Assessment of Multiple Health Risks in a Single Obstructive Sleep Apnea Population

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Study Objectives: In order to provide a comprehensive estimate of the health risks for OSA patients, we analyzed multiple outcomes and independent predictors of these outcomes in an OSA population evaluated and followed at one sleep center.

Methods: Cox proportional hazard regression analyses were used in an 8-year follow-up analysis of consecutive OSA patients (N = 1025) and non-apneic snorers (apnea-hypopnea index < 5, N = 494).

Results: In our fully adjusted model, independent variables predictive of all-cause mortality, myocardial infarction, cerebral vascular accident, and pulmonary embolus were: older age, male gender, and history of cardiovascular diseases or procedures. In examining subgroups based on age and gender, severe OSA (AHI ≥ 30) was one of the independent predictors of mortality in males and in patients < 50 years old. Severe

OSA interacted with maleness, age, and hypertension to predict mortality and myocardial infarction. CPAP use ≥ 4 h/night was associated with lower mortality rates in males and those ≥ 50 years old with severe OSA.

Conclusions: Mortality and cardiovascular event outcomes were predicted by demographics and cardiovascular disease history more commonly than by OSA severity. OSA severity was an important predictor of mortality in male and young OSA patients. CPAP use appeared protective in older and male severe OSA patients.

Keywords: Sleep apnea, myocardial infarction, cerebral vascular accident, pulmonary embolus

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Previous population- and clinic-based epidemiologic studies of obstructive sleep apnea (OSA) patient samples have examined the relationship between OSA severity and individual outcomes: mortality or acute cardiovascular (CV) event incidences. The purpose of this study was to identify demographic and clinical variables associated with the incidences of multiple outcomes: all-cause mortality, myocardial infarction, cerebral vascular accident and pulmonary embolus. We analyzed the interaction of these factors simultaneously among four groups of sleep center referral patients based on apnea hypopnea indices (AHI): < 5, 5–14, 15–29 and > 30.

Study Impact: In an urban sleep center sample, with a high concentration of obese young males, African Americans and patients with severe OSA, we found that CV histories were more often predictive of adverse outcomes than OSA severity; in young male patients, severe OSA also was predictive of mortality, which appeared to improve with CPAP use. In similar OSA populations, we propose that major health outcomes will be affected primarily by CV disease.

METHODS

Patient Sample

Patients 18 years of age, or older who underwent evaluation at the Henry Ford Sleep Disorders and Research Center in 2001 and 2002 diagnosed with either primary snoring or obstructive sleep apnea were studied (N = 1691). The Henry Ford Hospital electronic medical records (EMR), consisting of a wide breadth of data of patient care delivery, Sleep Center

Several population-based¹⁻¹⁰ and clinic-based¹¹⁻²⁶ retrospective and prospective studies have documented an increased incidence of death and cardiovascular events in obstructive sleep apnea (OSA) patients relative to different control groups. In separate studies, using different methodologies in different patient populations, OSA patients, usually those with untreated severe OSA (often defined as an apnea-hypopnea index [AHI] ≥ 30 events/h) have been shown to be at increased risk for mortality or major cardiovascular (CV) events, such as myocardial infarction (MI) and cerebral vascular accident (CVA). However, in nearly all of these studies, OSA severity was analyzed as a predictor of only one outcome, thereby limiting the clinical usefulness of these studies. The clinician must deal with OSA patients who are potentially facing several significant health risks simultaneously; therefore, assessment of multiple major health risks within an OSA clinic population would aid the sleep medicine clinician in the evaluation and care of OSA patients within that population, possibly contributing to an improvement in overall health quality. Assuming similarity in patient characteristics of OSA patient sample studied with other OSA patient populations, the results of this study would be generalizable.

A commentary on this article appears in this issue on page 19.

In this study, we evaluated the incidences of all-cause mortality, MI, CVA, and pulmonary embolus (PE) simultaneously and determined the predictors of these outcomes in a single large urban OSA population over an 8-year period.

diagnostic and continuous positive airway pressure (CPAP) polysomnogram (PSG) records were abstracted retrospectively. Complete data were available on 1519 patients, our study sample. From records of these patients, we collected age, gender, race, address of residence, the date of their initial clinic visit, and height and weight (calculated BMI) at the time of their initial consultative clinic appointment. The results of the polysomnogram were examined, and the apnea-hypopnea index (AHI) data were collected. Patients with an AHI of 0 to < 5 were classified as non-apneic snorers, 5-14 as mild OSA, 15-29 as moderate OSA, and ≥ 30 as severe OSA. The EMR was used to identify medical histories of hypertension (HTN), myocardial infarction (MI), cerebral vascular accident (CVA), pulmonary embolus (PE), congestive heart failure (CHF), diabetes mellitus (DM), asthma, chronic obstructive lung disease (COPD), and a history of invasive cardiovascular diagnostic and therapeutic procedures (CP) conducted prior to the patient's initial Sleep Center clinic visit. Cardiac procedures were any direct cardiac surgery, diagnostic catheterization or any therapeutic catheterization for coronary artery disease, intractable arrhythmia, cardiac valvular repair or replacement, or repair of aortic or major vessel atherosclerotic narrowing or aneurysm. The determination of these entities was made from physician notes, EMR problem lists and the EMR listing of diagnostic codes (International Classification of Diseases, 9th Edition, Clinical Modification [ICD-9-CM]) and procedure codes (Current Procedural Terminology, Version 4 [CPT4]). The date(s) of the occurrence of one or more of our outcome variables (all-cause mortality, MI, CVA, and PE), from the date of a patient's diagnostic PSG to December 31, 2008, was/were recorded. Death ascertainment was obtained by using both recorded death in the EMR and by linking patients by social security number to the Michigan Death Certificate Database. OSA patient records were reviewed for OSA treatment documentation. Patients treated with CPAP were placed in a treatment subgroup. Those patients who underwent pharyngeal surgery or chose isolated weight loss therapy were not included in the analysis. Follow-up visit records were reviewed to obtain data on CPAP adherence (see below). If BMI was not found in the EMR within one year of the patient's initial visit to the sleep center, that patient was eliminated from the data set. In order to provide more information, subgroup analyses were conducted examining results for males, females, and for patients < 50 and ≥ 50 years old (yo).

