MAA treatment with one-piece or two-piece type. The influence of long-term use of MAA on masticatory system is to be examined in more detail.

Based on the results, side effects on occlusal function might be transient, but unstable mandibular position for a long time in every morning could predispose snoring and OSA patients to the permanent occlusal change. In conclusions, two-piece MAA that can allow jaw movement in various directions might avoid excessive stiffness of masticatory muscles and distribute the harmful force widely on the dentition. Thus, it is shown that two-piece MAA could be superior to the one-piece one in terms of the degree of the side effects on occlusal function.

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Clinical Study

Efficacy of Submucosal Sodium Tetradecyl Sulfate in the Soft Palate as a Treatment of the Mild Obstructive Sleep Apnea Syndrome: A Pilot Study

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Background. As described by Mair et al. in 2001, snoreplasty, the application of sclerosant agents in the palate is a promising and cheap alternative to treat snoring. We decided to try this kind of therapy for the management of mild sleep apnea. *Study Design*. Experimental, longitudinal, prospective, nonrandomized, self-controlled pilot study. *Methods*. 11 patients were included, all of them with a polysomnographic study showing an Apnea-Hypopnea Index (AHI) from 5 to 20, and with a Müller maneuver showing only retropalatal collapse. *Results*. We found significant decrease in the number of apneas hypopneas and oxygen desaturation as well as in the snoring index ($P < 0.05$), although no differences were found in the number of arousals. *Conclusion*. Sclerosant agents might become a relevant part in the treatment of sleep apnea, in very well-selected patients.

1. Introduction

The obstructive sleep apnea syndrome (OSAS) is one of the most commonly found sleep disorders around the world. A number of studies show that it may be present in 5–20% of the adult population, and about 40 million Americans seem to be affected [1]. The obstruction in the upper airway may be present at one or many anatomical locations: the nasal septum, turbinates, tonsils, adenoids, soft palate, base of tongue, and even epiglottis, [2] and its presentation includes not only adults, given that children can be affected as well [3].

Many authors have demostrated a strong association between OSAS and a high incidence of traffic accidents, becoming one of the most important risk factors, just following alcohol [4]. OSAS has also shown to be an important factor in the development of cardiovascular conditions such as systemic hypertension and stroke [5, 6].

According to the International Classification of Sleep Disorders (ICSD, 2005), diagnosis of OSAS has to be suspected on patients complaining of snoring, astenia, cognitive disorders, and excessive daytime somnolence. Polysomnography should be performed on these patients in order to confirm the diagnosis, getting the apnea-hypopnea index (AHI) and rule out the presence of central or mixed apnea periods [5, 6].

The site or sites of obstruction at the airway should be suspected during the physical examination. The use of imaging studies like cephalometric measures, computed tomography, and magnetic resonance have been proposed, but none of them have shown to be more effective. Flexible fiberoptic nasopharyngoscopy with Müller maneuver may be a more accurate method to determine the obstructive area, despite its usefulness is still controversial [7].

There are many options for the OSAS treatment, according to its severity and to the site of obstruction. Medical treatment includes exercise programs, weight control, management of associated medical conditions (such as hypothyroidism and gastroesophageal reflux disease) mandibular advance devices, and nasal continuous positive airway pressure, which remains as the gold standard [8].

Surgical treatments also include different approaches, and all of them remain controversial. Uvulopalatopharyngoplasty (UPPP) is the most commonly used technique. However, it is a surgical procedure performed under general anesthesia, which increases costs and risks. Laser-assisted uvulopalatoplasty (LAUP) can be performed at the office, under local anesthesia. Nevertheless, it has 2 important disadvantages: it is an expensive and very painful procedure [9]. The use of controlled temperature radiofrequency energy (Somnoplasty, Gyrus ENT, Bartlett, TN) is a relatively new kind of therapy. It could be used at the palate, turbinates, and base of tongue and it is performed at the office with a minimal or null discomfort. Again, its price is its main disadvantage [10].

Brietzke and Mair, in 2001, reported the use of a widely known sclerosant agent, sodium tetradecyl sulfate (STS), as a painless and cheaper procedure (injection snoreplasty) to successfully treat snoring in 27 patients [11]. Only primary snoring was considered for the treatment, excluding OSAS patients. In the present study, we decided to try this injection snoreplasty to treat mild OSAS, but only when the obstruction site was located exclusively at the soft palate.

2. Methods

Eleven consecutive patients with the diagnosis of mild OSAS from the Sleep Disorders Clinic of the National University of Mexico were enrolled in this experimental, longitudinal, prospective, nonrandomized, and self-controlled pilot study, performed with the approval of the Ethics and Research Board of the General Hospital of Mexico. All patients underwent clinical assessment and full overnight sleep study (Alice 3, USA).

Our inclusion criteria included both genders, from 18 to 65 years old, with no metabolic or coagulation diseases, with small palatal tonsils (included between the anterior and posterior pillars), AHI from 5 to 20, and obstruction located at the palate. AHI was defined as the number of both, apneas (obstructive, mixed or central) and hypopneas, during the full night and divided by the number of hours the patient kept asleep, and snoring index (SI) was defined as the number of snoring events per hour of sleep. Only patients with body mass index (BMI) from 24 to 26 were included, trying to avoid obesity as a confusing factor. Pregnant women were excluded from the study, because the security range of STS has not been established in such cases. Septal abnormalities, turbinal hypertrophy, uvula longer than 1 cm, and base of tongue obstruction were also exclusion criteria, given that the aim of the study was to determine the usefulness of STS only at the palate.

Elimination criteria included patients who did not accept to participate in the trial and those who decided to stop their participation at any time.

Confirmation of the obstruction site was achieved using the Müller maneuver, accepting only the cases with palatal collapse and eliminating those whose obstruction sites were located at the nose, base of tongue, lateral walls, or epiglottis.

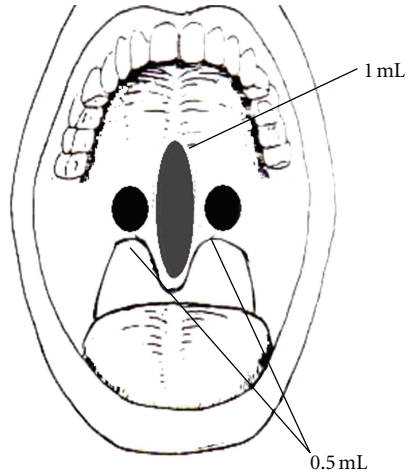

Figure 1: Injection procedure technique at the soft palate.

In a previous study, we found a concordance *kappa* test value of 0.9.

Once the patients were properly selected, we injected 2 mL of 3% STS (Fibro-Vein 3%, STD Pharmaceutical Products LTD, Harreford, England). The whole procedure was performed at the office. Topical anesthesia was applied using 10% spray lidocaine, about 5 minutes before the procedure was performed. The injection technique was similar to the one described by Brietzke and Mair in 2001, but only 1 mL was injected submucosally at the midline and 0.5 mL on each side, using a tongue depressor to improve visualization of the area (Figure 1). Another difference from the original technique by Brietzke and Mair was that they used 1% STS instead of 3%, given that they were looking only for an improvement on snoring. We decided to use 3% STS in order to increase the possibility of volumetric tissue reduction, leading to an improvement on OSAS as well. All of the patients complained of a mild burning pain at the application site during a couple of minutes, but it was self-limited. All of them were sent home after 15 minutes, with a prescription for ketorolac tromethamine 10 mg, just in case that pain would be present. No antibiotics were prescribed. An appointment for followup was scheduled 6 months after the procedure, for clinical and fiberoptic assessment, and to perform a control overnight sleep study 6 months after the procedure.

AHI, snoring index, mean oxygen saturation, and arousals index were analyzed using a Student's t-test for related samples. Central tendency measures were performed as well, using SPSS 11.0 for Windows (LEAD Technologies, Chicago IL). Statistical significance was established at the $P < 0.05$ level.

3. Results

Descriptive statistics are shown in Table 1. The age of the 11 patients ranged from 22 to 62 years old, with a mean of 43.36 years old. 9 of them were males and 2 females. Only one

Table 1: Descriptive statistics.

	Number	Minimum	Maximum	Mean	STD
Age	11	22	62	43.3636	11.39537
AHI pre	11	7.9	20	14.4727	4.49513
AHI post	11	0	8	4.1364	2.32348
Snore index pre	11	33	672	149	185.45044
Snore index post	11	4	114	20.4	31.65691
O_2 mean pre	11	81	88	83.5364	2.2686
O_2 mean post	11	89	98	91.6336	3.31051
Arousals index pre	11	10	491	148	131.79378
Arousals index post	11	8	224	86.6364	58.41279
BMI	11	24	26	25.1727	0.69151

AHI: Apnea-Hypopnea Index. Pre: Preoperative. Post: Postoperative. O_2: Oxygen. BMI: Body Mass Index.

Table 2: Student's t-test and P values.

	Student's t	P values
AHI	6.649	<0.001*
Snoring index	2.744	0.021*
Mean oxygen saturation	8.504	<0.001*
Arousals	1.736	0.113
Epworth sleepiness scale	2.88	0.016*

AHI: Apnea-Hypopnea Index. *indicates significant P values.

patient complained of a small ulcer in the site of application, which required no treatment at all.

For the preoperative AHI, we found a range from 7.9 to 20 (mean 14.47), while the postoperative AHI ranged from 0 to 8 (mean 4.13). We found only obstructive apneas and hypopneas, and no central or mixed were found. Standard deviation was 5.156, the 95% Confidence Interval (CI) for the difference was 6.87/13.8, with a Student's $t = 6.649$, and a $P < 0.001$. All measures had 10 degrees of freedom and a 2-tailed value for the t-test.

Regarding preoperative snoring index, it ranged from 33 to 672 (Mean 149), and the postoperative range was from 4 to 114 (Mean 20.4), the 95% CI showed 24.21/233.51. Standard deviation was 155.776, for a Student's $t = 2.744$, and a $P = 0.021$.

On the mean oxygen saturation, we found preoperative values ranging from 81 to 88 (Mean 83.53), while the postoperative values ranged from 89 to 98 (Mean 91.63), with a 95% CI of −10.21/−5.97, standard deviation of 3.158, for a Student's $t = 8.504$, and a $P < 0.001$.

Finally, in terms of the number of arousals, we found that the preoperative mean was 148, and the postoperative mean was 86.6; there was a 95% CI of −17.38/140.11 and standard deviation of 117.218, for a Student's $t = 1.736$, and a $P = 0.113$, which is non statistically significant.

As a subjective measure we used the Epworth Sleepiness Scale, in order to evaluate day-time excessive sleepiness. We found a preoperative mean of 9.6364 (4–13), and postoperative mean of 8.2727 (5–12), for a $t = 2.88$ and a $P = 0.016$.

All the pre and posttreatment "Student's t-test" and "P" values are shown in Table 2.

We also asked the bed partner about the subjective improvement regarding snoring (improved, remained the same, or got worse). 10 patients improved, while only one referred that snoring had no changes. No patients got worse in this study.

In all cases, the last clinical and polysomnographic assessment was made 6 months after the initial procedure. After a followup of 6 months, we did not find any permanent complication, and patients as well as their bed partners were satisfied with the clinical results.

4. Discussion

Both objective and subjective outcome measures were used to assess the efficacy in this study. Hawthorne effect, that is, clinical improvement due only to the fact of being treated, represents a high risk on every self-controlled trials [12], so the elimination of day-time somnolence, headache, and other complaints should never be the best way to evaluate the success of any treatment modality. Nevertheless, we present numeric values that cannot be affected by the subjective perception of the patient: the AHI, the snoring index, the number of arousals, and the mean oxygen saturation level.

The small number of patients is a weak issue in our study. The reason why we present a pilot study is that when we tried to estimate the sample size properly, we were not able to find in the English language literature, adequate statistical data that we could use, not even standard deviation. One of the main objectives of any pilot study is to provide descriptive statistics that may be used to calculate the sample size in future well-designed studies [12].

All of the patients showed a significant improvement in the subjective variables, specially regarding snoring referred by the bed partner. All of them referred that the morning headache diminished importantly. Epworth Sleepiness Scale did not show significant changes, perhaps due to the fact that all of the patients had only mild sleep apnea, so day-time sleepiness was not a real complain on these patients.

We were very careful to include in our study only patients whose obstruction site was located exclusively at the soft palate. This fact gives to the study strong internal validity, so we shall remind that similar results will only be reached when the selection criteria are fullfilled, including a very methodical search for the site of obstruction.

The statistical analysis shows a highly significant change when comparing the AHI, the mean levels of oxygen, and the snoring index. This statistical significance was very evident on both, the *P* value and the 95% confidence intervals of the difference. Despite these changes, no significant difference was found on the arousal index. However, we should keep in mind that the lack of statistical significance does not always mean a lack of biological one.

There is an antecedent regarding the effectiveness of sclerosant agents in the treatment of primary snoring, reported by Brietzke and Mair [11], but this cheap and painless therapy choice had never been tried to treat OSAS. Our results support the possibility of keeping it as an important tool when treating sleep breathing disorders but only when the site of obstruction is exclusively located at the soft palate, with mild OSAS, and in no obese patients, and as a primary treatment modality. In our series, after a followup of 6 months, a single application seems to be effective.

In 2008, Al-Jassim and Lesser [13], used injection snoreplasty in 60 primary snorers, as a part of their assessment, in order to rule out if the snoring was originated at the palate or anywhere else, so they could eventually decide if further and more aggressive palatal surgery could be indicated. They did not evaluate OSAS patients. We believe that the main reason why the surgical management of OSAS remains so controversial is the fact that the otolaryngologists keep looking for a surgery that cures every case of OSAS, even performing surgeries to patients who were not candidates for surgical management from the begining. We think that the key point in the managements of this kind of patients is to perform a complete preoperative evaluation, using every tool that we have available, including polysomnography, endoscopy, and a thorough clinical assessment.

5. Conclusions

The application of sodium tetradecyl sulfate in the soft palate (injection snoreplasty) has been proved as a treatment for primary snoring, and it may play an important role in the management of mild obstructive sleep apnea syndrome, but only when its origin lies exclusively at the soft palate. It represents a cheap and painless procedure, easily and quickly performed at the office, with no convalescence, and no complications in our study.

We should keep in mind that the most important point when treating OSAS patients is an accurate preoperative evaluation and the concept of looking for the best surgical procedure should be changed for the concept of accurately finding the level or levels of obstruction, and treating the different obstructive areas as a whole, as a patient and not as an obstructed anatomic area.

New studies, adequately designed and with a proper sample size, and with a longer followup must be performed in the next future, in order to determine the role of the injection snoreplasty in the treatment of moderate or severe OSAS, or when the site of obstruction is located at the base of tongue, either as a single procedure or as a part of a multilevel approach (which may include mandibular advance devices and other medical and conservative treatment modalities). Nevertheless, this procedure must be considered as a realistic alternative when treating mild OSAS if the site of obstruction is located exclusively at the soft palate.

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Review Article

Obstructive Sleep Apnoea Syndrome and Weight Loss: Review

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Obstructive sleep apnoea (OSA) syndrome is common, and obesity is a major risk factor. Increased peripharyngeal and central adiposity result in increased pharyngeal collapsibility, through increased mechanical loading around the upper airway, reduced tracheal traction on the pharynx, and reduced neuromuscular activity, particularly during sleep. Significant and sustained weight loss, if achieved, is likely to be a useful therapeutic option in the management of OSA and may be attempted by behavioural, pharmacological, and surgical approaches. Behavioural therapy programs that focus on aspects such as dietary intervention, exercise prescription patients and general lifestyle counselling have been tested. Bariatric surgery is an option in the severely obese when nonsurgical measures have failed, and laparoscopic adjustable gastric banding and Roux-en-Y gastric bypass are the most commonly employed techniques in the United Kingdom. Most evidence for efficacy of surgery comes from cohort studies. The role of sibutramine in OSA in the obese patients has been investigated, however, there are concerns regarding associated cardiovascular risk. In this paper the links between obesity and OSA are discussed, and the recent studies evaluating the behavioural, pharmacological and surgical approaches to weight loss in OSA are reviewed.

1. Introduction

Obstructive sleep apnoea (OSA) syndrome is common with a prevalence of approximately 4% in middle-aged men and 2% in middle-aged women [1]. Frequent partial (hypopnoea) or complete (apnoea) closure of the upper airway during sleep leads to oxygen desaturation, increased respiratory effort, arousal, and sleep fragmentation. Patients typically present with witnessed apnoeas, loud intermittent snoring, and excessive daytime somnolence [2]. The syndrome is associated with impairment in quality of life [3], cognitive functioning, and work performance [4], and with an increased risk of road-traffic accidents [5]. OSA is considered an independent risk factor for hypertension [6, 7] and has associations with coronary artery disease [8], stroke [9], heart failure [10], arrhythmias [11], metabolic syndrome [12], and type 2 diabetes [13]. Obesity is an important risk factor for the development of OSA [14–16] and is unique amongst the major risk factors in being modifiable [17]. There is a wealth of studies evaluating the effects of weight loss, achieved by behavioural, pharmacological, and surgical approaches, in the management of OSA in the obese patients. In this review, we will discuss the links between excess body weight and development of OSA and the different methods of achieving weight loss and their effectiveness.

2. Obesity as a Risk Factor for OSA

The evidence to support the role of excess weight as a causal factor in the aetiology of OSA is convincing. In a population study involving 2148, prevalence of obesity was significantly higher in those with OSA than those without, whether male (22% versus 8%) or female (32% versus 18%) [18]. Another study of 161 obese patients (BMI $\geq$ 30 kg/m^2) showed that OSA was present in over 50%, and in 25% this was severe [19]. Amongst the morbidly obese patients (BMI $\geq$ 40 kg/m^2), prevalence of OSA as high as 98% has been reported [20]. Using data from the population-based Wisconsin Sleep Cohort Study [1], Young et al. estimated that, in 41% of adults with mild or worse sleep disordered breathing (SDB) (AHI $\geq$ 5) and in 58% of those with moderate or worse SDB (AHI $\geq$ 15), sleep disordered

breathing (SDB) was attributable to excess weight (defined as BMI $\geq 25\,kg/m^2$) [16]. In a study based on data from the 2005 National Sleep Foundation Sleep in America poll, 59% of 379 obese individuals were at high risk for OSA as defined by the Berlin Questionnaire [21]. In the Sleep Heart Health Study based on 5615 adults, the odds ratio for an AHI of 15 or greater with a BMI difference of $10\,kg/m^2$ was 2.4 [22]. A longitudinal population-based study of 690 adults followed up at 4 years demonstrated that a 10% weight gain predicted a 32% (95% confidence interval (CI) 20–45%) increase in AHI while a 10% weight loss predicted a 26% (95% CI 18–34%) decrease in AHI. Further, a 10% increase in weight predicted a 6-fold (95% CI 2.2–17.0) increase in the odds of developing moderate-to-severe SDB [23]. The Sleep Heart Health Study similarly confirmed progression and regression of sleep-disordered breathing (as quantified by respiratory disturbance index (RDI)) with weight gain and loss but also demonstrated that the association was stronger for males than for females [24]. Several studies have confirmed obesity and BMI [22, 25, 26] as predictors of OSA. Likewise, other relevant anthropometric measures have been associated with OSA such as neck circumference [22, 26–28], waist circumference [29], waist-hip-ratio [25], and visceral adiposity [30, 31].

3. Mechanisms for the Development of OSA in the Obese Patients

There are several mechanisms by which obesity could result in OSA, and these may act synergistically. It is proposed that increased peripharyngeal fat deposition results in mechanical loading that offsets the maintenance of airway patency by the dilator muscles and that this increase in collapsibility is particularly prominent during sleep when there is a reduction in neuromuscular activity [32–34]. In addition, there is some evidence to suggest that central obesity in particular may have detrimental effects on neuromuscular activity in the upper airway [35]. Obesity is associated with a reduction in functional residual capacity (FRC) [36]. Pharyngeal collapsibility may be further accentuated by this reduction in FRC and subsequent decrease in tracheal traction on the pharynx [34]. Finally, a self-perpetuating cycle may develop in which sleep disruption leads to increased appetite (especially for calorie-rich high-carbohydrate foods) [37], reduced activity levels, further weight gain, and increased severity of OSA [38].

4. Weight Loss as a Therapeutic Approach in OSA

4.1. Behavioural Methods (See Table 1). Several studies have been performed to evaluate the effects of approaches including dietary modification and exercise, as well as counselling. Two small cohort studies [39, 40] and a larger randomised, controlled, parallel study [41] have assessed the effects of a very low-calorie diet (VLCD) given over two to three months. In each of these studies, significant improvements in weight and BMI occurred. Johansson et al. [41] reported a significant reduction in AHI with 17% "cured," while, in the study of Kansanen et al. [40], RDI was significantly decreased with "cure" in 20%. All three studies demonstrated improvements in nocturnal oxygenation, and a reduction in daytime somnolence was reported by two [39, 41]. In a follow-on study [42], Johansson et al. enrolled patients, on the completion of the VLCD, into a weight-loss maintenance programme incorporating behaviour modification group therapy focusing on elements such as nutrition education and increased physical activity. After one year, anthropometric measures and sleep variables had increased compared to post-VLCD values but were still significantly better than at baseline, with "cure" in 10%. In another study, patients with mild-to-moderate OSA were randomised to CPAP, an oral appliance or conservative measures (sleep hygiene), and overweight individuals (BMI $\geq 23\,kg/m^2$) were invited to attend a weight control programme in the local Dietetics Unit [43]. Weight loss occurred in 45 participants across the three treatment groups after 10 weeks (75.8 (1.6) kg to 72.5 (1.5) kg), and this was accompanied by a decrease in AHI (24.6 (1.7) to 19.1 (2.0)). 8 participants were cured (AHI < 5) with a mean weight loss of 2.9 (1.0) kg. In addition, there was a linear relationship between change in AHI and body weight ($r = 0.298$, $P = 0.004$) independent of treatment modality. Kemppainen et al. performed a prospective, and randomised, controlled parallel study comparing a VLCD and supervised lifestyle intervention with routine lifestyle counselling over 3 months [44]. BMI decreased by $5.4\,kg/m^2$ in the intervention group compared to only $0.49\,kg/m^2$ in the control group ($P < 0.001$). The reduction in AHI was not significantly different between groups, however (intervention group: 3.2 events/hour, control group: 1.3 events/hour). Likewise, a small cohort study in which patients completed a 16-week program including VLCD and an exercise program showed significant weight loss and reduction in daytime sleepiness but no significant change in AHI after 16 weeks [45]. In this study, at one year, patients had again regained weight although weight was still significantly less than at baseline. In a randomised and controlled, parallel study, Tuomilehto et al. reported improvements following a VLCD for 12 weeks with supervised lifestyle counselling focussing on diet, exercise and lifestyle modification [46]. After one-year significant improvements were seen in AHI, number of patients cured, nocturnal oxygenation, weight, and BMI in the intervention group. Nerfeldt et al. [47] have recently reported the results of a 2-year weight reduction program that included an 8-week low-calorie diet and behavioural change support. Disappointingly, no change in AHI was found; however, there were significant reductions in BMI, ODI, arousal index, and ESS. Promising results have been reported for a program including formal cognitive behavioural therapy [48] and one including a 6-month exercise training program [49].

Thus, the outcomes of behavioural therapy for weight loss in OSA are mixed. Furthermore, for these programmes to be available in the clinical setting may not be economically feasible due to the costs involved such as employment of dietician, physiotherapist, and nurse. Moreover, drop-out rate is not insubstantial; in the study by Nerfeldt et al.

Table 1: A summary of studies of behaviourally and pharmacologically induced weight loss in obstructive sleep apnoea.

Paper	Design	*n*	% Male	Group	Intervention	Followup months	ΔBMI	ΔAHI	% With OSA cure
Johansson et al., 2011 [42]	Prospective cohort	63	100	BMI 30–40, AHI ≥ 15	VLCD and weight maintenance programme	12	35 → 31	36 → 19	10
Nerfeldt et al., 2010 [47]	Prospective cohort	33	73%	BMI ≥ 30, AHI ≥ 10 and/or ODI ≥ 6, OSAS symptoms	LCD and behavioural change support	24	40 → 35	43 → 28	?
Johansson et al., 2009 [41]	Randomised, controlled, and parallel group	63	100	BMI 30–40, AHI ≥ 15	VLCD	2	34 → 29 v 35 → 35	37 → 12 v 37 → 35	17 v 0
Tuomilehto et al., 2009 [46]	Randomised, controlled, and parallel group	72	74	BMI 28–40 kg/m^2, AHI 5–15 events/hr	VLCD, supervised lifestyle counselling	12	33 → ? v 31 → ?	10 → 6 v 9 → 10	63% v 35%
Barnes et al., 2009 [45]	Cohort	12	25	BMI > 30 kg/m^2, AHI 10–50 events/hr	VLCD and exercise programme	12	36 → 30	25 → 18	0
Foster et al., 2009 [94]	Randomised, controlled, and parallel group	264	41	BMI ≥ 25 kg/m^2, AHI ≥ 5 events/hr, type 2 diabetes	Intensive lifestyle intervention (diet/exercise)	12	37 → ? v 37 → ?	23 → 18 v 24 → 28	14 v 4
Kemppainen et al., 2008 [44]	Randomised, controlled, and parallel group	52	79	BMI 28–40 kg/m^2, AHI 5–15 events/hr	VLCD, supervised lifestyle counselling	3	33 → ? v 32 → ?	11 → 8 v 9 → 8	?
Kajaste et al., 2004 [48]	Cohort	31	100	BMI > 35 kg/m^2, ODI > 10 events/hr	VLCD, CBT weight reduction program	24	44 → 40	51 → 32 (ODI)	?
Kansanen et al., 1998 [40]	Prospective, cohort	15	93	Overweight with OSA	VLCD	3	38 → 35	31 → 19 (ODI)	20
Suratt et al., 1992 [39]	Cohort	8	62	Obese with OSA	VLCD	?	54 → 46	90 → 62	?
Ferland et al., 2009 [56]	Nonrandomised, parallel group	40	88	BMI ≥ 30 kg/m^2, OSAS	Sibutramine, diet and exercise v CPAP	12	37 → 35 v 36 → 36	40 → 37 v 44 → 4	?
Phillips et al., 2009 [55]	Cohort	93	100	BMI 30–38 kg/m^2, RDI ≥ 15 events/hr	Sibutramine, diet and exercise	6	34 → 32	46 → 30 (RDI)	?
Yee et al., 2007 [54]	Cohort	87	100	BMI 30–38 kg/m^2, RDI ≥ 15 events/hr	Sibutramine, diet and exercise	6	34 → 32	46 → 30 (RDI)	5
Martinez and Basile, 2005 [53]	Randomised, double-blind, and controlled group	19	100	BMI 25–35 kg/m^2, AHI ≥ 10 events/hr	Sibutramine v placebo	1	?	28 → 27 v 28 → 28	?

Abbreviations: ΔAHI: apnoea hypopnoea index before and after intervention, ΔBMI: body mass index before and after intervention, CBT: cognitive behavioural therapy, CPAP: continuous positive airway pressure, *n* number, ODI: oxygen desaturation index, OSA: obstructive sleep apnoea, OSAS: obstructive sleep apnoea syndrome, RDI: respiratory disturbance index, (V)LCD: (very) low calorie diet.

30% of patients did not complete the two-year program [47]. Maintenance of the weight loss achieved is variable particularly if long-term followup is not provided [50]. For lifestyle changes such as integration of regular exercise into the routine to be sustained is heavily dependent on individual motivation [51].

4.2. Pharmacological Methods (See Table 1). Sibutramine is a serotonin and noradrenaline reuptake inhibitor that promotes weight loss by enhancing satiety and increasing energy expenditure through thermogenesis [52]. A randomised, placebo controlled trial of sibutramine, given to overweight males with OSAHS, found no change in AHI or weight over one month [53]. More recently, the results of a cohort study, in which obese males with OSAS were enrolled into a 6-month sibutramine-assisted weight loss program incorporating a dietary prescription and advice on exercise, have been reported [54, 55]. Significant improvements were seen in weight (-8.3 ± 4.7 kg), RDI (-16.3 ± 19.4 events/hr), and ESS (-4.5 ± 4.6), and 4/87 (5%) were "cured" with RDI < 5 events/hr by 6 months [54]. Significant, though modest, improvements in insulin sensitivity and lipid profile were also reported [55]. In a further study, sibutramine-assisted weight loss was compared with conventional CPAP treatment and lifestyle recommendations over one year in a nonrandomised, parallel study in obese patients with OSAS [56]. Weight decreased by 5 kg in the sibutramine treated group while remaining unchanged in the CPAP group. Sibutramine treatment was associated with no change in AHI or in ESS but an improvement in mean nocturnal oxygen saturations and also an improvement in sleep architecture. CPAP on the other hand significantly improved both AHI and ESS, led to greater improvement in sleep architecture, and led to improvements in other sleep and respiratory variables. Overall, sibutramine-assisted weight loss was concluded to be inferior to CPAP. More recently, in January 2010, the marketing authorisation for sibutramine has been suspended by the Medicines and Healthcare products Regulatory Agency due to concerns that cardiovascular risks outweighed benefits and that there may be an increased risk of nonfatal myocardial infarction and stroke [57, 58]. Orlistat is another therapeutic option for management of weight loss and this agent inhibits gastrointestinal lipase thus reducing fat absorption [59]. To the authors' knowledge no trial has evaluated the use of orlistat in management of obese sleep apnoea patients.

4.3. Surgical Methods (See Table 2). The National Institute for Health and Clinical Excellence Guidelines state that bariatric surgery should be recommended as a treatment option for adults with BMI of 40 kg/m^2 or more, or between 35 and 39.9 kg/m^2 in the presence of significant comorbidities such as type 2 diabetes or hypertension. In addition, all nonsurgical measures should have been employed with failure to achieve or maintain adequate weight loss over at least 6 months. Further, individuals should be managed within a specialist obesity service, be both fit for anaesthesia and surgery, and willing to commit to long-term followup [57]. There are several surgical procedures that can be performed including laparoscopic adjustable gastric banding (LAGB), Roux-en-Y gastric bypass (RYGB), laparoscopic sleeve gastrectomy (LSG), and laparoscopic biliopancreatic diversion. Of these, the LAGB and RYGB are more commonly available in the UK [60]. The mechanisms by which bariatric procedures lead to weight reduction incorporate gastric restriction and/or malabsorption and can be summarised as the BRAVE effects: bile flow alteration, restriction of gastric size, anatomical gut rearrangement and altered flow of nutrients, vagal manipulation, and enteric gut hormone modulation [61]. The LAGB procedure entails placement of a band around the proximal stomach forming a pouch with a narrow outlet just distal to the gastrooesophageal junction. The degree of restriction can be altered by inflating or deflating a balloon within the band with saline via a subcutaneous port [62, 63]. In RYGB surgery, the proximal stomach is transected forming a small gastric pouch which is joined to the roux limb of jejunum with the result that the more distal stomach, the complete duodenum, and proximal jejunum are bypassed [62].

Since the 1980's, the results of several studies of the effects of surgical weight loss in patients with OSA have been published (see Table 2). To the authors' knowledge, with the exception of one [64], these have all been cohort studies either of obese individuals [65–68], specifically those with OSA [63, 69–80] or, in one case, those with respiratory comorbidity (chronic obstructive pulmonary disease, OSA, or obesity hypoventilation syndrome) requiring noninvasive positive pressure ventilation [81]. In all studies, where measured, a significant improvement in AHI occurred after surgery, in addition to the expected reduction in BMI. Furthermore, resolution of OSA occurred in up to 80% [72] however, this was variable; in the study of Lankford et al. [70], "cure" did not occur in any patient. Post-operative evaluation was carried out between 3 [72] and 28 months [71]. Other benefits have also been reported. An improvement in nocturnal oxygenation is seen with reduced oxygen desaturation index [63, 79] and time with saturation less than 90% [79, 81], increase in minimum oxygen saturation [63, 66, 69, 71, 73, 74, 78, 79] and mean oxygen saturation [63, 71, 78, 79]. Daytime hypoxaemia [80, 81] and hypercapnia [81], too, are improved. Sleep efficiency is increased [63, 69, 74, 77] and sleep architecture enhanced with decreases in stages 1 [76] and 2 [76, 77], increases in stages 3 [63, 75–77, 82] and 4 [75–77, 82], reduced REM latency [69, 74, 77], and increased REM sleep [63, 75–77, 82]. CPAP use [69, 73, 75, 78, 81] and CPAP pressure requirements [69–71, 73] are less. Likewise, there is a reduction in daytime sleepiness (ESS) [69, 73–75, 80, 83], snoring [63, 83], witnessed apnoeas [83], and other OSA-related symptoms [83] and improvement in both quality of life and depression scores [75]. One study demonstrates that spirometric measures increase significantly one year after surgery [81], and similar results were reported 6 months after intragastric balloon insertion in another study [80]. Finally, reduction in glucose, HbA1c, triglycerides, and insulin with increase in HDL have been reported with an overall reduction in metabolic syndrome [75].

Table 2: A summary of studies of surgically induced weight loss in obstructive sleep apnoea.

Paper	Design	*n*	% Male	Group	Procedure	Followup months	ΔBMI	ΔAHI	% with OSA cure
Behrens et al., 2011 [65]	Retrospective, cohort	34 (21 OSA)	3	BMI > 30	LSG	10	50.3 → 39.9	?	76
Martí-Valeri et al., 2007 [81]	Cohort	30 (14 OSA)	90	Obese with associated respiratory comorbidity requiring NIPPV	RYGB	12	56 → 32	64 → 17 (RDI)	?
Fritscher et al., 2007 [78]	Cohort	12	75	BMI ≥ 35 with obesity-related comorbidity or ≥40 without and AHI ≥ 15	RYGB	18	56 → 34	46 → 16	25
Haines et al., 2007 [69]	Prospective, cohort	101	?	Obese, RDI > 5, ESS ≥ 6	RYGB	11	56 → 38	51 → 15 (RDI)	?
Kalra et al., 2005 [66]	Retrospective, cohort	34 (19 AHI ≥ 5)	?	Adolescent, BMI ≥ 40, obesity-related comorbidity	RYGB	5	60.8 → 41.6	9.1 → 0.6	?
Lankford et al., 2005 [70]	Retrospective, cohort	15	40	Obese, OSA	RYGB	12	48 → 32	40 → ?	0
Guardiano et al., 2003 [71]	Retrospective, cohort	8	12	Obese, OSA	RYGB	28	49 → 34	55 → 14 (RDI)	50
Peiser et al., 1984 [72]	Cohort	15	93	Morbidly obese with OSA	RYGB	3	?	82 → 15	80
Lettieri et al., 2008 [73]	Retrospective, cohort	24	25	Obese with EDS, AHI ≥ 5	GB	12	51 → 32	48 → 24	4
Rasheid et al., 2003 [74]	Prospective, cohort	11	?	Obese, ESS ≥ 6, RDI > 5	GB	12	62 → 40	56 → 23 (RDI)	?
Rao et al., 2009 [63]	Retrospective, cohort	46	?	BMI ≥ 32.5 with obesity-related comorbidity or ≥37.5 without and AHI ≥ 15	LAGB	13	45 → 30	38 → 13	78
Dixon et al., 2005 [75]	Prospective, cohort	25	68	BMI > 35, AHI > 25	LAGB	18	53 → 37	62 → 13	?
Busetto et al., 2005 [80]	Cohort	17	100	BMI > 50, AHI > 20	IGB	6	56 → 49	59 → 14	59

Table 2: Continued.

Paper	Design	*n*	% Male	Group	Procedure	Followup months	ΔBMI	ΔAHI	% with OSA cure
Grunstein et al., 2007 [64]	Prospective, controlled, nonrandomised	3023	30	Female: BMI ≥ 38, male: BMI ≥ 34	Various	24	42 → 32	?	?
Valencia-Flores et al., 2004 [67]	Prospective, cohort	29	45	Morbidly obese	Various	14	56 → 39	52 → ?	46
Poitou et al., 2006 [79]	Prospective cohort	35	17	BMI > 40, AHI > 10	RYGB, LAGB	12	51 → 40	24 → 10	63
Pillar et al., 1994 [76]	Cohort	14	79	Morbidly obese with OSA	RYGB, VBG	4	45 → 33	40 → 11	43
Charuzi et al., 1992 [77]	Cohort	47	?	Morbidly obese with OSA	RYGB, VBG	10	?	61 → 8	40
Omana et al., 2010 [68]	Retrospective, cohorts	123	24	Obese	LSG (49) v LAGB (74)	15 17	52 → ? 44 → ?	? ?	55 25

Abbreviations: ΔAHI: apnoea hypopnoea index before and after intervention, ΔBMI: body mass index before and after intervention, EDS: excessive daytime somnolence, ESS: epworth sleepiness scale, GB: gastric bypass, IGB: intragastric balloon, LAGB: laparoscopic adjustable gastric banding, LSG: laparoscopic sleeve gastrectomy, *n* number, NIPPV: noninvasive positive pressure ventilation, OSA: obstructive sleep apnoea, RDI: respiratory disturbance index, RYGB: roux-en-Y gastric bypass, VBG: vertical banded.

From these reports, it is tempting to conclude that surgical weight loss is the panacea for OSA at least in the obese population. Caution is required in the interpretation of these studies, however, the main criticisms being that they did not include a control group, and in many cases data collection was retrospectively carried out. A large multicentre prospective controlled study with 2-year followup was carried out in Sweden by Grunstein et al. [64]. For ethical reasons, participants were not randomised and the study was questionnaire based. 1592 obese individuals undergoing various bariatric procedures were compared with 1431 matched controls that were provided with routine obesity management including dietary advice, physical training, low-calorie diets and behaviour modification. The odds ratios for development of new symptoms of apnoea, snoring, and daytime sleepiness were 0.28, 0.18, and 0.66, respectively, for the surgical group compared to the control group. Likewise, persistence of these symptoms was markedly lessened in the surgical group (approximately 20–30%) compared to controls (approximately 50–70%). Thus, surgery was associated with a marked reduction in OSA-related symptoms. Unfortunately no attempt was made to objectively measure sleep disordered breathing in this study at baseline or followup.

In summary, the aforementioned studies report promising results regarding the effects of bariatric surgery on sleep apnoea symptoms and polysomnography at least in the short term up to one to two years. What of the long term are benefits maintained? One study of LAGB surgery for obesity showed progressive loss of weight over the first 2 to 3 years with a plateau in BMI to 6 years [83], similar results being found in another study of 157 obese patients over a 5-year period [84]. This finding is at odds with the results of another study in which significant weight gain was found over a 10-year period following RYGB surgery, the increase being more in the super-obese (BMI $\geq 50\,kg/m^2$) than in the morbidly obese (BMI $< 50\,kg/m^2$) [85]. In a study of 14 obese subjects with OSA, BMI decreased significantly from baseline ($45\,kg/m^2$) to 4.5 months postop ($33\,kg/m^2$) and increased only insignificantly ($35\,kg/m^2$) at 7.5 years. However, while AHI decreased significantly from 40/hr to 11/hr at 4.5 months a twofold increase to 24/hr occurred at 7.5 years, the change in AHI at 7.5 years was independent of change in BMI [76]. Another older study documented substantial weight gain and relapse of OSA in a small subgroup of obese sleep apnoea patients for which data was available at 7 years [77]. Thus, the results are conflicting but overall would suggest that weight loss is not maintained and that OSA may relapse in the years following surgery, perhaps due to factors other than just weight gain.

The morbidity and mortality related to surgical intervention should also be considered in the overall evaluation of the benefits of bariatric surgery. Grunstein et al. reported a perioperative mortality rate of 0.21% and an incidence of other complications (including bleeding, thromboembolism, wound complications, deep infections, pulmonary, and other complications) of 13% [64]. Omana et al. reported no mortalities or major complications and a rate of 15% for minor complications for LABG in 74 subjects [68]. Complications specific to LAGB surgery include band slippage or erosion, pouch enlargement, oesophageal dilatation, and oesophageal or gastric perforation while those for RYGB include staple line disruption and leak, stricture, small bowel obstruction and hernia (both internal and incisional) [86]. A large meta-analysis of mortality after bariatric surgery reported up to 30-day mortality of 0.28% and >30-day to 2-year mortality of 0.35% [87]. Concerns have been raised over the use of risk of bowel distension and subsequent anastomotic leak in association with the use of bilevel positive airway pressure in the immediate postop period after gastric bypass; however, this seems rare complication [88].

5. Mechanisms for the Resolution of OSA after Weight Loss

The mechanisms by which weight loss results in a reduction in severity of OSA or even resolution have been explored in a number of studies. Following weight loss, there is a reduction in nasopharyngeal collapsibility and resistance implying that the calibre of the upper airway increases [39, 89]. In the study of Busetto et al. discussed earlier, acoustic pharyngometry was utilised to measure pharyngeal cross-sectional area [80]. At baseline, pharyngeal cross-sectional areas were significantly reduced in obese individuals with OSAS compared to nonobese controls. Six months after intragastric balloon insertion, weight loss was associated with significant increases in cross sectional area at the oropharyngeal junction both upright and supine and the mean pharyngeal cross-sectional upright. However, mean pharyngeal cross-sectional area and crosssectional area at the glottis level were still significantly lower than for nonobese controls. Pharyngeal and glottic function appears to be improved [90]. The level to which the upper airway critical pressure (i.e., the nasal pressure below which inspiratory airflow ceases) falls following weight loss determines whether there is complete resolution of OSA or not [91]. The improvements seen in pharyngeal function may be related to reductions in mechanical loading particularly due to parapharyngeal fat pads. One study using CT imaging showed that velopharyngeal volume and lateral diameter are increased while facial and abdominal fat volumes decrease along with parapharyngeal fat pad volume [17]. In this study, reduction in upper airway length and in visceral abdominal fat best explained improvement in AHI after weight loss (R^2 0.31, $P = 0.004$), and, interestingly, changes in parapharyngeal fat did not correlate with changes in AHI. An alternative explanation is that reduction in central adiposity and the resulting reduction in production of adipokines that act on the central nervous system may lead to enhanced neuromuscular control of pharyngeal calibre [35]. Weight loss is associated with significant improvement in vital capacity, total lung volume, functional residual capacity, and forced expiratory volume [92], and this increase in lung volumes may result in increased tracheal traction on the pharynx. In the study discussed earlier by Kemppainen et al., no significant differences were found in nasal resistance or nasal volume after successful weight loss indicating that

the improvement in OSA is not related to changes in nasal airflow [44]. Absence of attenuation of OSA after weight loss may be related to presence of concomitant otorhinolaryngoiatric pathology [93].

6. Conclusion

Obesity is a major (and perhaps the leading) risk factor for obstructive sleep apnoea. The prevalence of OSA is increased in the obese patients and vice versa; OSA is related to various anthropometric measures; the severity of OSA increases in association with weight increase. Pathophysiological mechanisms by which obesity can lead to OSA have been identified. It follows that weight loss may lead to an improvement in the severity of OSA and perhaps even it's resolution. This has been borne out in studies evaluating behavioural and surgical approaches to weight loss. Behavioural methods have focussed on dietary intervention, encouragement of exercise, and support in lifestyle change, and randomised studies have been encouraging. The evidence for benefits in association with bariatric surgery stems from cohort studies, many of them retrospective, but nonetheless persuasive. However, surgical intervention is recommended only after nonsurgical measures have failed and is associated with an albeit low mortality rate and also significant morbidity.

Although the studies of both behavioural and surgical interventions aimed at weight loss in the management of OSA have shown promising results, there are some limitations to these studies that should be noted. The majority of studies reviewed were uncontrolled and involved low subject numbers often with a male predominance. There were varying criteria for inclusion in studies with respect to the severity of obesity and both the presence and severity of OSA; the inclusion criteria for some studies included the presence of excessive daytime somnolence or other obesity-related comorbidities while other studies did not. Likewise, different methodologies were utilised for the confirmation of OSA such as polysomnography, limited sleep studies, and respiratory polygraphy, and there was variation in the outcome measures reported such as apnoea hypopnoea index, respiratory disturbance index, oxygen desaturation index, and other measures of nocturnal oxygenation. For these reasons, it is difficult to compare the different studies and to extrapolate to the wider population. The proportion of subjects lost to followup was often significant and this may lead to bias with overestimation of the improvement associated with the intervention as those not benefitting are more likely not to return for reassessment. The time to reevaluation varied from as little as 2 months to over 24 months. The benefits reported in studies with shorter durations may have been influenced by short-term simultaneous behavioural changes such as reduction of alcohol intake or increase in exercise which may not be maintained in the longer time. Alternatively shorter studies may have underestimated the potential for weight loss and attendant improvements in OSA that may be possible with longer behavioural interventions.

For either approach, behavioural or surgical, to be successful, weight loss has to be maintained in the long term to prevent relapse, and "maintenance of weight loss programmes" necessarily incorporating similar features to the behavioural weight loss programmes may not be economically feasible. Furthermore, success of such programmes or of maintenance of weight loss independently is heavily dependent on the motivation of the individual. Further randomised, controlled trials are required to confirm the beneficial effects of bariatric surgery, and those of the behavioural interventions. Studies are necessary to identify those in which behavioural therapy is likely to be effective so that limited resources are efficiently utilised.

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Clinical Study

Clinical Features and Polysomnographic Findings in Greek Male Patients with Obstructive Sleep Apnea Syndrome: Differences Regarding the Age

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Background-Aim. Although sleep disturbance is a common complaint among patients of all ages, research suggests that older adults are particularly vulnerable. The aim of this retrospective study was to elucidate the influence of age on clinical characteristics and polysomnographic findings of obstructive sleep apnea syndrome (OSAS) between elderly and younger male patients in a Greek population. *Methods*. 697 male patients with OSAS were examined from December 2001 to August 2011. All subjects underwent an attended overnight polysomnography (PSG). They were divided into two groups: young and middle-aged (<65 years old) and elderly (≥65 years old). We evaluated the severity of OSAS, based on apnea-hypopnea index (AHI), and the duration of apnea-hypopnea events, the duration of hypoxemia during total sleep time (TST) and during REM and NREM sleep, and the oxygen saturation in REM and in NREM sleep. *Results*. PSG studies showed that elderly group had significant higher duration of apnea-hypopnea events, longer hypoxemia in TST and in NREM sleep, as well as lower oxygen saturation in REM and NREM sleep than the younger group. Otherwise, significant correlation between BMI and neck circumference with AHI was observed in both groups. *Conclusions*. The higher percentages of hypoxemia during sleep and longer duration of apnea-hypopnea events that were observed in the elderly group might be explained by increased propensity for pharyngeal collapse and increased deposition of parapharyngeal fat, which are associated with aging. Another factor that could explain these findings might be a decreased partial arterial pressure of oxygen (PaO_2) due to age-related changes in the respiratory system.

1. Introduction

Obstructive sleep apnea syndrome (OSAS) is a highly prevalent disorder characterized by instability of the upper airway during sleep, which results in markedly reduced (hypopnea) or absent (apnea) airflow at the nose/mouth [1]. Episodes are typically accompanied by oxyhemoglobin desaturation and terminated by brief microarousals that result in sleep fragmentation [2]. Patients usually present with loud habitual snoring, witnessed apnea, and excessive daytime sleepiness [1]. Several physical and psychological changes are known to occur with normal aging. It is well known that there are differences of OSAS regarding the elderly [3]. Aging is associated with several well-described changes in patterns of sleep. Although sleep disturbance is a common complaint among patients of all ages, research suggests that older adults are particularly vulnerable [3]. Studies about the clinical characteristics of OSAS have been done mainly in middle-aged adults and there is little information on the differences in polysomnographic findings of OSAS between elderly and younger adults. A high prevalence of OSAS of 30.5% [4] up to 81% [3] was reported in the elderly (≥65 years old) when OSAS was defined as an apnea-hypopnea index (AHI) of more than 5 events per hour. Therefore, aging could be considered as a risk factor for the development of OSAS [5]. In addition, in previous studies, body mass index (BMI)—one of the most typical parameters which correlates significantly with AHI in young patients with

OSAS—was not associated with OSAS in elderly patients [6]. The differences in clinical characteristics of OSAS between young or middle-aged and elderly patients are not fully explained.

2. Methods

2.1. Subjects. We enrolled 924 Greek male patients who were referred to our sleep laboratory, from December 2001 to August 2011. All subjects underwent an attended overnight polysomnography (PSG). 697 of them were found to have OSAS (AHI ≥ 5 events per hour of sleep), while COPD patients and patients with heart failure excluded. Patients were divided into two groups: young and middle-aged (<65 years old, $n = 568$) and elderly (≥65 years old, $n = 129$). The severity of OSAS was determined from the apnea-hypopnea index (AHI) for TST [2]. The patients completed a full report with their daytime and nocturnal symptoms. The principal daytime manifestation was excessive sleepiness but other symptoms, such as unrefreshing sleep, poor concentration, fatigue, and headache, were also reported. The most common nocturnal symptoms were snoring, choking, or gasping during sleep and recurrent awakening. In order to measure the subjective daytime sleepiness, all patients completed the Epworth Sleepiness Scale (ESS) [7]. The diagnosis of OSAS was based on the combination of these symptoms and the results of PSG [2].

2.2. Polysomnography (PSG). All subjects underwent an attended overnight polysomnography (Alice 4, Sleepware; Phillips-Respironics, USA, and Somnoscreen-Domino 2.3.0; Somnomedics, Germany). Briefly, sleep state was recorded with two channels of EEG (C4/A1, C3/A2), two channels of electro-oculogram, and one-channel submental electromyogram. Breathing was assessed by monitoring chest wall and abdominal movements using strain gauges and nasal and oral flows using thermistors (until 2005) and nasal pressure transducers (after 2005). Arterial oxygen saturation was measured continuously by pulse oximetry, using a finger probe. Body position was assessed continuously with a body position sensor. Leg movements were monitored with two channels of electromyogram, and an ECG was recorded continuously. Sleep stages and respiratory events were scored manually according to the old "Chicago criteria" of American Academy of Sleep Medicine (AASM) until 2007 [2] and with the new criteria of AASM after 2007 [8]. Apnea was defined as reduction in airflow greater than ≥90% of baseline, which was lasting ≥10 sec and affecting at least the 90% of the event. Obstructive apnea was estimated when respiratory effort was recorded throughout the event, central apnea was estimated when respiratory effort was absent, and mixed apnea was estimated when respiratory effort was absent at the beginning of the event followed by increasing respiratory effort during the second half. Hypopnea was defined as reduction in airflow by ≥30% from baseline, which was lasting ≥10 sec, affecting at least 90% of the event, followed by reduction in saturation at least ≥4% from baseline $SatO_2$% prior to the event. Alternatively, hypopnea was defined as a reduction in airflow ≥50% from baseline, which was lasting ≥10 sec, affecting at least 90% of the event followed by reduction in saturation ≥3% from baseline $SatO_2$% prior to the event or appearance of an arousal [9]. Apnea-Hypopnea Index (AHI) was defined as the total number of episodes of apneas and hypopneas per hour of real sleep [8].

In addition, we measured AHI in REM and NREM sleep, mean duration of apnea and hypopnea events, duration of hypoxemia during TST and during REM and NREM sleep, and oxygen saturation in REM and in NREM sleep.

2.3. Statistical Analysis. SPSS version 14.0 for Windows (SPSS Inc., Chicago, Ill, USA) was used for the statistical analysis. The results are presented as means ± SD. The Kolmogorov-Smirnov test was used to confirm normality. Differences in clinical variables among the three groups were assessed by analysis of variance (ANOVA) followed by Tukey's post-hoc test or the Kruskal-Wallis test for continuous variables and the χ^2 test for categorical variables. Spearman's correlation coefficients were calculated to determine the relationships between AHI and obesity-related variables, and stepwise multiple regression analysis was used to identify factors that contributed to the severity of OSAS. A value of $P < 0.05$ was considered as the threshold for statistical significance.

3. Results

There were no significant differences in baseline characteristics such as BMI and neck circumference among the two groups (Table 1).

Also, there were no differences between two groups in relation with subjective characteristics and symptoms as daytime sleepiness, fatigue, headache, and so forth. Differences were observed in cardiac arrhythmias as they were the commonest in elderly patients, as it was expected (Table 1).

Findings obtained from PSG studies showed that there was no significant difference in AHI between the two groups (Table 2). Other findings revealed that the elderly group had significant higher mean duration of apnea-hypopnea events ($P < 0.001$) and longer duration of hypoxemia in TST ($P = 0.004$) and in NREM sleep ($P = 0.021$) than the younger group. Also they had significant lower oxygen saturation in REM ($P = 0.013$) and NREM sleep ($P = 0.027$) than younger patients (Table 2).

In both groups, there were significant correlations between obesity-related anthropometric variables and the severity of OSAS (value of AHI). So there was significant correlation between BMI with AHI in elderly group ($r = 0.157$, $P = 0.026$) and in the younger group ($r = 0.326$, $P < 0.001$, Table 3). Also, there were significant correlations between neck circumference and AHI in the above groups ($r = 0.245$, $P < 0.001$ and $r = 0.380$, $P < 0.001$, resp., Table 3).

In the stepwise multiple regression analysis of obesity-related variables, BMI and neck circumference were independently related with AHI in the elderly group ($r = 0.043$, $P = 0.035$ and $r = 0.227$, $P = 0.001$, resp.), as well as in

Table 1: Demographic and clinical characteristics of Greek male patients with OSAS.

	Young and middle age ($n = 568$, m ± SD)	Elderly ($n = 129$, m ± SD)	P value
AGE	47.62 ± 5.34	70.54 ± 4.22	<0.001^{+}
BMI	33.31 ± 6.42	32.18 ± 4.78	NS
Neck circumference	44.93 ± 4.06	44.72 ± 3.41	NS
Daytime sleepiness (ESS)*	11.21 ± 2.81	10.89 ± 2.62	NS
Cardiac arrhythmias**	7%	11%	<0.001^{+}
Fatigue**	65%	60%	NS
Headache**	14%	14%	NS
Inability to concentrate**	2%	1.5%	NS

AGE: in years. BMI: body mass index (Kgr/m^2), neck circumference, measured in cm. $^{+}P < 0.05$, which was considered significant, *ESS: Epworth Sleepiness Scale (expressed as mean ± SD), **data are presented as %, NS: not significant.

Table 2: Polysomnographic findings in Greek male patients with OSAS.

	Young and middle age ($n = 568$, m ± SD)	Elderly ($n = 129$, m ± SD)	P value
AHI (events per hour)	35.14 ± 13.26	33.14 ± 12.09	NS
AHI-REM (events per hour)	30.72 ± 9.32	28.16 ± 7.89	NS
AHI-NREM (events per hour)	33.82 ± 12.14	31.73 ± 11.09	NS
Mean apnea/hypopnea duration (sec)	20.12 ± 6.12	22.37 ± 6.09	<0.001*
Hypoxemia duration in TST (min)	51.1 ± 19.12	73.50 ± 19.07	0.004*
Hypoxemia duration in REM sleep (min)	8.88 ± 2.46	7.98 ± 2.68	NS
Hypoxemia duration in NREM sleep (min)	28.08 ± 5.43	42.43 ± 6.98	0.021*
$SatO_2$-REM	91.89 ± 7.12	89.91 ± 7.02	0.013*
$SatO_2$-NREM	92.64 ± 5.21	90.32 ± 5.11	0.027*

AHI: apnea/hypopnea index, AHI-REM: apnea/hypopnea index in REM sleep, AHI-NREM: apnea/hypopnea index in NREM sleep, TST: total sleep time, Hypoxemia: time spent with $SatO_2$ <90%, in minutes. $SatO_2$-REM: oxyhemoglobin saturation in REM sleep. $SatO_2$-NREM: oxyhemoglobin saturation in NREM sleep, NS: Not significant. $^{*}P < 0.05$, which was considered significant.

Table 3: Correlation coefficients and results of stepwise multiple regression analysis between obesity-related variables and AHI.

	Young and middle age ($n = 568$)		Elderly ($n = 129$)	
	Correlation coefficient	Regression coefficient	Correlation coefficient	Regression coefficient
BMI	0.326 ($P < 0.001$*)	0.012 ($P = 0.008$*)	0.157 ($P = 0.026$*)	0.043 ($P = 0.035$*)
Neck circumference	0.380 ($P < 0.001$*)	0.368 ($P < 0.001$*)	0.245 ($P < 0.001$*)	0.227 ($P = 0.001$*)

BMI: body mass index. $^{*}P < 0.05$, which was considered significant.

the younger group ($r = 0.012$, $P = 0.008$ and $r = 0.368$, $P < 0.001$, resp., Table 3).

4. Discussion

In the present retrospective study, patients with OSAS were evaluated for about a decade ago. There were no significant differences in BMI and AHI between the two age groups, but neck circumference and BMI were the most significant determinants of AHI in all patients based on the stepwise multiple regression analysis.

BMI has been one of the most typical parameters in evaluating the relationship between OSAS and obesity [1, 10]. In this study, BMI was significantly related with AHI in both groups. A previous study reported that BMI and neck circumference were not associated with OSAS in elderly patients [6], but that study might be limited by small sample size. The higher prevalence of OSAS in elderly adults could be explained by other factors besides, obesity: decreases in ventilatory control, muscular endurance, and thyroid function, and increased upper-airway collapsibility and sleep fragmentation potentially contribute to the development of OSAS in the elderly [11]. In addition, only a few elderly patients ($n = 11$) with normal BMI (under 25 Kgr/m^2) had OSAS. Therefore, obesity still plays an important role in patients with OSAS.

It is generally accepted that obesity characteristics like neck circumference is a major risk factor of OSAS [12]. In our study, neck circumference is the most independently related factor with AHI in all patients. It is also accepted that neck's circumference increasing is a factor for an increased parapharyngeal fat deposition [13, 14]. It is well known that aging increases the propensity for pharyngeal collapse [11, 13], as well as the deposition of parapharyngeal fat in the elderly [13], but the size of this parapharyngeal fat pad increases independently of body mass index [11, 13]. This age-related upper-airway collapsibility could also explain the increased prevalence of OSAS in elderly patients [11, 14].

Neck circumference in combination with a decreased reflex sensitivity in upper airways which increase with age [11, 15] may cause severe OSAS in the elderly in the present study.

Some studies have suggested that cardiac arrhythmias are common problems in OSAS patients, although the true prevalence and clinical relevance of cardiac arrhythmias remain to be determined [16]. There are many different types of arrhythmias linked to OSAS, such as atrial and ventricular premature extrasystoles, nonsustained ventricular tachycardia, sinus arrest, and second-degree atrioventricular conduction block, which are reported 30%–50% in patients with OSAS and increased with the number of apneic episodes and severity of the associated hypoxemia [17]. In our study, 20% of elderly patients suffer from cardiac arrhythmias.

In the present study, apnea/hypopnea duration and nocturnal hypoxemia duration with oxyhemoglobin saturation under 90% were longer in the elderly group compared to the other group. This nocturnal hypoxemia is more severe in NREM sleep, stage at which elderly patients sleep more [18]. With age, the percentage time of rapid eye movement (REM) sleep decreases, while the percentage of light sleep (stage 1 and stage 2 of NREM sleep) increases [18]. However, in the current theoretical framework, such changes in sleep architecture are considered nonpathological and might reflect age-related neural degeneration [19]. In addition, the adaptive potentialities of external respiration were found to be limited. Ware et al. [20] also reported that the duration of apnea events was longer in their elderly compared to middle-aged OSAS patients, and breakdown in sensing apnea events and reduction in the stimulus triggering arousals were speculated to affect the long duration of apnea events and therefore of hypoxemia duration in elderly patients. In addition, increased pharyngeal collapsibility with aging might also explain the longer duration of hypoxemia in our study as previously reported [13, 21, 22]. Also, aging is associated with a decrease in partial arterial pressure of oxygen (PaO_2) due to age-related changes in the respiratory system [23]. Therefore, it is obvious that the degeneration of respiratory center and oxygen receptors due to age results in longer hypoxemia during sleep.

This retrospective study was performed based on the data from a real clinical setting with a relatively large sample size. Therefore, the differences in the clinical characteristics and in polysomnographic findings of OSAS between elderly and young or middle-aged patients could have clinical relevance. However, the patients were referred to the clinic for evaluation of possible sleep apnea. Thus, the results may have been influenced by referral bias and survivorship effects.

In conclusion, BMI and neck circumference still influence the severity of OSAS in elderly patients. It seems that aging increases the propensity for pharyngeal collapse, as well as the deposition of parapharyngeal fat in the elderly. Also, it is associated with a decrease in partial arterial pressure of oxygen (PaO_2) due to age-related changes in the respiratory system (with degeneration of respiratory center and oxygen receptors), which results in longer hypoxemia during sleep. These structural and functional changes could explain higher percentages of hypoxemia (particularly in NREM sleep) and longer duration of apnea-hypopnea events were observed in the elderly group. Therefore, further studies are needed to determinate the causes of all these findings.

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Review Article

Pathogenesis of Cognitive Dysfunction in Patients with Obstructive Sleep Apnea: A Hypothesis with Emphasis on the Nucleus Tractus Solitarius

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OSA is characterized by the quintessential triad of intermittent apnea, hypoxia, and hypoxemia due to pharyngeal collapse. This paper highlights the upstream mechanisms that may trigger cognitive decline in OSA. Three interrelated steps underpin cognitive dysfunction in OSA patients. First, several risk factors upregulate peripheral inflammation; these crucial factors promote neuroinflammation, cerebrovascular endothelial dysfunction, and oxidative stress in OSA. Secondly, the neuroinflammation exerts negative impact globally on the CNS, and thirdly, important foci in the neocortex and brainstem are rendered inflamed and dysfunctional. A strong link is known to exist between neuroinflammation and neurodegeneration. A unique perspective delineated here underscores the importance of dysfunctional brainstem nuclei in etiopathogenesis of cognitive decline in OSA patients. Nucleus tractus solitarius (NTS) is the central integration hub for afferents from upper airway (somatosensory/gustatory), respiratory, gastrointestinal, cardiovascular (baroreceptor and chemoreceptor) and other systems. The NTS has an essential role in sympathetic and parasympathetic systems also; it projects to most key brain regions and modulates numerous physiological functions. Inflamed and dysfunctional NTS and other key brainstem nuclei may play a pivotal role in triggering memory and cognitive dysfunction in OSA. Attenuation of upstream factors and amelioration of the NTS dysfunction remain important challenges.

1. Introduction

Obstructive sleep apnea syndrome (OSA) is characterized by the upper airway instability during sleep, reduction or elimination of airflow (hence oxygen desaturation), periodic arousals (hence sleep disruption), and daytime hypersomnolence. About 40% of adults are habitual snorers. The prevalence of OSA has been estimated to be 24% in men and 9% in women [1]. The male : female ratio of the OSA patients has been reported to range from 4 to 1 to 4 to 2 [2]. OSA therefore is a major intrinsic sleep disorder. The alarming degree to which OSA is clinically diagnosed in middle-aged men and women makes it a significant public health problem, and increasing evidence indicates that untreated OSA can lead to several comorbid disorders. OSA is a risk factor for cardiovascular disorders including hypertension, congestive heart failure (CHF), myocardial ischemia, arrhythmias and infarction, and cerebrovascular conditions including stroke [3]. The normal physiologic interactions are disrupted by OSA, and the cardiovascular and cerebrovascular systems are therefore impacted [4, 5]. Overnight polysomnography (PSG) is the gold standard for the evaluation of sleep-related breathing disorders. Apnea-hypopnea index (AHI) is the number of apneic and hypopneic events per hour of sleep. These nocturnal respiratory disturbances result in brief arousals from sleep (i.e., sleep fragmentation) that considerably disturb sleep architecture and may lead to a significant deprivation of rapid eye movement (REM) sleep and stages 3 and 4 of nonrapid eye movement (NREM) sleep. Sleep disturbances and hypoxemia contribute to excessive daytime sleepiness—a common symptom of the syndrome. Approximately 1 in 5

adults possess an AHI of 5–15, that is, mild OSA, and 1 in 15 adults may have moderate OSA, that is, 15–30 AHI [3]. A retrospective study of a cohort of 1,010 patients (844 males, 166 females; similar BMI) found that the AHI in NREM sleep was higher in men than in women (42.9 ± 28.9 versus 32.6 ± 28.7); however, in REM sleep, AHI was similar in men and women (36.0 versus 34.9) [6].

Nocturnal hypoxia in OSA is a major pathological factor associated with cardiorespiratory diseases [3, 7]. In normal physiologic sleep, distinct sleep stage-related changes occur in cardiovascular regulation. There is a progressive decrease in sympathetic activity, blood pressure (BP), stroke volume, heart rate, cardiac output, and systemic vascular resistance, during deeper NREM sleep stages [4]. However, REM sleep is characterized by increased sympathetic drive; BP and heart rate on average are similar to levels noted during wakefulness [4]. Repetitive apneic episodes disrupt the normal physiologic function and trigger sympathetic activation, vascular endothelial dysfunction, increased oxidative stress, inflammation, increased platelet aggregability, and metabolic dysregulation. During intermittent apneic episodes, hypoxemia and CO_2 retention activate chemoreflexes and there is vasoconstriction [5]. The above contributory factors impact on the neural and circulatory responses. At apnea termination, there is resumption of breathing, increased cardiac output, and the inhibition of sympathetic vasoconstriction [5].

Apart from obesity, another problem having enormous impact on society is sleep-disordered breathing—notably OSA. Our knowledge of the upstream factors responsible for the pathogenesis and underlying etiology of memory decline in OSA is still unclear. Animal experiments have shown that intermittent hypoxia for just three days in rats produced memory impairments [8]. Nocturnal chronic intermittent apnea and hypoxemia upregulate humoral, metabolic (including thrombotic), neural, and proinflammatory mechanisms in OSA patients. All of these are, however, known to be associated with the vascular pathophysiology. There is copious evidence to suggest that cerebrovascular pathology/neuroinflammation in patients with OSA may conceivably contribute to the initiation and progression of cognitive dysfunction; furthermore, AD neuropathogenesis may be facilitated by hypoxia. The emphasis, therefore, in the current paper is on linking OSA, neuroinflammation, oxidative stress (generation of reactive oxygen species, ROS), coagulation, metabolic disturbances, and dysfunctional brainstem nuclei such as nucleus tractus solitarius (NTS) and hypoglossal in triggers of cognitive dysfunction. The delineation of the above association may lead to a better understanding of the pathogenetic factors that underpin cognitive decline; this obviously has important therapeutic implications [9, 10].

2. Synergistic Pathological Stigmata in OSA

2.1. OSA and Metabolic Dysfunction. Models of intermittent hypoxia have significantly improved our understanding of the metabolic impact in OSA. Intermittent hypxia in mice is associated with metabolic dysfunctions, including dyslipidemia, insulin resistance, and pancreatic endocrine dysfunction, similar to those observed in human OSA [11]. OSA is a well-known risk factor for metabolic perturbations and susceptibility to cardiovascular risk and weight gain [3, 12]. Higher leptin (from adipocytes) levels reflect resistance to the normal metabolic effects (appetite suppression and satiety) of this hormone in OSA patients and obese persons [12]. Leptin may predispose to increased cardiovascular risk including platelet aggregation also [13]. Independent of body weight, OSA patients are known to possess higher levels of fasting blood glucose, insulin, and glycosylated hemoglobin [14]. The severity of OSA correlates with the degree of insulin resistance [15]. Although CPAP may reduce leptin levels and decrease visceral fat accumulation [16], glucose tolerance is not improved invariably. This aspect is worth noting since impaired glucose tolerance in OSA patients may be linked to sympathetic activation, leptin resistance, and sleep deprivation [17–19].

2.2. OSA and Coagulation. The relatively higher level of the primary fibrin degradation product—PAI-1—and lower level of the primary fibrin degradation product—D-dimer—across the 24h period in OSA patients reflects evidence for a prothrombotic state in OSA [20]. A decreased fibrinolytic capacity and elevated nocturnal levels of catecholamines in OSA may enhance platelet aggregability. OSA may be causally related to increase in clotting activity [21] owing to the documented increases in fibrinogen [22], blood viscosity, and hematocrit [23]. CPAP therapy, however, may reduce platelet aggregability in conjunction with downregulation of catecholamine levels [24] and factor VII clotting activity [25].

2.3. OSA and Oxidative Stress. There is persuasive evidence from both animal and human studies for an association between hypoxia and upregulation of oxidative damage [2, 3, 21, 26, 27]. ROS are generated during intermittent hypoxia and reperfusion during repetitive episodes of nocturnal apnea. In OSA, repeated intermittent arterial oxygen desaturation and reoxygenation and ischemia-reperfusion injury to the vascular wall trigger ROS generation [28].

2.4. Inflammation. Hypoxia is implicated in the production of inflammation [21, 29] and hence increased levels of inflammatory cytokines, for example, IL-6, TNF-α, and of C-reactive protein (CRP) [21, 30]. CRP may play an important role in inhibiting nitric oxide synthase [31], enhancing cell adhesion molecule expression [32], thereby contributing to cerebrovascular disease. Several sources of proinflammatory cytokines and neurotoxicity may occur in OSA patients. These may include (1) obesity [33], (2) infection [34], (3) psychosocial stress [35–37], (4) alcohol abuse [38], and (5) aging itself (see below). Inflammation decreases the efficiency of the capillary system and oxygen supply to the brain, thus reducing metabolic function and oxygen intake in neurons. The above risk factors can exert synergistic and additive actions and increase systemic and brain cytokine production in neuroinflammation.

2.4.1. Aging-Altered Immune Function in Aging/OSA. Aging is characterized by alterations in several functions, including an altered immune function and stress response [39]. There is accumulation of DNA damage due to various factors [40], and indeed there is substantial evidence for elevated production of inflammatory cytokines and oxidative stress in aging [41]. Recurring systemic inflammation may occur due to heterogeneous risk factors—including aging-related diseases, smoking, trauma, infection, psychosocial stress, and indeed sleep disordered breathing. The spatiotemporal interplay of acute and chronic bouts of the above risk factors may be critical in the upregulation/transactivation of inflammatory gene expression at different stages of aging, malnutrition, and pathological states. The peripheral inflammatory insult acts as stimulus that produces in tandem the central phase, namely, the "neuroinflammation," which is characterized by increases in proinflammatory cytokines in the neocortex and brainstem [42]. The proinflammatory state has an impact on the microglia and switches them to a primed phenotype to synthesize proinflammatory cytokines [43–45]. Consequently, neuroinflammation and the glia-related proinflammatory cascades continue as slow, of low level, progressive, nevertheless of relentless pathology that brings about gradual neuronal degeneration.

Elderly subjects possess poor physiological reserve and stress tolerance; ongoing cascades of inflammatory response would perpetuate various pathologies including vascular endothelial cell damage, vascular permeabilization, hypotension, and indeed myocardial depression [7]. LPS-induced expression of IL-1β, ICAM-1, and IL-6 genes is significantly prolonged and augmented in the aged mice compared with young mice [46]. Several stresses, namely, ischemia due to endotoxin and/or hypoxia may be inducers of gene activation for the expression of the IL-6, ICAM-1, and other cytokines [47, 48]. The synthesis of proinflammatory cytokines exceeds the anti-inflammatory mediators such as IL-10; there is evidence that in the ageing brain anti-inflammatory mediators such as IL-10 are decreased [49]. The inflammatory pathology may be unstoppable or irreversible—unless the peripheral inflammatory insults are stopped and the central neuroinflammation ameliorated [50].

Studies on the human endothelial cell (EC) cytotoxicity have shown that, following stimulation of ECs with TNF-α, the EC toxicity increases greatly [51]. Importantly, age-related oxidative stress itself is sufficient to promote vascular inflammation even in the absence of other well known risk factors such as hypertension or metabolic diseases [52]. Recent experimental data suggest that ROS, innate immunity, the local TNF-α-converting enzyme (TACE), and the renin-angiotensin system may underlie NF-κB induction and endothelial activation in aged vasculature; thus, multiple proinflammatory pathways may converge on NF-κB to enhance transcriptional activity of NF-κB during aging [52]. Peripheral inflammation can affect brainstem regions via the circumventricular organs, vagal afferents, and the brain endothelium [53]. Indeed LPS can directly activate the brain endothelium [54], and/or systemic administration of proinflammatory cytokines can cause inflammatory changes in the CNS [53, 55]. A large number of studies have shown neurodegenerative changes in the brains of older adults. Even high-functioning older individuals possess some cognitive complaints (similar to pre-MCI CDR = 0.5) and gray matter atrophy [56–59]. It is posited that most aged persons in fact may harbor circulating peripheral inflammatory cytokines and some neuroinflammation in the neocortex and brainstem nuclei including the NTS, nucleus ambiguous, and DMNV; these nuclei have been documented to undergo aging-related gray matter loss [60]. Consequently, those suffering from long-term snoring/OSA and neuroinflammation could conceivably manifest cognitive deterioration.

2.4.2. OSA/Snoring and Inflammation. Snoring and sleep apnea resulting from incomplete obstruction of the UA may exist in up to 40% of the general population. Nonapneic snorers are known to possess narrower UA. Major independent risk factors for development of habitual snoring are male gender, age between 40 and 64 years, obesity, use of alcohol, sleep medications, and cigarette smoking [61]. The mechanism of snoring is vibration of anatomical structures in the pharyngeal airway, causing high-frequency oscillations of the soft palate, pharyngeal walls, epiglottis, and the tongue. The snoring vibrations have been shown to cause pathologic lesions of the UA mucosa, pharyngeal muscles, and their innervating nerves [62]. The UA mucosa in snorers is edematous, inflamed, and hyperplastic. The levels of proinflammatory cytokines TNF-α and IL-6 are elevated in the uvula of nonapneic snorers, although they are much higher in apneic patients [63]. Snoring is associated with cytokine release from blood cells and promotion of inflammation [64]. PCR measurement of mRNA showed that vibration induced a significant expression of proinflammatory cytokines [65]. In a cell model of snoring-induced airway inflammation, mechanical vibration simulating snoring triggered an inflammatory cascade in human bronchial epithelial cells, reflected by the increase in IL-8 release mediated by MAPK pathways [66]. Finally, BMI, alcohol consumption, and cigarette smoking have been repeatedly confirmed to be positively associated with habitual snoring; these are well known to provoke inflammation in both men and women [67]. A recent detailed study found higher CRP, IL-6, and lysozyme in subjects with AHI $\geq$15 compared with low AHI controls. In multiple linear regressions adjusted for age, waist circumference, and smoking, independent correlation was shown between IL-6 and TNF-α and intermittent hypoxia [68].

Recently, pharyngeal lavage (PHAL) was utilized as a new tool to evaluate pharyngeal mucosal inflammation in OSA patients with and without snoring. PHAL showed lymphocytic inflammation of the pharynx in OSA patients, with neutrophil predominance. Snoring OSA patients had significantly increased numbers of lymphocytes (3.2% compared to nonsnoring OSA and controls group (0.5% and 0.6%, resp.). The cellular infiltration was in accordance with severity; patients with moderate to severe OSA had significantly higher numbers of lymphocytes compared to patients with mild OSA [69].

2.4.3. OSA/Snoring: Cigarette-Smoking-Induced Inflammation. Cigarette smoke produces UA inflammation and edema and is a major contributor to habitual snoring. Habitual snoring was reported in 19.8% of even passive smokers (independent of obesity and sex). A strong link between passive smoking and habitual snoring has been documented in children and adults [70]. Worth noting is that the risk for snoring is four times higher due to smoking than obesity (17% versus 4.3%) [61]. Smoke-induced inflammatory damage affects mucosa including its neural component [71].

2.4.4. Sleep Deprivation and Inflammation. Although sleep deprivation is not a component of stigmata related to OSA, it has been included here since it promotes inflammation. Sleep deprivation may contribute to weight-gain/obesity [72] and promote ROS risk, heart disease, and diabetes [72–74]; these factors potentiate the CNS dysfunction. Even in healthy subjects, sleep deprivation causes a 50% decline in vasodilation reflecting reduced endothelium-dependent NO availability [75]. Proinflammatory cytokines CRP, IL-6, TNF-α, and platelet adhesion/coagulation cascade are elevated due to sleep deprivation [76, 77].

2.4.5. OSA and Vascular Endothelial Dysfunction/Inflammation. Vascular endothelial dysfunction reflects a loss of normal homeostatic functions in the macro- and microvasculature. This dysfunction encompasses reduced vasodilation and enhanced vasoconstriction functions, as well as inflammatory/prothrombotic activity. There is extensive evidence for endothelial dysfunction in OSA [78–80].

Hypoxia, hypercapnia, and pressor surges are potent stimuli for the release of vasoactive substances and for impairment of endothelial function during obstructive episodes. Increased levels of endothelin in response to the hypoxemia may promote sustained vascular changes such as vasoconstriction in OSA [81]. Indeed, OSA patients free of any other overt cardiac or vascular disease have been shown to possess impaired endothelial function [82]. Endothelial dysfunction is prominent in smokers [83] and subjects having hypertension [84], hyperlipidemia [85], and diabetes [85, 86]. OSA patients may possess one or all of the above conditions; therefore, OSA alone or in conjunction with comorbidity may result in overt endothelial dysfunction [87].

Normal endothelium plays an important role in regulating vasomotor tone and maintaining inflammatory and coagulation homeostasis; however, these functions are altered in OSA patients [82, 88]. In OSA, there is increased endothelial cell apoptosis with concomitant impaired endothelial repair capacity [88, 89]. Endothelial dysfunction in conjunction with increased sympathetic activity is implicated in the development of cardiovascular dysfunction of OSA [90, 91]. The reason for endothelial dysfunction in OSA is considered to be due to repetitive hypoxia/reoxygenation during apnea and hypopnea [92]. Despite perfusion during apneas, there is an increase in ROS/inflammation and reduced NO availability in OSA patients [82, 92, 93]. Reduced NO availability in OSA impacts endothelial function and enhances vulnerability for vascular diseases [88]. OSA is characterized by (a) chronic systemic inflammation evidenced, for example, by elevated levels of plasma CRP [30, 94], soluble adhesion molecules [95], and leukocyte superoxide [30, 95], and (b) vascular inflammation noted by upregulation of cyclooxygenase-2 (COX-2) and inducible NOS in endothelial cells [88]. In OSA, aggregation and adhesion of circulating leukocytes to the vascular endothelium may cause blood vessel inflammation [96]. Increased expression of adhesion molecules CD15 and CD11c from monocytes in OSA patients [95] has been implicated in adverse effect on diurnal vascular proinflammatory/antiinflammatory homeostasis [95]. The above has been confirmed by increased production of proinflammatory cytokine IL-4 and a decreased production of an antiinflammatory cytokine IL-10, in patients with moderate to severe OSA [97]. Upregulation of COX-2 in OSA may increase superoxide production resulting in increased oxidative stress, platelet activation, endothelial dysfunction, and vasoconstriction [92, 98–100].

Finally, an increase in lipid peroxidation and generation of ROS are important features in OSA patients [101, 102] and experimental animals [93, 103]. The reoxygenation phase in OSA is said to be the culprit that promotes ROS production and oxidative stress increase. NO is swiftly scavenged by ROS, producing the toxic metabolite—peroxynitrate. Thus, higher nitrotyrosine expression in endothelial cells depicts enhanced endothelial oxidative stress in the OSA patients [88]. The endothelial oxidative damage and ROS production in conjunction with a decrease in NO perpetuate a cyclical pattern of endothelial injury and inflammation [104]. The above-mentioned scenario may upregulate cell death receptors and mitochondria-dependent apoptotic pathways, culminating in endothelial apoptosis [105].

2.5. Pathological Risk Factors and Cognitive Impairment. Even a couple of days of intermittent hypoxia produces detectable spatial memory impairments in rats [14]. There is a large literature showing that each of the cardiovascular risk factors, including abdominal obesity, hypertension, dyslipidemia, and hyperglycemia, is individually associated with cognitive impairment in older adults. In a recent study, up to 20.6% older persons suffered from cognitive impairment, but no dementia (CIND), and hypertension was the significant and independent factor associated with CIND [106]. Cumulative epidemiological evidence emphasizes that vascular and vascular-related factors may be crucial in the development of age-related cognitive decline. It is important to underscore the important pathophysiological link between inflammation (e.g., in metabolic syndrome) and cognitive impairment (of vascular/degenerative origin) [107, 108].

There is enhanced procoagulant and thrombotic activity in OSA patients [21]. Several studies correlate elevated prothrombotic levels with increased risk for cognitive dysfunction. It has been suggested that the association between amyloid β and fibrinogen causes aberrant fibrin hemostasis that could lead to compromised blood flow and increased

inflammation, thereby contributing to cognitive decline [109].

In a recent Baltimore longitudinal study, obesity indices were associated with poorer performance in a variety of cognitive domains, including global screening measures, memory, and verbal fluency tasks [110]. Let alone obese elderly, even obese adolescents may possess disinhibited eating behaviour associated with reductions in orbitofrontal cortex (OFC) volume [111]. Obese subjects have decreased dopaminergic activity and reduction in glucose utilisation in dorsolateral prefrontal (PFC) and orbitofrontal (OFC) areas (areas subserving inhibitory control and salience attribution) [112]. Recent data have also demonstrated reductions in frontal lobe function tests and correlated reductions in OFC volumes in the obese individuals [113].

As emphasized throughout this paper that systemic inflammatory signals communicate with the brain (causing neuroinflammation) and lead to oxidative stress and other changes in its metabolism. Notably, the primed microglia undertakes enhanced synthesis of proinflammatory mediators. There is copious evidence that neuroinflammation contributes to the exacerbation of acute symptoms of chronic progressive neurodegeneration and cognitive impairment [114]. Various circulating inflammatory mediators may directly or indirectly gain access and influence the activity of NTS neurons. Adjacent to NTS is the area postrema (AP); it lacks a blood brain barrier (BBB), and its prominent axons project to the NTS. The NTS has direct and indirect connections to a wide range of neural structures including the PFC and hippocampus, thus possessing the capacity to affect their physiological processes. The gustatory afferents project to the NTS. The prefrontal neural network including the OFC and medial PFC is one of the pivotal regions for bidirectional functional association between the brain and autonomic and immune activities [115, 116]. A dysfunctional and inflamed NTS (see further discussion of this point in Section 3) would have an adverse impact and perturb the physiological functions of the PFC as well as other key brain regions. Ascending from the NTS, the vagus reaches a large number of cortical and subcortical regions, including the PFC. Chronic oxidative stress plus systemic/neuroinflammation may cause dysfunctional synaptic transmission and attenuate multitude of efferent signaling pathways. The above points have been further delineated in the following sections.

3. Disparate Pathophysiologic Mechanisms

Aging is a biological process characterized by time-dependent, progressive, physiological decline including attenuated CNS functions of sensory, motor, and cognitive modalities. Aging is accompanied by increasing incidence of age-related diseases such as OSA and Alzheimer's disease (AD). Inflammation is considered pivotal in age-related physiological alterations and pathogenesis of many age-related diseases, owing to a wide variety of inflammatory mediators mentioned above. Aging has been suggested to be a state of chronic, low-grade molecular inflammation which may trigger the pathogenesis of several diseases [117, 118]. In this regards, available data have established two facts: (1) aging-associated dysregulation of the immune system and (2) aging-associated alteration of redox status. Both processes intertwine and exacerbate systemic inflammatory status. Several studies have highlighted an increased inflammation in old age [119, 120]. Glial cells from old mice also secrete more proinflammatory IL-6 and less of anti-inflammatory IL-10, compared to young adults [121]. An insidious close relationship exists between systemic infection/inflammation and cognitive dysfunction in the aged [119, 122]. Stimulation of the peripheral innate immune system (e.g., with lipopolysaccharide, LPS) causes increased neuroinflammatory response in the brain of aged mice [123] and humans [124]. Aged animals undergo neuroinflammatory alterations whether LPS is injected directly into the brain or into the systemic circulation. Old animals infected with *Escherichia coli* possess increased hippocampal interleukin IL-1β and several other inflammatory cytokines and undergo deficits in hippocampus-dependent memory, in comparison with similarly infected younger animals [125]. This is because of inherent propensity in aging—in that systemic circulating inflammatory cytokines (CIC) impair synaptic function/plasticity [43, 126] and may decrease gray matter volume in the hippocampus [127, 128] and brainstem nuclei [60]. There is strong clinical evidence that AD is associated with an inflammatory response, particularly due to higher peripheral concentrations of IL-6, TNF-α, IL-1β, IL-12, and IL-18 [129]. Consequently, an increase in neuroinflammatory response is fundamental in being correlated with susceptibility to cognitive impairment.

3.1. Afferent Dysfunction in OSA. The UA anesthesia increases pharyngeal airflow resistance and can induce or increase apneas and hypopneas in normal subjects and snorers [130–132]. Other data also suggest that impairment of sensory receptor function could conceivably produce sleep apnea [132, 133]. Thus, interruption of an afferent feedback mechanism, that is, of sensory stimuli arising in the UA mucosa, leads to apnea. This provides support for the concept that it is the status of afferent stimuli (arising in peripheral receptors) that plays a cardinal role in the patency of UA or its occlusion. In snoring subjects with or without OSA, vigorous snoring-related vibration and repeated forceful suction collapse of the pharynx could be traumatic to the UA mucosa and thus produce inflammation, edema, disturb sensory function, inducing neural damage [62, 134]—analogous to peripheral nerve injury resulting from low-frequency vibration [135]. Neural injury and dysfunction in OSA patients are widespread in several sites causing anatomicophysiological perturbations. This is consistent with data that palatopharyngeal muscle biopsies of OSA patients (undergoing uvulopalatopharyngoplasty) show mucosal edema and neurogenic damage [62, 136]. Indeed, UA mucosal edema has been demonstrated by magnetic resonance imaging [137] in OSA patients. There is also demyelination of motoneurons in palatal tissue in OSA [138]; consistent with this, EMG data on palatopharyngeus muscle in OSA subjects demonstrated long polyphasic

potentials and reduced amplitude [139]. Not surprisingly, therefore, proapoptotic proteins including caspases are upregulated following intermittent hypoxia-related mucosal injury [50, 103, 140]. The circulating systemic cytokines, as delineated above, may lead to microglial activation and inflammation-mediated neurotoxicity.

3.2. Dysfunctional Circadian Rhythm in OSA. Chronic intermittent hypoxia (CIH), repeated arousals, and irregular sleep-wake rhythm in OSA patients are related to abnormal circadian rhythm reflected in daytime somnolence and overall dyshomeostasis [141]. Studies have emphasized that OSA per se contributes to altered circadian rhythm in autonomic activity and BP thus promoting the cardiovascular diseases [142].

3.3. OSA and Cerebrovascular Factors. Sleep is a state in which consolidation of newly acquired information into memory takes place. This process is facilitated by neuromodulatory activity patterns and electric field potential oscillations; NREM and REM sleep support system consolidation and synaptic consolidation, respectively. Reactivation and redistribution of hippocampus-dependent memories to neocortex occur during slow wave sleep (SWS) via slow oscillations, spindles, and ripples [143, 144]. OSA, hypertension, and increased body weight correlate with decreased brain volumes, including the prefrontal cortex and cognitive dysfunction [60, 145, 146]. Thus, perturbations in CNS homeostasis due to disparate risk factors including intermittent apnea impact on sleep-related hippocampal and posterior cortical regions' memory processes [144–146].

Normally, brain perfusion is a function of tightly coupled metabolic demand and oxygen availability. A major pathological factor in OSA is nocturnal hypoxia; the resultant hypoxemia is deemed to impose stress on the brain, in particular. The brain is particularly vulnerable to the hypoxic stress, and chronic nocturnal intermittent hypoxia may directly damage the brain tissue. The pathological loss of neocortical/CNS gray matter due to hypoxia as mentioned above may correlate with impaired cognitive function. Normally, the hypoxic repercussion is mitigated during wakefulness; a decrease in O_2 supply causes a decrease in cerebral vascular tone and a consequent increase in cerebral blood flow (CBF), being linearly related to the fall in arterial O_2 saturation (Sa_{O2}) [147]. During NREM stage 3/4 sleep, the control of the cerebral vascular system is rather tenuous, in that there is a decrease in both cerebral blood flow and cerebral metabolism [148]. It has been observed that the CBF response to hypoxia is absent during stage III/IV NREM sleep [149, 150]. In response to isocapnic hypoxia, cortical blood flow increases during wakefulness; however, the same degree of isocapnic hypoxia may decrease the cortical blood flow during sleep [149, 150]. Importantly, light sleep (stage II) is characterized by CBF and cerebral oxygen metabolic rate (CMR) reduction by 3–10% (below the level associated with wakefulness), whereas CBF and CMR during deep sleep (stage III-IV) are dramatically reduced by 25–44% [151]. This may explain the possible interrelationship between a reduction in cerebral vascular response to hypoxia. Another potential factor that may be integral to hypoxia-related vasoconstriction is endothelin-1 (ET-1) which is known to exert a potent constrictor action on the cerebral circulation [152]. Plasma ET-1 level measured by radioimmunoassay was significantly increased in the rats having intermittent hypoxia/hypercapnia (IH) [152]. The arteries show increased constrictor sensitivity to endothelin-1 in the hypoxic animals. Finally, in terms of circadian variation, ET-1 levels are highest during the night and in the early hours of the morning [153]. NO promotes cerebral vasodilatation and couples blood flow and brain activity. NO is produced by active neurons and may couple brain activity and blood flow in sleeping lambs [154]. In humans, circulating blood NO levels are reported to be lowest during the night and in the early hours of the morning [153]. Therefore, a reduced endothelial and/or neuronal NO production would be an important factor in reducing the vasodilation of cerebral vasculature, reducing the cortical CBF response and attenuating gray matter volume in OSA patients [155, 156].

3.4. Central Inflammation Affects CNS Homeostasis and Promotes Cognitive Decline. Several studies confirm that preexisting inflammation increases vulnerability to a subsequent peripheral immune challenge, thus exacerbating the deleterious effects [125, 129, 157]. Furthermore, it is well documented that peripheral inflammatory cytokines stimulate central inflammatory cytokine mRNA and protein synthesis [157–159]. Aged rats, that exhibit signs of neuroinflammation, are inherently more responsive to the subsequent exposure/effect of LPS or infection. Increase in peripheral cytokines increases synthesis of IL-1β in the CNS [158]. Higher levels of proinflammatory cytokine mRNAs for IL-1β, IL-6, and TNF-α in CNS are induced by the individual/additive effect of the stimulated peripheral cytokines. Consequently, the proinflammatory and anti-inflammatory balance is perturbed, thus causing the activation of different downstream pathophysiological cascades. Following activation, platelets adhere to leukocytes and endothelial cells via p-selectin, platelet endothelial cell adhesion molecule-1 (PECAM), and intercellular adhesion molecule-1 and -2 (ICAM-1 and -2) and secrete phospholipase A2 and cyclooxygenase-2 (COX-2) as well as other proinflammatory chemokines and interleukins [160]. Further, they are a rich source of intraplatelet Aβ-40 [161]. Although platelets promote coagulation, wound healing, angiogenesis, and other functions, they are also essential for the innate immune response to combat infection (viruses, bacteria, microorganisms). They help maintain and modulate inflammation and are a major source of proinflammatory molecules such as P-selectin, tissue factor, CD40L, and metalloproteinases; they are major players indeed in promoting pathologies in several diseases, including AD [161].

Hypoxia stimulates the expression of inflammatory cytokines (IL-1β, TNF-α), chemokines (IL-8, MCP-1/CCL2), and adhesion molecules (ICAM-1) in the brain, in cultured astrocytes and in brain endothelial cells [162–166]. Chronic

intermittent hypoxia activates several factors including hypoxia-inducible factor-1 (HIF-1), c-fos, activator protein-1, and NF kappaB. Hypoxia-induced HIF-1α expression occurs both in tissues and cultured cells [163, 167, 168]. HIF-1α is an essential molecule that regulates oxygen homeostasis and mediates hypoxia-induced expression of IL-1β in astrocytes [166]. Astroglial cells are the most abundant cells in the brain and play an important role in the initiation and progression of hypoxia-induced neuroinflammation. HIF-1α initiates upregulation of inflammatory cytokines; upregulation of inflammatory genes by hypoxia is mediated by different transcription factors including HIF-1, NFκB, and AP-1 [162, 163, 169]. Recent work further demonstrated the role of HIF-1α in hypoxia-induced upregulation of inflammatory chemokines, human monocyte chemoattractant protein-1 (MCP-1/CCL2), and mouse MCP-5 (CCL12), in human and mouse astrocytes, respectively [164, 165, 170–172]. Activation of the HIF-1α pathway by risk factors such as age, cerebral atherosclerosis, and neuroinflammation may contribute to Aβ deposition and cognitive dysfunction.The above data, therefore, provide an important link for understanding the involvement of OSA and inflammation [173] as upstream mechanisms that may promote the downstream cascades (namely, of Aβ deposition and tau phosphorylation) of neuropathogenesis causing cognitive decline.

3.5. Nucleus Tractus Solitarius (NTS): Not Just an Innocent Bystander. The NTS is a compact network of neurons; its copious afferent and efferent pathways affect central homeostatic control [174]. This nucleus contains an enormous range of neuroactive substances; indeed, most of those identified within the CNS are also found in the NTS, as neurotransmitters and neuromodulators [175]. NTS located in the dorsal brainstem is the primary site for termination and integration of sensory afferents, such as baroreceptor, chemoreceptor, nocioceptors, and afferents from several key body systems, including gastrointestinal, respiratory, and cardiovascular, and indeed from UA and tongue. Thus, the NTS is the first CNS region for synaptic contact of the above afferents. The signal processing at these synapses determines the output of the sensory information from the heart, lungs, gut, airways, and the tongue to all downstream NTS synapses in the reflex pathways. The second-order NTS neurons spatially and temporally integrate the sensory information including the vagal afferent inputs, orchestrate an efferent output, and transmit it to various interconnected foci including the hypoglossal nucleus and the parasympathetic preganglionic neurons of the DMNV [176]. There is evidence that inflammatory mediators can influence the brainstem neuronal function directly and the NTS itself is a primary CNS detector of cytokines [177]. Indeed, NTS neuronal function can be affected directly through local synthesis of inflammatory mediators [53]. Thus, binding of cytokines, for example, IL-1β to its receptors on the neuronal membrane, initiates signaling cascades upregulating transcription of genes such as COX-2, TNF-α, and IL-6; these then recruit leukocytes and macrophages that release additional inflammatory cytokines [53, 178, 179]. There is bound to be an overall general impact of neuroinflammation on several brain regions including the hippocampus [180, 181]; such an impact would not only perturb their functions but would also have an adverse impact on the NTS owing to their reciprocal projection. The efferent parasympathetic pathways constitute the "cholinergic anti-inflammatory pathway" [182, 183]. Ascending from the NTS, the vagus reaches the thalamus, the paraventricular nucleus, the central nucleus of the amygdala, the hippocampus, the insula, the anterior cingulate cortex (ACC), and the medial prefrontal cortex (MPFC) [184]. The NTS provides input to the parabrachial nucleus, the DMNV, and the nucleus ambiguous (NA); these nuclei provide extensive efferent signals [140]. Chronic neuroinflammation may cause dysfunctional synaptic transmission and thus impact many key brain regions adversely, attenuating multitude of efferent signaling pathways of the NTS [37, 185–188]. A dysfunctional NTS would be deleterious to numerous key CNS foci and body systems that project their afferents to this strategically essential nucleus (many with reciprocal connections) [174, 180, 184–188]. Taken together, the abovementioned studies suggest that the dysfunctional NTS has the propensity to promote cognitive disturbances in OSA. Conceivably, a proportion of such elderly may progress to mild cognitive impairment and AD.

The GMV loss in specific brainstem nuclei in asymptomatic elderly reflects an ongoing silent pathophysiological change [60]. The elderly, suffer from on one hand, subclinical ongoing decreases in olfactory, gustatory, and somatosensory modalities of senescence [189–192] and, on the other, dysfunctional NTS activity due to neuroinflammation mentioned above. This then may lead to further decreases in sensory modalities projecting to the thalamocortical system and the NTS. Since the NTS projects to the hypoglossal nucleus, a decrease in the NTS function could conceivably affect in the direction of low NTS function → low hypoglossal function → low genioglossus activity → decrease in pharyngeal patency, resulting in → intermittent hypoxia/hypoxemia. The recurring hypoxic episodes of OSA may further potentiate pathology of the parietal, temporal, and frontal lobes, and the basal forebrain in the neocortex, and indeed in the key brainstem nuclei. Conceivably then, the neuroinflammation and OSA-related neuropathological alterations may promote cognitive dysfunction. Neuroinflammation, oxidative stress gene activation, and ROS production cause protein, lipid, and nucleic acid oxidation and negatively impact the neuronal homeostasis in the NTS. This conclusion is supported by experimental studies employing ROS/neuronal degeneration approach [193]. Importantly, neuroinflammation, intermittent/episodic apnea/hypopnea, and ROS/oxidative stress may synergize to augment pathology in CNS including apoptosis in the neocortical regions, brainstem, and indeed the NTS [194–198]. Compelling evidence therefore supports OSA/neuroinflammation/oxidative stress explanation in the causation of cognitive pathology—whose epicenter is the multifunctional highly interconnected NTS hub.

Recent studies have implicated the microvasculature inflammation in brainstem, specifically in the NTS, in the pathogenesis of hypertension [199–205]. It has been shown that vessels within brainstem regions of hypertensive animals

(SHR) (an animal model of human essential hypertension) are inflamed and release ROS and cytokines; these pathological messengers then alter neuronal activity in the NTS [201–205]. In the NTS of SHR, the gp39 precursor was upregulated [201]; the gp39 precursor is homologous to chitinase 3-like protein 1, also known as human cartilage-gp39 or YKL40. High levels of this molecule are present in many different inflammatory conditions including rheumatoid arthritis, glioblastoma, inflammatory bowel disease, atherosclerosis, asthma, and indeed AD [206]. Furthermore, gp39 precursor also promotes chemotaxis [207]. Thus, upregulation of gp39 precursor in the NTS reflects an inflammatory state that may attenuate neuronal activity in this brainstem nucleus [201–205]. Furthermore, the brainstem vessel inflammation could conceivably elevate the resistance to blood flow causing inadequate perfusion and exerting deleterious effects on neuronal excitability/viability in the NTS. An inflamed and dysfunctional NTS consequently may cause widespread disruption of many key biological functions in both brainstem and neocortex causing dyshomeostasis.

4. Focus on Correlates of Cognitive Dysfunction and the Unifying Hypothesis

4.1. Chronic Intermittent Hypoxia and Cognitive Dysfunction. Hypoxia due to OSA has been shown to cause neuropathological changes and memory impairments. Cognitive dysfunction may result due to decreased oxidative metabolism in the brain and impairment of neurotransmission. OSA is associated with unique cerebral alterations that may explain the behavioral and neurocognitive alterations observed. Several data utilizing several different techniques such as transcranial Doppler, event-related potentials, MR spectroscopy, and structural and functional MRI have clearly demonstrated changes in blood flow, metabolism, morphology, and activation in neurocognition-related brain regions in aging and OSA patients [150, 208–210]. Decreased cerebral activation during the working memory task in OSA patients reflects that these individuals possess impaired cerebral responses during executive function [211].

Compared to healthy subjects, the gray matter concentrations of OSA patients were significantly decreased in the left gyrus rectus, bilateral superior frontal gyri, left precentral gyrus, bilateral frontomarginal gyri, bilateral anterior cingulate gyri, right insular gyrus, bilateral caudate nuclei, bilateral thalami, bilateral amygdale and hippocampus, bilateral inferior temporal gyri, and the cerebellum [156]. Another study exhibited markedly declined signals in the ventral thalamus, hippocampus, and insula in OSA patients, compared to controls [212]. Neuroimaging data have provided evidence of hippocampal atrophy in OSA patients with a linear relationship between hippocampal volume and memory performance [213]. Freshly dissociated hippocampal CA1 neurons, exposed (Cyc) neurons exposed to hypoxia, showed decreased excitability; they showed action potentials (AP) with smaller amplitude and a longer duration and a more depolarized resting membrane potential, compared to controls [214]. Since the hippocampus is particularly susceptible to hypoxia, its bioenergetics is negatively impacted. Indeed, proton MR spectra obtained from the left hippocampus of OSA patients showed lower levels of hippocampal creatine-containing compounds; furthermore, they correlated with worse OSA severity and neurocognitive performance [215]. This further suggests that OSA has the propensity to impact regions that subserve cognitive processes.

Depression is not uncommon in OSA patients. Neural injury differed between OSA patients with and without depressive symptoms. Depressive symptoms accompanying OSA exacerbated injury. When MRI maps were compared between OSA and control groups, injury appeared in symptomatic relative to asymptomatic OSA subjects in the mid- and anterior cingulate, anterior insular, medial prefrontal, parietal, and left ventrolateral temporal cortices, left caudate nucleus, and internal capsule. However, symptomatic OSA patients with depression showed damage in the bilateral hippocampus and caudate nuclei, anterior corpus callosum, right anterior thalamus, and medial pons [216]. Additionally, when objectively measured disturbed sleep was consistently related to poorer cognition, whereas total sleep time was not; thus, it is the disturbance of sleep rather than quantity of sleep that affects cognition [217–219].

Various data have shown gray matter loss in cognitively relevant brain regions in hypoxia [60, 146, 220]. The above observations are in keeping with cortical neuronal cell damage due to intermittent hypoxia associated with neurocognitive dysfunction [103, 220, 221]. Another mechanism analogous to intermittent hypoxia is the ischemia/reperfusion-related reoxygenation [222], where enhanced ROS generation causes damage [223, 224]. Of note are data on 100 healthy male and female subjects of different age groups; magnetic resonance angiograms (MRA) displayed a lower number of MRA-discernible microvessels in aged individuals [210]. In addition, there was a significant increase in vessel tortuosity with age, limited to the middle cerebral distribution [210]. In healthy aging, OSA is associated with reduction of blood flow from the middle cerebral artery to the cortex that may negatively impact cortical neurons [225, 226]. In several elegant studies, Gozal, Kheirandish, and their colleagues have documented the interplay between OSA, NO, inflammation, and oxidative stress as pathological culprits that cause memory disturbance and neurodegeneration [103, 227, 228].

4.2. Episodic Hypoxia, Repercussion, and the NTS. There is significant evidence that OSA is independently associated with metabolic dysfunction, including dyslipidemia, insulin resistance, and overweight/obesity [229]. The latter as well as other factors in OSA may contribute to sleep debt, repetitive hypoxemia, increased sympathetic tone, and indeed hypertension. Recent studies have provided new insights in that OSA affects lipid and glucose metabolism by increasing adipose tissue lipolysis with subsequent free fatty acid flux to the liver, upregulating lipid synthesis in the liver and inhibiting lipoprotein clearance. OSA enhances inflammation and sympathetic activation that may affect glucose metabolism and counterregulatory hormones. Indeed models of OSA

have also improved our understanding of the metabolic impact of intermittent hypoxia [230].

A common neuronal protective adaptive reaction to hypoxic stress (hypoxia and inflammation) is the lowering of the cellular metabolic rate and energy decrease, preventing hypoxic excitotoxicity, and depression of synaptic activity. This could conceivably occur in the stressed NTS neurons exposed to hypoxia and inflammation in OSA patients. ROS enhance cellular inflammatory responses and reduce the expression of genes required to maintain synaptic structure and function. Documented evidence shows that pathological neurons synthesize proinflammatory cytokines and activate microglia [231, 232]. TNF-α and IL1-β are known to induce each other and their own production; thus, these cytokines may exacerbate the NTS pathology causing its neuronal dysfunction further. Thus, aberrations in NTS neural signaling, in the presence of hypoxia, ROS, and neuroinflammation, may promote neuronal degeneration in brainstem and cortex and lead to cognitive decline.

In addition to hypoxemia reoxygenation, OSA is characterized by other stressors, including intrathoracic pressure swings, and arousals from sleep, peripheral vasoconstriction, and rises in blood pressure (BP), and indeed inflammation. There is copious evidence from animal and human studies that sympathetic nervous system activation caused by hypoxia and arousals links OSA and BP. An important marker of cardiovascular risk is the vascular endothelium which may be dysfunctional in OSA. The dilatory response of small vessels to vasoactive substances such as acetylcholine may be blunted in sleep apnea [233, 234]. Levels of endothelin, a potent vasoconstrictor, may also be elevated in OSA patients [235]. In addition, bioavailability of NO is reduced in OSA patients owing to decreased eNOS activity and increased nitrotyrosine production (byproduct of nitric oxide degradation) in endothelial cells in this disorder [88]. Heightened inflammation, reflected by elevated C-reactive protein (CRP), leukocyte adhesion factors in OSA [236, 237], neutrophil-derived oxidative stress [238], and abnormalities in coagulation markers in patients with OSA may modulate vascular risk and upregulate predisposition to endothelial injury.

Episodic deoxygenation/hypoxemia stimulates the peripheral arterial chemoreceptors. Thus, the carotid body afferents, relaying in the NTS, elicit reflex increases in sympathetic efferent function [239, 240]. Each CNS arousal from sleep is accompanied by enhanced sympathetic neural outflow [241] that may exacerbate autonomic dysregulation in OSA. Hence, chemoreflex activation and/or arousal in OSA increases sympathetic drive to the peripheral vasculature and enhances BP [242, 243]. Normally, stimulation of parenchymal vagal receptors in lung (i.e., lung inflation) tempers sympathetic outflow; however, during apneas (i.e., a lack of lung inflation), sympathetic neural activity potentiates sympathetic responses to hypoxia/hypoxemia [244, 245]. The combination of advanced age with increased oxidative stress, hypertension, inflammation, and other risk factors provides a rich background—for altered regulation of blood flow, deposition of amyloid β protein and neurofibrillary tangles, altered cholinergic transmission, and autonomic dysfunction. These pathways interact in a complex pattern. For example, changes in BP negatively affect brain perfusion and metabolism, and clearance of amyloid β protein from the brain is dependent on vascular reactivity, which in turn is affected by endothelial/vascular injury and remodelling. Presence of comorbidities and multifaceted pathophysiological interactions may result in cortical/subcortical dysfunction, neuronal atrophy/death, and cognitive decline [173].

In OSA, the dysfunctional NTS/vagal mechanisms are correlated with reduced lung inflation, baroreflex and chemoreflex dysfunction, and dysregulation of cardiorespiratory homeostatic mechanisms. Both cardiac phasic and pulmonary tonic activity of the vagus participate in the function of cardiovascular and respiratory systems and play a pivotal role in coordinating their normal activity. Vagal nerve blockade (by atropine) results in an increased alveolar dead space and reduced P_{aO2} and S_{pO2}. Attenuated vagal activity due to the NTS dysfunction impacts physiological adjustment to improve pulmonary gas exchange efficiency—enhancing hypoxia, hypercapnia, and tracheobronchoconstriction [246]. The above leads to the vicious cycle of dysfunctional parasympathetic phenomena that impact cognitive outcomes; the following current hypothesis is therefore consistent with the above implications.

4.3. The Hypothesis. Based on the above-mentioned evidence that underscores the role of inflammation and OSA in cognitive disturbances, one can hypothesize highlighting that—aging plus several risk factors generate proinflammatory cytokines/oxidative stress/ROS → Neuroinflammation—deleterious impact on neurons/glia of neocortex and brainstem → brainstem nuclei including the NTS-inflamed and dysfunctional → attenuation of hypoglossal nucleus activity → genioglossus dysfunction promoting snoring/OSA/dysfunctional breathing → chronic intermittent hypoxia and hypoxemia → further neuroinflammation and neuronal degeneration → global deleterious impact on a host of key physiological functions in brain (e.g., in hippocampus) → memory and cognitive dysfunction (Figure 1). The implications of the current perspective are considerable; attenuation of the predisposing upstream risk factors delineated here warrants future research.

5. Conclusions

Nocturnal intermittent hypoxia and hypercapnia are cardinal features of OSA. Altered cerebral circulation, brain hypoperfusion/ischemia, and the pathological loss of gray matter are associated with OSA. Aging is accompanied by a low-grade, chronic, and clinically indolent upregulation of proinflammatory state. A simple and potentially pragmatic hypothesis is posited on the cognitive decline in OSA patients. The immune system and inflammation have been implicated in a wide variety of neurodegenerative conditions. Relatively common sources of systemic inflammation may be significant risk factors that may potentiate neuroinflammation in the CNS. The latter causes microvascular changes, switching of microglial phenotype and activity, and physiological

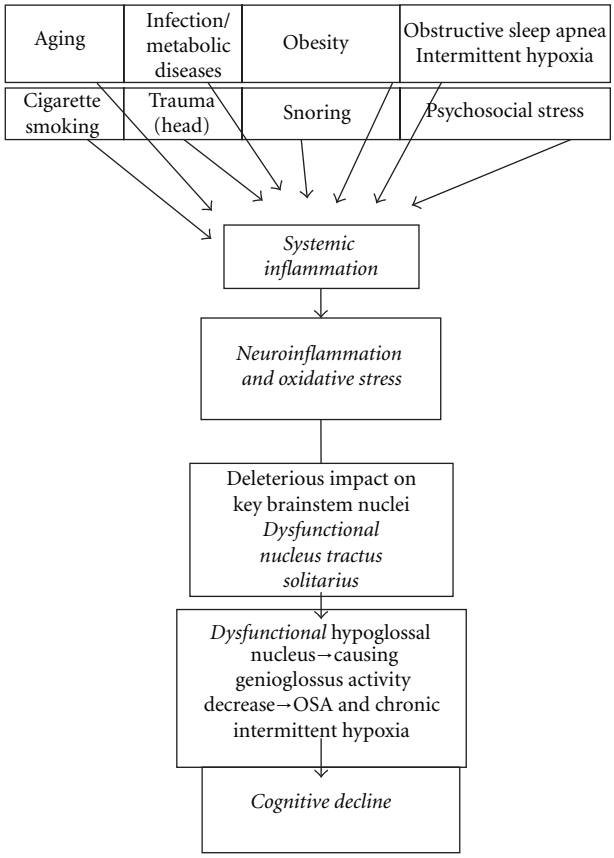

Figure 1: Schematic representation of the pathogenesis of cognitive decline in patients with sleep disordered breathing. Several risk factors upregulate proinflammatory cytokines and induce systemic inflammation. The latter then promotes neuroinflammation which augments further inflammation; this has a negative impact on neuronal, glial, and vascular endothelial cell functions. Inflammation, intermittent hypoxia, and oxidative stress provide a rich milieu causing the NTS inflammation and dysfunction. Being a central hub for processing disparate afferents and owing to its widespread projections in the CNS, the dysfunctional NTS would negatively impact several key brain foci and their physiological functions. Dysfunctional NTS and hypoglossal nuclei would cause genioglossus dysfunction resulting in pharyngeal obstruction/collapse. This leads to snoring, OSA, intermittent hypoxia, and hypoxemia. Thus, neuroinflammation and sleep apnea are major contributing factors that may cause neuronal degeneration and provoke cognitive dysfunction.

dysfunctions in key brainstem nuclei, notably, the NTS and the hypoglossal. Their inflammation and dysfunctional activity result in genioglossus dysfunction, leading to UA obstruction and intermittent hypoxia/hypoxemia. The latter has widespread impact on several physiological activities, including the CNS structure and function—thus further enhancing inflammation and causing grey matter volume decrease. Neuroinflammation plus hypoxia may therefore underpin the CNS physiopathology leading to cognitive dysfunction. The NTS is the central integration hub for afferents from the UA somatosensory/gustatory, gastrointestinal, respiratory, cardiovascular (baroreceptor and chemoreceptor), and several other afferents from the brain (e.g., from amygdale and hypothalamus). It also has important role in sympathetic and parasympathetic systems. The current hypothesis, therefore, implicates inflamed and dysfunctional NTS as the central player in the neuropathogenesis of cognitive decline. The current hypothesis is the first to sequentially connect aging plus several risk factors → generate proinflammatory cytokines/ROS/oxidative stress → dysfunctional NTS and hypoglossal → snoring/OSA/dysfunctional breathing → hypoxia and hypoxemia → further neuroinflammation and neuronal degeneration → global deleterious impact on a host of key physiological functions in CNS → memory and cognitive dysfunction. In some OSA patients, however, this may lead to age-associated dementing disease such as AD. The implications of the current perspective are considerable and warrant future research.

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Research Article

Association of Duration of Sleep and Cardiovascular and Metabolic Comorbidities in Sleep Apnea Syndrome

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Background/Aim. Previous population-based studies found association between duration of sleep and cardiovascular and metabolic comorbidities. Our aim was to investigate the association between the duration of sleep and cardiovascular and metabolic comorbidities in OSAS. *Patients and Methods*. The study enrolled 312 patients, who had polysomnography (PSG) during 2006-2007 and responded to a telephone-administered questionnaire providing information on characteristics of sleep on average 12 months after PSG. *Results*. Of the patients, 90 were female (28.8%), 173 (58.5) received the diagnosis of OSAS, 150 (45%) had no comorbidities, 122 had hypertension (HT), 44 had diabetes mellitus (DM), and 38 had coronary heart disease (CHD). Mean ± SD of age in years was 47.2 ± 10.6, 56.5 ± 9.3, 53.2 ± 8.9, and 59.9 ± 9.0 for the no comorbidity, HT, DM, and CHD groups, respectively. Reported duration of sleep was not associated with any of the comorbidities in the overall group. In the analysis restricted to OSAS patients, sleep duration ≤6 hours was significantly associated with CHD after the adjustment for age, gender, and other associated factors (OR: 5.8, 95% CI: 1.0–32.6). *Conclusions*. Confirmation of the association between shorter duration of sleep and CHD will provide prognostic information and help for the management of OSAS.

1. Introduction

Sleep loss is a common condition in modern society. Although the health effects of sleep deprivation have been obscure, recent epidemiological studies have revealed relationships between sleep deprivation and hypertension (HT), coronary heart disease (CHD), and diabetes mellitus (DM) [1]. Because sleep deprivation increases sympathetic nervous system activity, this increased activity serves as a common pathophysiology for HT, DM, and CHD. Previous studies showed that sleep duration less than 6 hours or more than 8 hours is associated with increased morbidity and mortality due to cardiovascular diseases in the general population [2, 3].

Obstructive sleep apnea syndrome (OSAS) is a common medical disorder that is growing in prevalence worldwide. It is characterized by recurrent cycles of intermittent hypoxia and there is increasing evidence that intermittent hypoxia plays a role in the development of cardiovascular risk in OSAS patients through the activation of inflammatory pathways. Some excellent review articles have already summarized the effects of OSAS on HT, CHD, and DM [4–6]. The pathogenesis of cardiovascular disease in OSAS is not completely understood but is likely to be multifactorial, involving a diverse range of mechanisms including sympathetic nervous system overactivity, endothelial dysfunction, and selective activation of inflammatory molecular pathways [7–9]. Expanding our understanding of these pathways, which include chronic intermittent hypoxia and provocation of inflammation by sleep deprivation, will yield novel therapeutic targets with the scope of reducing the cardiovascular risk in OSAS.

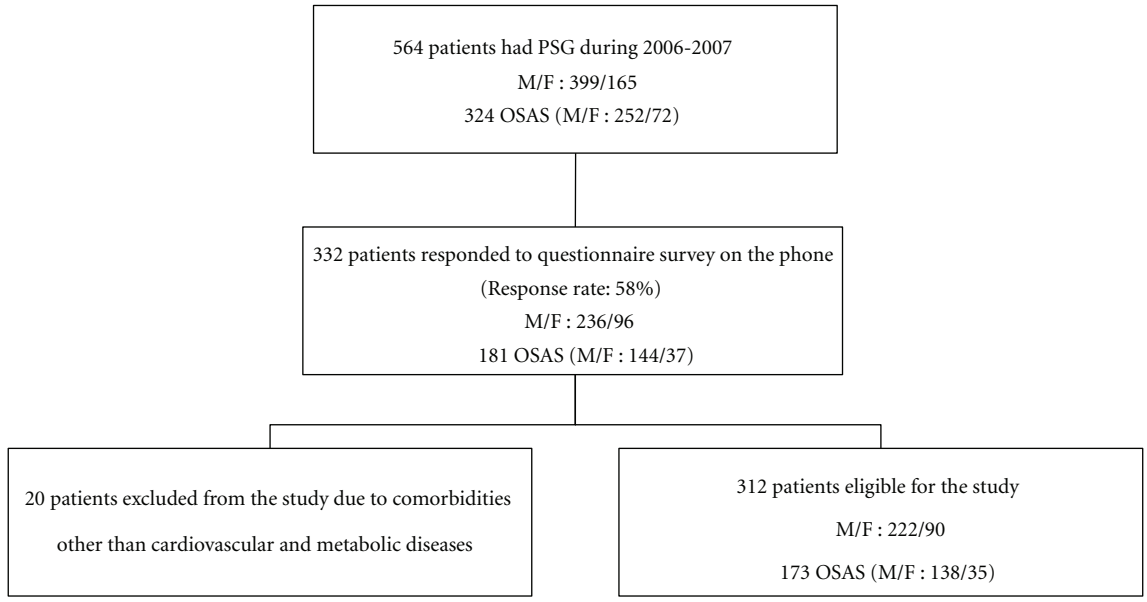

Figure 1: Flowchart of the study, describing the study population: PSG: polysomnography, M: male, F: female, OSAS: obstructive sleep apnea syndrome defined as excessive daytime sleepiness (Epworth Sleepiness Scale score >10) and AHI (apnea-hypopnea index) ≥5 or AHI ≥ 15, regardless of excessive daytime sleepiness.

Hence, both sleep deprivation and OSAS are related to the occurrence and consequences of cardiovascular and metabolic diseases. To our knowledge, there have been no reports on the relationship between sleep duration and risk of comorbidities in OSAS patients. Our aim was to investigate the association between duration of sleep and cardiovascular and metabolic comorbidities in patients admitted to sleep lab with sleep apnea symptoms and in patients who received the diagnosis of OSAS.

2. Material and Methods

2.1. Patients and Study Protocol. Of the 564 patients, who had polysomnography during 2006-2007 with a preliminary diagnosis of sleep apnea in the sleep center, 332 (response rate: 58%) gave consent and responded to a telephone administered survey on average 12 months after polysomnography (PSG), which included information on characteristics of sleep and physician diagnosis of systemic diseases. The study protocol was approved by the Institutional Review Board of the research hospital. Cardiovascular and metabolic diseases (comorbidities) included hypertension, diabetes mellitus, and coronary heart disease. Patients were grouped in hypertension, diabetes mellitus, and coronary heart disease, and no comorbidity groups according to their responses. In the condition of reporting more than one of these diseases, the patient was grouped in all these disease groups; that is, the groups were not exclusive. Twenty patients, who reported none of these three diseases (DM, HT, and CHD), but a systemic disease including neuromuscular diseases, heart failure, and chronic obstructive lung diseases were omitted from the analysis. Thus, the study population comprised of 312 subjects (55% of the original sample). Figure 1 describes flowchart of the study population. There was no significant difference between the age, gender, and OSAS percentage of the patients in the study population and the patients who did not respond to the telephone administered survey.

Duration of sleep was assessed by the question: "On average how many hours do you sleep at night?" In the analysis, duration of sleep was categorized as 6 hours or less, 7-8 hours, and more than 8 hours, based on the previous studies, which suggested 7 hours of sleep as normal.

2.2. Polysomnography. PSG was performed in the Sleep Laboratory with Grass Technologies Comet Series EEG/PSG with AS40 Amplifier System running Grass Technologies Twin software version 4 (Grass Technologies, Astro-Med Inc. Product Group, USA) and included four electroencephalography (EEG) channels (C3 to A1, C4 to A2, O1 to A2, and O2 to A1), right and left electrooculography (EOG) channels, one chin electromyography (EMG) channel and four tibialis anterior EMG channels, finger pulse oximeter, strain gauges for thoracoabdominal movements, one electrocardiography (ECG) lead, a nasal airflow (pressure cannula), a nasal thermistor and a digital microphone for snoring detection. PSG recordings were scored in 30-second epochs for sleep, breathing and oxygenation according to the standard criteria of the American Academy of Sleep Medicine (AASM) [10]. Obstructive apnea was defined as a 90% cessation of oronasal airflow for at least 10 seconds in the presence of chest-wall motion. Hypopnea was defined as a reduction in the airflow of 50% or more associated with 3% or more arterial oxygen desaturation and/or arousal, or a reduction in respiratory airflow of 30% or more associated with 4% or more arterial oxygen desaturation and/or arousal for at least

Table 1: Demographic features of the patients.

	N	No comorbidity	HT	DM	CHD
N	*312*	150	122	44	38
Male/Female, (%)	*222/90*	116/34 (77.3)/(22.7)	**76/46**** **(62.3)/(37.7)**	29/15 (63.4)/(36.6)	28/10 (74.3)/(25.7)
Age, (year)		47.2 ± 10.6	**56.5 ± 9.3*****	**53.2 ± 8.9****	**59.9 ± 9.0*****
BMI, (kg/m^2)		30.0 ± 4.8	**32.5 ± 6.0*****	**32.3 ± 5.9***	30.6 ± 4.8
Educational status					
Primary or less, %	*149*	43.9	51.3	47.5	**82.4*****
Secondary, %	*98*	36.6	31.9	27.5	**11.8**
University, %	*59*	19.6	16.8	25.0	**5.9**
Smoking status					
Nonsmoker, %	*120*	36.7	46.3	36.6	31.4
Ex-smoker, %	*94*	34.7	24.0	36.6	20.0
Current smoker, %	*97*	28.7	29.8	26.8	48.6
Shift work, %	*73*	23.3	21.7	31.7	25.7

Means and ±SDs are given in the table, unless otherwise specified.
$^{*}P < 0.05$;
$^{**}P < 0.01$;
$^{***}P < 0.001$.
Significant findings are marked in bold type.
HT: hypertension, DM: diabetes Mellitus, CHD: coronary heart disease, and OSAS: obstructive sleep apnea syndrome.

10 seconds. Apnea hypopnea index (AHI) was calculated as the total number of apneas and hypopneas per hour of sleep. Diagnosis of OSAS was based on PSG findings, according to the International Classification of Sleep Disorders 2 (ICSD-2) [11], as in the following:

(i) Excessive daytime sleepiness and AHI ≥ 5;

(ii) AHI ≥ 15, regardless of excessive daytime sleepiness.

Excessive daytime sleepiness was defined as the score of Epworth sleepiness scale >10 [12]. Subjects were classified in the control group if they had AHI < 5 regardless of excessive daytime sleepiness.

2.3. Statistical Analysis. Descriptive statistics and comparison of the comorbidity groups with the no comorbidity group are shown in the tables. Frequency (percentage) and mean ± standard deviation were used for the descriptive statistics of the categorical and continuous variables, respectively. Chi-square testing was used for the univariate analysis of categorical variables. Fisher's exact test was used in the case of an expected frequency of less than five in 25% of the cells. Student's *t*-testing and Mann-Whitney *U* test were used for the univariate analysis of continuous variables, where appropriate (normal and not-normal distribution, resp.). Logistic regression analysis models were constructed to adjust the association between duration of sleep and comorbidities for age, gender, BMI, other potential risk factors, and factors which were found significant in the univariate analysis. Models were constructed both in the overall group and in the OSAS group, to investigate the association between duration of sleep and comorbidities both in the overall study population and in OSAS patients. *P* value less than 0.05 was used to define statistical significance in the two-sided tests.

3. Results

The study enrolled 312 patients, who had PSG with a preliminary diagnosis of sleep apnea between 2006 and 2007 and answered a telephone administered questionnaire providing information on characteristics of sleep. Table 1 shows the personal characteristics of the subjects in the cardiovascular and metabolic comorbidity groups. Of the subjects 90 were female (28.8%), 150 (45%) had no comorbidity, 122 had HT (39.1%), 44 had DM (14.1%), and 38 had CHD (12.1%). Diagnosis of OSAS was made in 173 (58.5%) of the patients, without a significant difference between the groups of HT (60.2%), DM (48.7%), and CHD (48.4%) and no comorbidity group (58.5%). Of the OSAS patients 138 were men and 35 were women. Coronary heart disease group compared to no comorbidity group had a higher percentage of less educated patients. In the PSG record, time percentage spent <90% of oxygen (T90%) was significantly higher in the HT group than no comorbidity group. Table 2 shows the association between PSG findings and cardiovascular and metabolic comorbidity groups.

Of the patients 58 reported onset of sleep delayed (delayed sleep onset) more than 30 minutes (18.5%), 211 had fragmented sleep (67.6%), 174 had unrefreshening sleep (55.7%), and 78 had excessive daytime sleepiness defined as ESS score above 10 (25%). There was no significant difference in the prevalence of sleep symptoms between comorbidity groups and no comorbidity group, except for the significantly higher percentage of delayed sleep onset in the HT group than the no comorbidity group (25.4% versus 13.3).

Duration of sleep was reported as 6 hours or less in 15%, >6 hours to 7 hours in 25.2%, >7 hours to 8 hours in 47.9%, and >8 hours in 11.8% of the subjects. There was no significant difference between the sleep duration of the

Table 2: Polysomnography findings and features of OSAS of the patients in different cardiovascular and metabolic comorbidity groups.

	N	No comorbidity	HT	DM	CHD
N	*312*	150	122	44	38
Total sleep time, min		385.4 ± 82.1	**346.5 ± 88.6****	**335.8 ± 87.0****	348.5 ± 98.9
T90%, (%)		13.4 ± 21.8	**22.8 ± 30.8***	23.6 ± 5.0	16.2 ± 26.8
Sleep efficiency, (%)		87.5 ± 10.5	**84.5 ± 10.5***	84.0 ± 13.3	84.8 ± 11.4
WASO, (%)		2.2 ± 6.3	**4.3 ± 8.4***	4.0 ± 9.1	3.5 ± 7.6
REM, (%)		11.3 ± 6.4	**9.5 ± 7.1***	10.4 ± 5.8	11.3 ± 7.4
N3, (%)		21.8 ± 12.4	21.0 ± 14.6	**16.4 ± 5.8***	20.0 ± 15.0
AHI, (/hour)		30.3 ± 27.9	33.1 ± 30.7	31.3 ± 31.5	22.4 ± 22.2
Obstructive AHI		27.6 ± 26.4	31.9 ± 30.1	27.1 ± 27.9	19.9 ± 19.0
OSAS, %	*173*	58.5	60.2	48.7	48.4
Severe OSAS, %	*120*	38.5	38.0	34.1	27.8
CPAP prescribed, %	*116*	33.3	37.7	48.8	38.9
CPAP compliance, %	*61*	52.0	55.6	60.0	42.9

Means and ±SDs are given in the table, unless otherwise specified.
*$P < 0.05$;
**$P < 0.01$.
Significant findings are marked in bold type.
HT: hypertension, DM: diabetes mellitus, CHD: coronary heart disease, ESS: Epworth Sleepiness Scale, OSAS: obstructive sleep apnea syndrome, and WASO: wake after sleep onset.
OSAS: excessive daytime sleepiness and AHI ≥ 5 or AHI ≥ 15, regardless of excessive daytime sleepiness.
Severe OSAS was defined as AHI above 30/h.
CPAP compliance: reported usage of CPAP every night for more than 4 hours a night. CPAP compliance percentage was calculated in the patients who were prescribed CPAP therapy.

Table 3: Association between reported sleep duration and cardiovascular and metabolic comorbidities in the models adjusting for other risk factors.

	Whole group		OSAS patients	
Comorbidities and duration of sleep	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
HT				
6 hours or less	1.0 (0.6–1.8)	0.6 (0.3–1.3)	1.3 (0.6–2.7)	0.7 (0.2–1.7)
8.5–10 hours	1.0 (0.4–2.2)	0.7 (0.3–1.8)	1.4 (0.5–4.4)	0.8 (0.2–2.7)
DM				
6 hours or less	1.6 (0.7–3.5)	1.2 (0.5–3.0)	2.7 (0.8–8.5)	2.3 (0.7–7.8)
8.5–10 hours	1.7 (0.6–4.8)	1.2 (0.4–3.7)	3.7 (0.9–15.9)	2.3 (0.4–11.4)
CHD				
6 hours or less	1.1 (0.5–2.9)	1.2 (0.4–3.8)	**3.6 (1.1–11.3)**	**5.8 (1.0–32.6)**
8.5–10 hours	0.4 (0.1–2.1)	0.3 (0.06–2.3)	NA	NA

Adjustments were made for OSAS, age, gender, and BMI in all models, and additionally for smoking status in HT and for smoking status and educational status in CHD.
For duration of sleep, 7-8 hours was considered as the reference category.
Significant findings are marked in bold type.
HT: hypertension, DM: diabetes mellitus, CHD: coronary heart disease, and OSAS: obstructive sleep apnea syndrome.

comorbidity groups and the no comorbidity group. Figure 2 shows the boxplot graph of the distribution of duration of sleep in HT, DM, and CHD groups compared to no comorbidity group in patients with and without OSAS. Among the OSAS patients, duration of sleep was significantly shorter in the CHD group than in the no comorbidity group.

Table 3 shows the association between reported sleep duration and cardiovascular and metabolic comorbidity groups in the models adjusting for other risk factors. In the whole group duration of sleep was not associated with any of the comorbidities. In the analysis restricted to OSAS patients, sleep duration of ≤6 hours was significantly associated with coronary heart disease as unadjusted and after the adjustment for age, gender, smoking status, and educational status.

4. Discussion

In this study, we have demonstrated that shorter duration of sleep (6 hours or less) was associated with CHD in

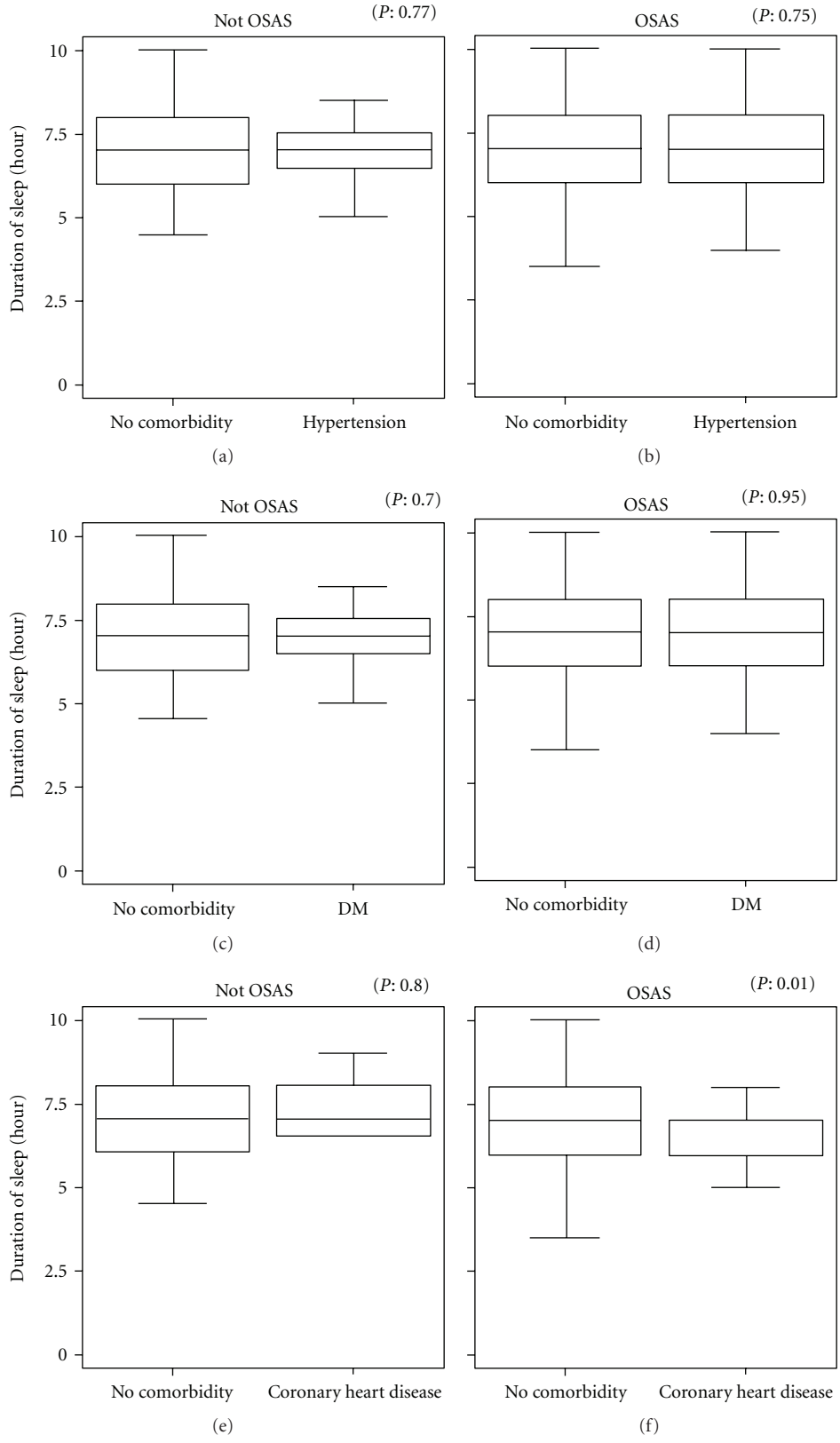

Figure 2: Boxplot graph of the distribution of duration of sleep in HT, DM, and CHD comorbidity groups compared to no comorbidity group in the subjects without OSAS (Not-OSAS) in graphs a, c and e and in the subjects with OSAS (OSAS) in graphs b, d and f: HT: hypertension, DM: diabetes mellitus, CHD: coronary heart disease, and OSAS: obstructive sleep apnea syndrome. Mann-Whitney *U* test was used in the comparisons.

patients with OSAS after adjustment for confounding factors in patients with OSAS.

To our knowledge, this is the first study which examined the association between sleep duration and cardiovascular and metabolic comorbidities in patients with OSAS. Previous studies found significant association between short (less than 6 hours) and long sleep duration (more than 8 hours) and CHD, DM, and HT in general population [2, 3].

Recent studies including follow-up data have shown that OSAS has a causal relationship with the development of cardiovascular disease independent of confounding factors such as sex, age, and obesity [13–22]. The mechanisms by which OSAS exerts its detrimental effects remain to be established, and future studies should actively pursue the identification of OSAS patients at high risk of cardiovascular diseases. Epidemiological studies have convincingly shown that type 2 diabetes is often associated with OSAS and daytime sleepiness [23–25]. For example, in a large series of OSAS patients, type 2 diabetes and impaired glucose tolerance showed a 30 and 20% prevalence, respectively [26], and studies in snorers reached similar conclusions [27, 28]. There is strong evidence that OSAS is an independent risk factor for systemic hypertension [29, 30]. Case-control studies have confirmed the association between sleep apnea and increased blood pressure independent of confounders such as obesity [31]. Severity of OSAS (AHI, ESS, and T90%) was not associated with DM and CHD in our study. Percentage of night time spent with oxyhemoglobin saturation below 90% was higher, and difficulty in initiating sleep was more frequent in patients with HT.

The pathogenesis of cardiovascular disease in OSAS is not completely understood but likely to be multifactorial, involving a diverse range of mechanisms including sympathetic nervous system overactivity, selective activation of inflammatory pathways, endothelial dysfunction, hypercoagulability, and metabolic dysregulation, the latter particularly involving insulin resistance and disordered lipid metabolism. Such a clinical context makes it difficult to assess the independent effects of OSAS on cardiovascular risk, and still there remains factors to be understood [32, 33].

The literature supports the view that short or long sleep duration is independently associated with an increased likelihood of coronary events [2, 34–39]. Increased unadjusted CHD risk was found in both short sleeper groups (extremely short $\leq$5 h, and 6 h sleepers) and extremely long sleepers ($\geq$10 h) in both genders when compared with midrange (7-8 h) sleepers. It was also reported as an important finding that 9-hour sleepers did not differ in their CHD risk when compared with midrange sleepers in the same study [40]. Short sleep duration (<6 h) has been shown as a significant risk factor for coronary events in a Japanese male working population [41]. The risk of CHD events was independent of prominent cardiovascular risk factors and occupational factors [41]. Short sleep duration imposed on a group of healthy subjects increased sympathetic nervous system activity and blood pressure elevation. Therefore, sustained short sleep duration could lead to adverse cardiovascular consequence. We investigated the association between reported sleep duration and cardiovascular and metabolic comorbidities in the models adjusting for the other risk factors including obesity and smoking [42–44]. In these models, only CHD in OSAS patients was associated with shorter sleep duration. Since a few subjects reported sleep duration of 10 hours or more, we could not investigate the association between longer sleep time and CHD.

The strengths of the study were examination of both PSG data and self-reported sleep duration and their association with comorbidities. We defined no comorbidity group as patients who did not report the investigated diseases and other systemic diseases. However, these patients might have comorbidities (which were not diagnosed yet), and this misclassification, if nondifferential, could be underestimating the association between sleep duration and comorbidities.

The present study had some limitations. The major limitations of the study were small sample size, which was a constraint for the adjustment of the potential confounders in the analysis. Since this is a cross-sectional study it is difficult to interpret the causality of our findings. However, there is not enough reason to believe that comorbidities strongly affected the duration of sleep. Sleep duration was only associated with CHD in the OSAS group. If comorbidities had strongly changed the sleep duration, this association must have also been observed in DM and HT. We did not have data about the other confounders like hyperlipidemia, alcohol intake, and exercise frequency and therefore could not control these factors in the analysis confounders. Objective measurements of sleep duration, blood pressure, and glucose were lacking, which is another limitation of our study. The prevalence of comorbidities in the control group was not significantly different from the patients with OSAS, which suggests that selection bias (i.e., higher degree of suspicion and screening for systemic diseases and thus finding higher prevalence of systemic diseases in OSAS patients) is not so likely. In this study, reported sleep duration and sleep symptoms were used as an estimate of the general status of sleep habits and sleep symptoms. Patients who were using CPAP therapy were asked to report the situation (duration of sleep and sleep symptoms) before treatment. We did not find a beneficial effect of CPAP compliance on the sleep-related symptoms, which could be due to questions asking the subjects about their symptoms before treatment. Duration of sleep and quality of sleep might have changed due to comorbidities, and this could influence the interpretation of the associations found in this study. Lack of association between sleep duration and other comorbidities (HT and DM) could be regarded as evidence against this possibility. Importantly, the control group consisted of patients who were admitted to the sleep center with sleep-related complaints, including snoring and poor quality of sleep. Previous studies which used snoring as a proxy for sleep-related breathing disorders have found significant association between snoring and cardiovascular diseases [45, 46]. Thus, the control group in this study was not representing the healthy individuals in the general population. This could, at least partially explain the lack of association between comorbidities and duration of sleep and OSAS, in the study population. Presence of sleep symptoms (excessive daytime sleepiness, unrefreshening sleep, or difficulty in initiating sleep) was not

associated with the comorbidities in the regression analysis. This could be due to the high prevalence of these symptoms in the no comorbidity group (which was almost similar to that of comorbidity groups). The only significant association was found between CHD and duration of sleep in the analysis restricted to OSAS patients. This could suggest the interaction between OSAS and short duration of sleep for the development of CHD. Confirmation of this finding requires follow-up data.

In conclusion, CHD was associated with shorter sleep duration in patients with OSAS in the present study. Our results, if confirmed, suggest that ensuring appropriate sleep hours through appropriate OSAS treatment and modifying lifestyle factors and sleep hygiene could be beneficial in the prevention of cardiovascular and coronary events in patients with OSAS.

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Research Article

Association of Plasma Homocysteine with Self-Reported Sleep Apnea Is Confounded by Age: Results from the National Health and Nutrition Examination Survey 2005-2006

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High levels of plasma homocysteine are implicated in the pathogenesis of cardiovascular diseases especially if accompanied by sleep apnea, but a direct pathogenetic link between plasma homocysteine levels and obstructive sleep apnea is debatable. This association can have far-reaching public health implications considering the inverse association between folate and plasma homocysteine. We used data from the 2005-2006 cycle of the National Health and Nutrition Examination Survey (NHANES) to test the hypothesized associations. Of the 4490 subjects included in analysis, 177 reported sleep apnea. Age-standardized and design-effect-corrected prevalence rates were differential across gender, plasma homocysteine, and red cell folate status. Plasma homocysteine was positively correlated with age ($r = 0.38$, $P < 0.0001$). Multivariate analyses using sociodemographic and clinical covariates demonstrated that plasma homocysteine levels retained their respective associations with self-reported sleep apnea in all models except when age was included as a covariate. Our results demonstrate that the claimed association of plasma homocysteine with sleep apnea may be confounded by age.

1. Introduction

Obstructive sleep apnea (OSA)—a disorder in which a person frequently stops breathing during sleep—results from an obstruction of the upper airway that occurs because of inadequate motor tone of the tongue and/or airway dilator muscles. In the United States, the prevalence of OSA is estimated to be 3–7% in men and 2–5% in women [1]. In addition, up to 93% of women and 82% of men may already have an undiagnosed moderate to severe OSA [2]. Further, the comorbid occurrence of OSA with obesity is well-recognized: prevalence of OSA is reported to be 41% among patients with a body mass index (BMI) greater than 28 Kg/m^2 and as high as 78% in morbidly obese patients who present for bariatric surgery [3, 4]. Of greater interest and importance, however, is the association of OSA with cardiovascular disorders [5]. OSA has been identified as a crucial intermediate factor in the pathophysiology of hypertension, ischemic heart disease, arrhythmias, stroke and diabetes. It has been shown that habitual snorers are at a 2 times higher likelihood of developing type 2 diabetes independently of other covariates [6]. Also, treatment of sleep-disordered breathing is known to improve outcomes after congestive heart failure and stroke [7, 8].

A possible mechanism for the strong correlation between OSA and cardiovascular risk factors is the concomitant association of plasma homocysteine levels with both these disorders [9–11]. Homocysteine—a homologue of cysteine is a biosynthesized amino acid in the metabolism of methionine. Its production correlates with the deficiency of vitamins B6, B12, and folic acid. Indeed, plasma homocysteine levels are considered a good indicator of the deficiency of these

vitamins [12]. The importance of homocysteine metabolism in the initiation or precipitation of cardiovascular diseases can be appreciated by the fact that the attributable risk of hyperhomocysteinemia in the epidemiology of cardiovascular diseases is nearly 25% and competes with that of other well-known factors like smoking and hyperlipidemia [13]. In contrast, the association of plasma homocysteine levels with the risk, severity and long-term complications of OSA is less clear. Over the last decade, 15 epidemiological studies [14–28] have examined the potential association of plasma homocysteine levels with OSA under varying scenarios (Table 1). Of these, nine studies [4–6, 12, 16, 17, 21, 24, 26] have reported overall or subgroup-specific association while six studies [3, 8, 9, 13, 20, 23] have not found any association. Some elegant reviews [9, 10] in this area have also not been fully conclusive about such an association.

In concept, this association—if statistically and truly existent–proffers an enticing opportunity for simple public health measures like vitamin supplementation for the prevention and control of OSA as well as its cardiovascular implications [29]. However, as can be gleaned from Table 1, most of the studies in this area have been based on relatively small sample sizes which somewhat limits the public health implication of these results. We therefore analyzed a large nationally representative sample which was collected during the National Health and Nutrition Examination Survey (NHANES) in the 2005-2006 cycle. Here we report the results of our investigation into the association of plasma homocysteine, and folate levels in the plasma as well as the red blood cell (RBC) with the risk of self-reported sleep apnea in an epidemiological context.

2. Methods

2.1. The NHANES 2005-2006 Dataset. The National Health and Nutrition Examination Survey (NHANES) is an annual survey conducted by the National Center of Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, USA. It comprises a combination of interviews, physical examination and laboratory tests to assess the health and nutritional status of adults and children in the United States. The NHANES 2005-2006 and 2007-2008 cycles contain a questionnaire to identify subjects with diagnosed sleep disorders. Preliminary results from this questionnaire and the relationship of sleep apnea with obesity in the 2005-2006 dataset have been described elsewhere [30]. Even though both the 2005-2006 and 2007-2008 datasets contain data on the sleep questionnaire, currently the plasma homocysteine levels are available for the 2005-2006 cycle only. Therefore, we included this dataset for our analysis. The NHANES 2005-2006 survey was approved by the NCHS Ethics Review Board, and all participants or parents (for minors) provided written consent. Total plasma homocysteine levels were determined using the fully automated fluorescence polarization immunoassay (Abbott Laboratories). The RBC and plasma folate estimations were conducted using the Quantaphase II folate/vitamin B12 radioassay (Bio-Rad Laboratories, Hercules, CA, USA) using ^{125}I and ^{57}Co as tracers. Detailed description of the NHANES 2005-2006 survey can be found online at http://www.cdc.gov/nchs/nhanes.htm.

2.2. Outcomes and Predictors. Our primary outcome of interest was presence of self-reported sleep apnea. Although the association of plasma homocysteine has been predominantly examined in the context of OSA, the NHANES sleep questionnaire did not explicitly probe into the type of sleep apnea. We therefore used the diagnosed, self-reported sleep apnea as our outcome of interest. Our primary predictors were plasma homocysteine levels and RBC and plasma folate. However, as described previously using this dataset, there were additional variables that were (or could have been) associated with altered risk of sleep apnea. These variables were age, gender, race, country of birth, obesity, hypertension, ever smoking, and ever alcohol use. We examined the potential association of these sociodemographic and clinical variables with the reported diagnosis of sleep apnea and included the significant variables as secondary covariates in multivariate models. For these analyses, we dichotomized plasma homocysteine, RBC folate, and age based on the basis of the receiver operating characteristic (ROC) curves. The optimum cut-off points for these variables were obtained at $\geq 8.02\,\mu$mol/L, ≥ 279 ng/mL, and ≥ 47 years, respectively. Education status was dichotomized as high (high school or above) or low (up to and including 11th grade), marital status as married or other, obesity was defined as BMI > 28 Kg/m^2, and hypertension was defined as an average (mean of three readings) systolic blood pressure > 140 mmHg and/or a diastolic blood pressure > 90 mmHg. Ever smoking was defined as having smoked at least 100 cigarettes in lifetime while ever alcohol use was defined as having had 12 alcoholic drinks in life time.

2.3. Statistical Analysis. Descriptive statistics included the means and standard errors (for continuous variables) and proportions (for discrete variables). Statistical significance for difference across study groups was assessed using the Student's t test (for continuous variables) or chi-square test (for categorical variables). For binarizing continuous variables, we made use of the ROC and selected the optimum cut-off point by finding the shortest distance from the upper-left corner of the ROC plot. The distance of a point on the ROC from the upper left corner was estimated as $d = \sqrt{((1 - Sn)^2 + (1 - Sp)^2)}$, where Sn is the sensitivity and Sp is the specificity of the binarized variable to predict self-reported sleep apnea. We estimated two important effect measures: age-standardized, design-effect-corrected prevalence rates of self-reported sleep apnea in various subgroups and the design-effect-adjusted multivariate association of the above-mentioned predictors with the risk of self-reported sleep apnea.

To determine the potentially independent association of high plasma homocysteine with self-reported sleep apnea, we decomposed the observed total plasma homocysteine levels into age-independent and age-dependent components using the following approach. We fitted a linear regression model HCY = b^* age + c, where HCY is the plasma homocysteine level, b is the regression coefficient, and c is constant. Using

Table 1: Summary of evidence for and against the association of plasma homocysteine with sleep apnea.

No.	Authors [Ref]	Year	Type of study	*N*	Results
1	Chen et al. [17]	2011	Cross-sectional	102	Severity of OSA is associated with increased homocysteine levels in subjects with ischemic heart disease
2	Basoglu et al. [14]	2011	Case control	36 cases, 34 controls	No association between plasma homocysteine and OSA in obese patients
3	Cintra et al. [18]	2011	Matched case control	75 cases, 75 controls	Cysteine but not homocysteine is differentially distributed across OSA and non-OSA patients
4	Wang et al. [27]	2010	Cross-sectional	83 patients with OSA, 52 without OSA	Oxidative stress might induce high plasma homocysteine levels in elderly patients with OSA
5	Cerbo et al. [16]	2010	Case report	1	Early onset homocystinuria is associated with apneic spells
6	Sariman et al. [25]	2010	Cross-sectional	38 cases of OSA	Plasma homocysteine levels correlate with the severity of OSA
7	Yavuz et al. [28]	2008	Cross-sectional	62 patients of OSA, 12 controls	Plasma homocysteine levels are elevated in patients with OSA
8	Ozkan et al. [23]	2008	Cross-sectional	34 OSA patients, 15 controls	Plasma homocysteine levels are raised in patients with severe OSA
9	Ryan et al. [24]	2007	Cross-sectional	80 patients with OSA, 30 controls	Plasma homocysteine levels are not associated with either the risk or severity of OSA
10	Kumor et al. [21]	2006	Cross-sectional	47 patients of OSA, 12 controls	Plasma homocysteine levels are not differentially distributed across patients and controls of OSA
11	Hachul de Campos et al. [19]	2006	Cross-sectional	38 insomniac postmenopausal women	Plasma homocysteine levels are not associated with risk of apnea
12	Can et al. [15]	2006	Cross-sectional	30 OSA patients, 32 controls	Serum homocysteine levels are significantly higher in OSA patients
13	Kokturk et al. [20]	2006	Cross-sectional	72 OSA patients, 42 controls	Serum homocysteine is significantly increased in patients with OSA
14	Svatikova et al. [26]	2004	Case control	22 OSA patients, 20 controls	Plasma homocysteine levels exhibit diurnal variation and are not differentially distributed across patients and controls of OSA
15	Lavie et al. [22]	2001	Case control	237 cases of OSA, 108 controls	Patients with ischemic heart disease and OSA have elevated plasma homocysteine levels

the results of this model, we generated the two components as $HCY_{dep} = b^*$ age and $HCY_{ind} = HCY - HCY_{dep}$, where the suffixes dep and ind indicate the age-dependent and -independent components, respectively. We then conducted multivariate logistic regression analysis to examine the association of the HCY_{ind} and HCY_{dep} components on the risk of self-reported sleep apnea. For all analyses, we used the svy commands contained in the Stata 12.0 statistical software (Stata Corp, College Station, TX, USA). These commands help account for the survey design effect. The survey was a single-stage, 30-cluster design, and we used the procedure described by the Centers for Disease Control to set the survey data in Stata. To calculate the prevalence rates, we used the svy: mean command with the stdize option while, to conduct the multivariate analyses, we used the svy: estimate command. Statistical significance was evaluated at a type I error rate of 0.05.

3. Results

3.1. Characteristics of Study Subjects. Plasma homocysteine levels, RBC folate levels, sleep questionnaire responses, and demographic information were available on 4490 subjects in the NHANES 2005-2006 dataset of whom 177 (3.94%) reported past diagnosis of sleep apnea. The distribution of the sociodemographic and clinical variables in subjects with and without reported sleep apnea is shown in Table 2. We found that the subjects with self-reported sleep apnea were on an average over 8 years older than subjects who did not report sleep apnea. Interestingly, the proportion of males, non-Hispanic Whites, and subjects born in the US were ~ 18% higher than the respective proportions in subjects with self-reported sleep apnea as compared to those without it. Also, a higher proportion of subjects with self-reported apnea were more educated and married. We also observed that the persons with self-reported sleep apnea had a higher body mass index, a higher percentage of ever smokers, and ever alcohol users as compared to those without sleep apnea. There was no significant difference in the economic status of the families as indicated by the poverty income ratio.

3.2. Prevalence of Self-Reported Sleep Apnea Based on Plasma Homocysteine and RBC Folate Levels. We observed that the mean plasma homocysteine and mean RBC folate levels were

Table 2: Sociodemographic, clinical, and relevant biochemical characteristics of the population included in this study (total $n = 4490$).

Characteristic	Sleep apnea ($n = 177$)	No sleep apnea ($n = 4313$)	P
Age (yrs); mean(SD)	56.5 (15.2)	48.1 (19.0)	<0.001
Males; n (%)	116 (65.5)	2036 (47.2)	<0.001
Race/ethnicity; n (%)			<0.001
Mexican American	11 (6.2)	899 (20.8)	
Other Hispanic	2 (1.1)	136 (3.12)	
Non-Hispanic White	120 (67.8)	2144 (49.7)	
Non-Hispanic Black	40 (22.6)	962 (22.3)	
Others	4 (2.3)	172 (4.0)	
Country of birth; n (%)			<0.001
United States	168 (94.9)	3345 (77.6)	
Mexico	4 (2.3)	583 (13.5)	
Elsewhere	5 (2.8)	385 (8.9)	
Education; n (%)			0.039
Less than 9th grade	10 (5.7)	543 (12.6)	
9–11th grade	20 (11.3)	670 (15.5)	
High school	48 (27.1)	1018 (23.6)	
Some college education	53 (29.9)	1228 (28.5)	
College graduate	46 (26.0)	849 (19.7)	
Refused/do not know	0 (0.0)	5 (0.1)	
Marital status; n (%)			0.016
Married	121 (68.4)	2340 (54.3)	
Widowed	11 (6.2)	388 (9.0)	
Divorced	15 (8.5)	412 (9.6)	
Separated	5 (2.8)	130 (3.0)	
Never married	14 (7.9)	675 (15.7)	
Living with partner	11 (6.2)	365 (8.5)	
Refused to answer	0 (0.0)	3 (0.1)	
Poverty income ratio; mean (SD)	2.84 (1.64)	2.68 (1.59)	0.194
Body mass index (Kg/m^2); mean (SD)	34.90 (0.62)	28.55 (0.10)	<0.001
Ever smoking; n (%)	101 (57.06)	2026 (46.97)	0.008
Ever alcohol use; n (%)	41 (23.16)	682 (15.81)	0.009
Plasma homocysteine (μmol/L); mean (SD)	9.49 (3.75)	8.44 (4.62)	0.003
RBC folate (ng/mL); mean (SD)	326.7 (180.4)	297.0 (135.4)	0.005
Plasma folate (ng/mL); mean (SD)	14.65 (15.4)	13.8 (9.5)	0.255

significantly higher in subjects with self-reported sleep apnea (Table 2), but the mean plasma folate levels were comparable in subjects with or without self-reported sleep apnea. Yet, we found that there was a negative correlation of the plasma homocysteine levels with both the RBC and plasma folate levels ($r = -0.08$, $P < 0.0001$ and $r = -0.03$, $P = 0.0321$, resp.).

Considering the several observed associations of the sociodemographic, clinical, and biochemical variables with self-reported sleep apnea, we first estimated the prevalence of self-reported sleep apnea in various subgroups defined by these variables. We observed (Figure 1) that the overall age-standardized prevalence rate of 4.3% was significantly differential across gender; males had a prevalence rate of ~6% while females had a prevalence of ~2.9%. Thus, we next estimated age-standardized prevalence rates for other subgroups separately for males and females. Since we had observed significant differences in the mean plasma homocysteine and RBC folate (but not plasma folate) across self-reported sleep apnea status, we first categorized these two variables into four groups based on the respective quartiles. The quartiles were generated for all subjects irrespective of the self-reported sleep apnea status. The quartiles for plasma homocysteine were as follows: Q1, <6.23 μmol/L; Q2, 6.23–7.76 μmol/L; Q3, 7.77–9.75 μmol/L; Q4, >9.75 μmol/L. The quartiles for RBC folate were Q1, <207 ng/mL; Q2, 207–268 ng/mL; Q3, 269–354 ng/mL and Q4, ≥355 ng/mL.

We observed that there was a consistent increase in the age-standardized prevalence of self-reported sleep apnea over the four quartiles of plasma homocysteine levels in both

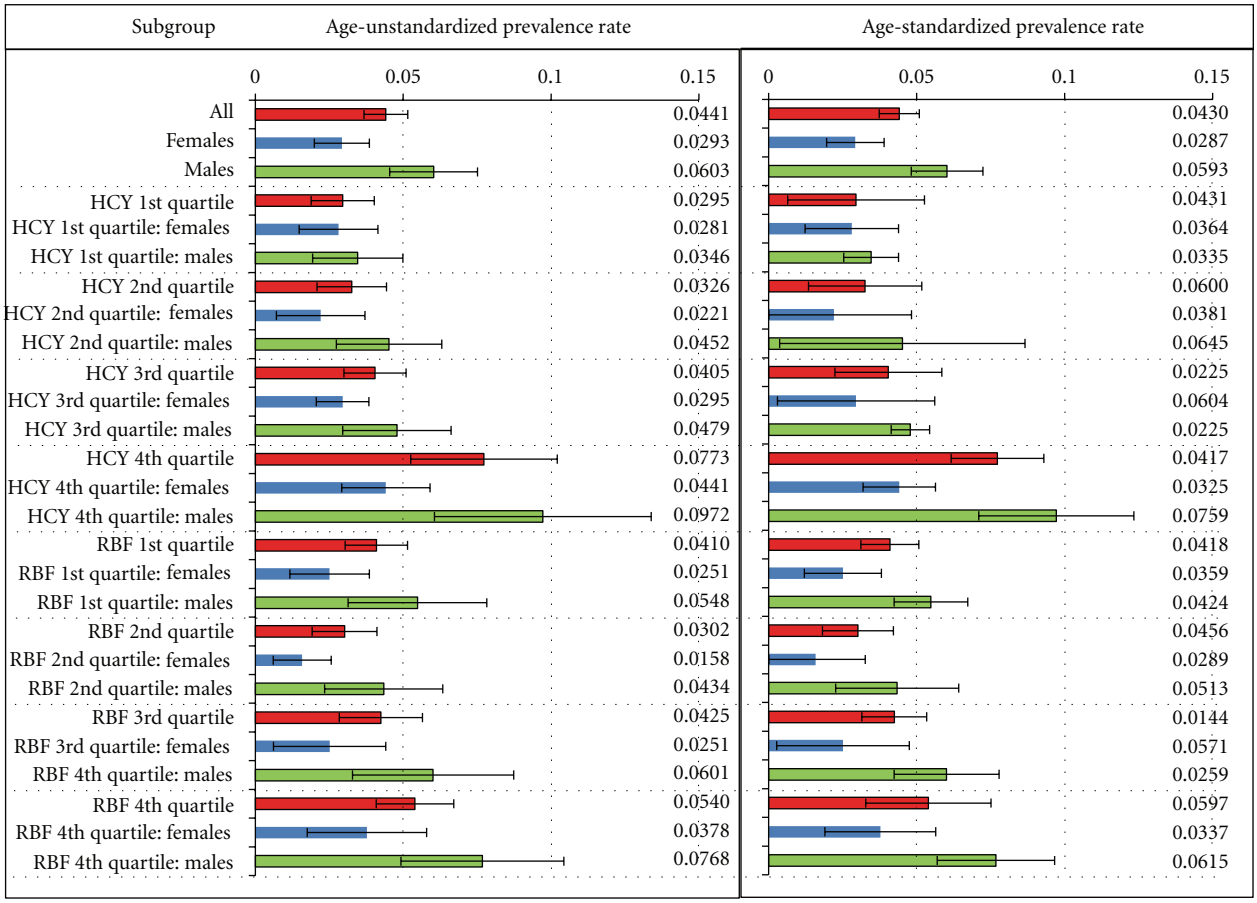

Figure 1: Prevalence of diagnosed, self-reported sleep apnea in the NHANES 2005-2006 dataset based on gender and quartiles of plasma homocysteine and RBC folate. The plot on the left is not standardized for age while the plot on the right shows age-standardized rates. Prevalence rates are shown as horizontal bars, and the estimates are indicated by the value at the right side of the plots. Error bars indicate the 95% confidence interval for the prevalence rates. Prevalence rates are shown for all subjects (red bars), females only (blue bars) and males only (green bars). Range of values for plasma homocysteine and RBC folate represented by their respective quartiles is described in text. HCY: plasma homocysteine; RBF: RBC folate.

males and females albeit the prevalence rates were always lower in females. However, a similar consistent trend was not observed for the quartiles of RBC folate. With the exception of the lowest quartile for RBC folate, the remaining three quartiles demonstrated a consistent increase in the age-standardized prevalence of self-reported sleep apnea. Again, this trend was observed in males as well as females with consistently lower rates in females.

We next estimated the age-standardized prevalence rates for a combination of the plasma homocysteine and RBC folate quartiles (Figure 2). We found some interesting patterns in these analyses. First, females with very low levels of plasma homocysteine as well as RBC folate had a very high prevalence of self-reported sleep apnea. Second, low levels of both plasma homocysteine and RBC folate were associated with a very low prevalence of self-reported sleep apnea in males. Third, highest prevalence of self-reported apnea in the males was found in those who had high level of both plasma homocysteine and RBC folate. Fourth, the mechanistically expected high prevalence of self-reported apnea in the low RBC folate/high plasma homocysteine subgroup was observed in males only but not in females. Together these findings indicated that there existed a complex and surprising combinatorial association of plasma homocysteine and RBC folate levels with self-reported sleep apnea.

3.3. Multivariate Association of Plasma Homocysteine and RBC Folate with Self-Reported Sleep Apnea. With the use of a series of 20 nested multivariate logistic regression models, we determined if inclusion of epidemiologically importantsignificant covariates influenced the association of plasma homocysteine and RBC folate with self-reported sleep apnea (Figure 3). When no covariates were included along with the two primary predictors, we found that both were independently associated with the risk of self-reported sleep apnea (Model 1, Figure 3). The addition of other important variables like gender, non-Hispanic White race, birth in the United States, education, marital status, obesity, ever smoking, and ever alcohol use somewhat decreased the strength of the associations of plasma homocysteine and RBC folate with self-reported sleep apnea, however, in most instances,

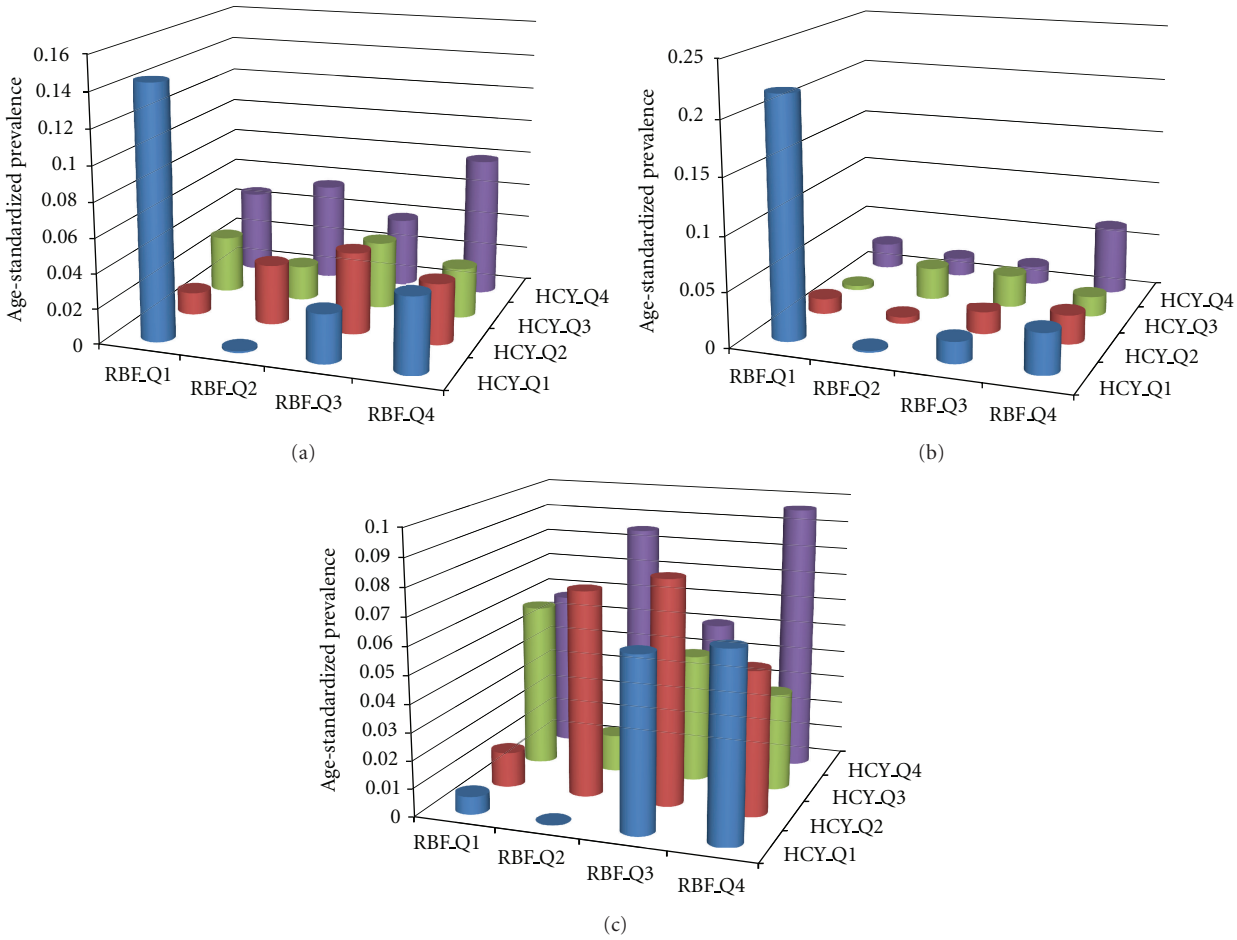

Figure 2: Age-standardized prevalence rates of diagnosed, self-reported sleep apnea based on combinations of quartiles of plasma homocysteine and RBC folate levels. Plots are for all subjects (a), females only (b), and males only (c). HCY: plasma homocysteine; RBF: RBC folate; Q: quartile.

the associations retained their statistical significance. Interestingly however, when age was added to the multivariate model (Models 10 and 18, Figure 3), the significance of both plasma homocysteine and RBC folate reduced drastically. The results of the full model (Model 18 in Figure 3) are shown in detail in Table 3.

It is noteworthy that high BMI, male gender, age > 46 years, alcohol use, high education, and married status continued to demonstrate independent association with self-reported sleep apnea in a multivariate context, but the association of high plasma homocysteine and high RBC folate became statistically insignificant (Table 3). Indeed, all the multivariate models (Models 18, 19, 20) that contained age as a covariate demonstrated a nonsignificant association of plasma homocysteine and folate with self-reported sleep apnea. Since the information of hypertension and cardiovascular disease was not available on large number of study subjects, we added these variables to the full model (Model 18) and observed that the strength as well as significance of the association of plasma homocysteine and RBC folate with self-reported sleep apnea was further diminished (Models 19 and 20).

Table 3: Results from the full multivariate logistic regression analysis (Model 18 in Figure 3) for the outcome of self-reported sleep apnea.

Covariate	OR	95% CI	*P*
High plasma homocysteine	1.24	0.85–1.83	0.244
High RBC folate	1.26	0.84–1.89	0.252
Male gender	2.22	1.45–3.4	0.001
Non-Hispanic White race	1.21	0.74–1.96	0.420
Birth in the United States	1.89	0.93–3.82	0.073
BMI > 28 Kg/m^2	7.56	4.14–13.79	<0.001
High education	1.71	1.21–2.41	0.005
Married	1.60	1.07–2.39	0.025
Ever smoker	1.28	0.76–2.14	0.334
Ever alcohol use	2.01	1.3–3.11	0.004
Age > 46 years	2.19	1.39–3.44	0.002

OR: odds ratio; CI: confidence interval; *P*: significance value.

The results presented thus far indicated a strong potential influence of age on the association of plasma homocysteine

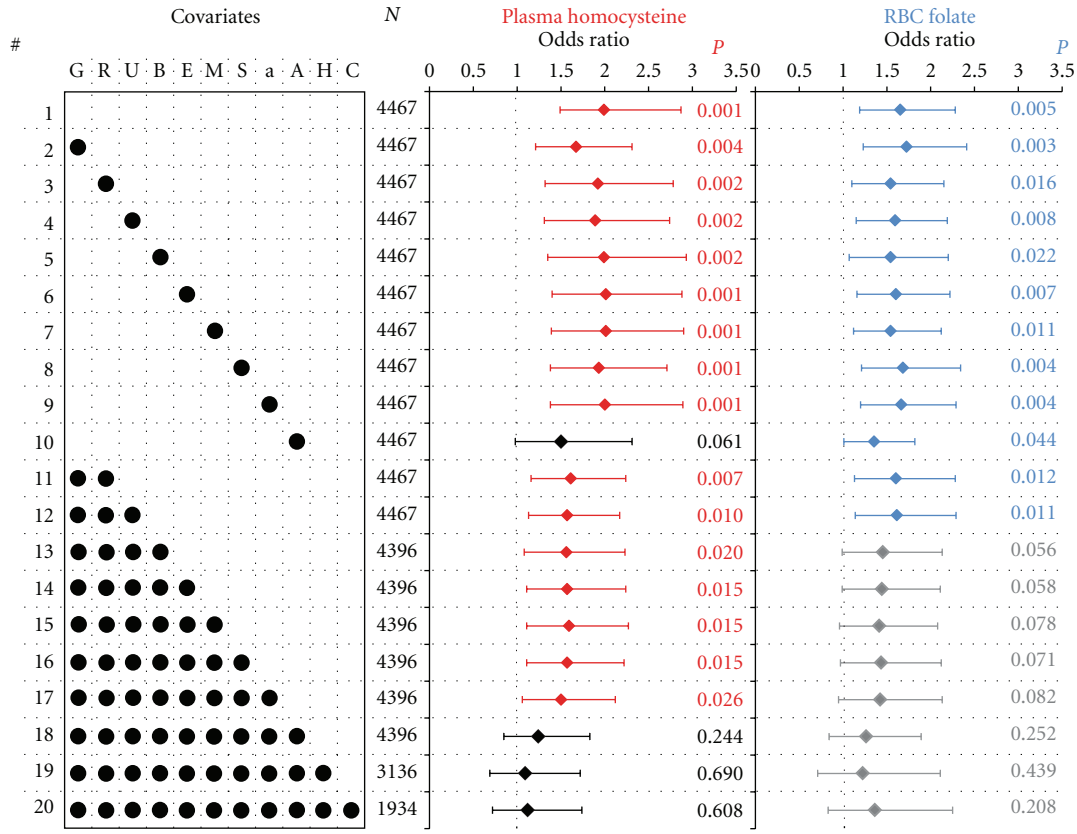

FIGURE 3: Multivariate association of high plasma homocysteine and RBC folate levels with the risk of self-reported sleep apnea. Results are shown as point (diamonds) and 95% confidence intervals (error bars) for odds ratios estimated through a series of nested logistic regression commands. Twenty logistic regression models (indicated by # on the left) were run with varying combinations of covariates. The covariates included were G: male gender; R: non-Hispanic white race; U: birth in the United States; B: body mass index > 28 Kg/m^2; E: high education; M: married; S: ever smoker; a: ever alcohol use; A: age > 46 years; H: hypertension; C: cardiovascular disease. Model 1 contained only high plasma homocysteine and high RBC folate as the independent variables. The results from models 19 and 20 cannot be directly compared with the remaining 18 models since the information for hypertension and cardiovascular disease was not available for a large number of subjects (shown under column titled *N*). Statistically significant associations (when the error bars did not straddle unity indicated by dashed vertical lines) are shown in red color for high plasma homocysteine and in blue color for high RBC folate. Statistically nonsignificant associations are shown in black color for plasma homocysteine and gray color for RBC folate. Statistical significance is shown on individual plots as color-coded *P* values.

with self-reported sleep apnea. Considering the disposition of the survey data that we analyzed, we further refined our analyses. We examined if the strong positive correlation of age with plasma homocysteine levels ($r = 0.38$, $P < 0.0001$) masked the potentially true, independent association of plasma homocysteine with self-reported sleep apnea. We found that the odds ratio associated with a unit increase in the HCY_{dep} levels was 1.51 (95% confidence interval 1.36–1.68), $P < 0.0001$ while that for a unit increase in HCY_{ind} was 1.02 (95% confidence interval 0.99–1.05), $P = 0.189$. These results demonstrated that the observed overall association of the plasma homocysteine levels with the risk of self-reported sleep apnea was indeed due to age.

4. Discussion

In this large, nationally representative sample of noninstitutionalized US subjects, we observed that plasma homocysteine is not independently associated with an altered risk of self-reported sleep apnea. Further, we found that age was the most important confounding factor that could have contributed to an apparent association of plasma homocysteine with the risk of self-reported sleep apnea. It has been shown by other investigators in differing contexts [31–34] that plasma homocysteine levels increase with age. It is also very well recognized that the risk of cardiovascular morbidity rises with age as well as plasma homocysteine levels. However, this concomitant elevation of homocysteine with age appears to be associative rather than causal in the context of sleep apnea. As identified by Lavie et al. [22], Svatikova et al. [26] and Winnicki and Palatini [9] sleep apnea and high plasma homocysteine levels can independently and additively increase the risk of subsequent cardiovascular morbidity; however, a potentially causal link between elevated plasma homocysteine and sleep apnea does not seem to be operative from our results.

Interestingly and intriguingly, we observed a positive association of the RBC folate levels with the risk of self-reported sleep apnea in spite of a mild negative correlation between

RBC folate and plasma homocysteine levels. Further, despite a strong positive correlation between plasma and RBC folate ($r = 0.49$, $P < 0.0001$; data not shown), we observed that plasma folate levels were not associated with an altered risk of self-reported sleep apnea. These observations have two important implications. First, these findings indicate that initial enthusiasm generated by the possibility of vitamin supplementation aimed at reducing the prevalence of sleep apnea may be an oversimplification of the apnea challenge. For example, even though folate fortification of grains has been attributed with a decrease in homocysteine levels as well as cardiovascular morbidity [35], such a decrease has not been observed in the prevalence of sleep apnea in the United States. Second, the National Pathology Alliance benchmarking guidelines [36] stipulate that RBC and plasma folate can act as surrogates of each other and that no additional insights are gained by screening samples by both these methods. However, our results demonstrate that these methods may not be redundant and that differential insights can be obtained by a careful examination of the results. Thus, the issue deserves a closer investigation.

Although recruiting a large, representative sample, the current study was an observational study, and, therefore, all limitations implicit in such study designs and compounded by the survey sample selection should be considered while interpreting these results. In addition, it should be noted that the NHANES survey methodology did not use established apnea screening questionnaires but rather recorded self-reported sleep apnea. Therefore, there exist possibilities of missed diagnoses and a consequent misclassification bias. Despite these limitations, our results indicate that increased plasma homocysteine levels, augmented cardiovascular morbidity, and enhanced risk and prevalence of self-reported sleep apnea may actually be representing a syndromic constellation of the aging phenomenon. Consequently, more involved and intense efforts to understand the genetic and environmental contribution and interaction need to be undertaken before a mechanistic understanding, and the public health implications thereof can be fully realized.

Authors Contribution

T. P. Thakre and M. Mamtani have contributed equally to this paper.

Conflict of Interests

The authors have no conflict of interests to declare.

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