Polysomnography

The montage of the diagnostic polysomnography included recordings of central and occipital electroencephalograms, electroculograms, submental electromyograms, and electrocardiogram. Airflow was measured by a nasal/oral thermistor and by nasal pressure. Leg electromyogram (anterior tibialis) was also recorded. Patients were studied during their usual sleeping hours. They were monitored in bed for 8 h. All studies were conducted and scored using previously published criteria.²⁷ Obstructive apneas were scored as $\geq 80\%$ decrease in nasal/oral flow or pressure with persistent thoracic and/or abdominal respiratory activity ≥ 10 sec. Obstructive hypopneas were scored when the following occurred: a 50% to 80% drop in either nasal/oral thermistor flow or the same degree of drop in nasal

pressure with an accompanying > 3% drop in arterial oxygen saturation or an > 3 sec arousal. Central apnea was defined as an absence of nasal/oral flow or pressure and thoracic and abdominal respiratory effort ≥ 10 sec.

CPAP Adherence

CPAP machine nightly average hours of use was determined by reviewing the return clinic notes. CPAP adherence was checked at the time of all follow-up visits. Medical assistants determined the average hours of nightly CPAP use by dividing the increase in the CPAP machine hour timer reading from the most recent return visit or start of therapy, to the current return visit by the interval number of days, thereby providing an average number of hours of nightly CPAP use. If CPAP adherence was checked in more than one follow-up visit, the CPAP hours of use/night calculated at each visit were averaged. (These CPAP adherence data were collected before the availability of CPAP machines that provided night-by-night CPAP adherence data). CPAP adherence was defined as ≥ 4 h/night average CPAP use. OSA patients with CPAP use ≥ 4 h/night were scored as "CPAP adherent." Patients prescribed CPAP who did not use the machine an average of ≥ 4 h/night or those who were offered but refused CPAP therapy were scored as "non-CPAP adherent."

Data Abstraction

Study variables were recorded on study patients by one research technician, trained and supervised for this task. Study data and identified clinical variables were placed into a computer spread sheet.

EMR Abstraction Accuracy

To test for consistency of data abstraction, after completion of the patient record abstraction for the entire population, 80 randomly selected records were re-abstracted by the same technician. This secondary record abstraction occurred months after the initial data abstraction, diminishing the chance for memory for individual patient records. Differences between the 2 abstractions on these 80 records were: Weight, N = 10, mean difference = 7 kg; Height, N = 5, mean difference = 7 cm; Age, N = 2, Mean difference = 9 years. In the analysis of treatment (CPAP or no CPAP group determination), four patients were categorized differently between the initial data abstraction and the verification abstraction.

Data Analysis

Multivariable Cox proportional hazards regression analysis, which involved proportional hazards survival modeling, was used to evaluate the independent variables of interest (apnea severity group, age, African American race, male gender, BMI, history of specific risk factors, and prior history of cardiopulmonary disease diagnoses mentioned above) as predictors of each potential outcome during the follow-up period. Outcomes were all-cause mortality, MI, CVA, and PE. Age and BMI were analyzed as continuous variables. Other variables were analyzed in a non-continuous fashion, by referencing the specified category of patients to all others. The Cox analysis was applied to each OSA severity level (mild, moderate, and severe) relative to the snorer (AHI < 5) group. The occurrence of each individu-

Table 1—Baseline characteristics of the study population

Variable	All Participants N = 1519	Snoring AHI < 5 N = 494	Mild Apnea AHI 5-14 N = 371	Moderate Apnea AHI 15-29 N = 226	Severe Apnea AHI ≥ 30 N = 428	Group Comparison p-value
Age ^a , years	49.3 ± 12.2	47.8 ± 12.3	50.1 ± 12.0	51.5 ± 11.6	49.1 ± 12.3	< 0.01
Age ≥ 50	48.5	45.3	51.2	54.0	47.0	0.10
Number	737	224	190	122	201	
BMI ^a , kg/m ²	36.8 ± 10.1	34.0 ± 9.1	37.0 ± 10.6	37.1 ± 9.8	39.9 ± 9.9	< 0.01
Male Gender ^b	62.4	48.8	60.1	70.8	75.7	< 0.01
Number	948	241	223	160	324	
AA Race	35.2	33.4	32.3	33.6	40.4	0.06
Diabetes ^{b,c}	16.5	14.4	14.6	18.6	19.6	0.09
Asthma	11.5	14.6	11.6	9.7	8.6	0.03
COPD	7.3	8.3	8.1	5.8	6.3	0.47
HTN	40.3	34.6	41.2	44.2	43.9	0.01
MI	1.0	0.4	1.3	0.4	1.6	0.19
CVA	1.8	1.8	1.1	2.7	1.9	0.56
PE	1.6	1.2	1.3	1.3	2.3	0.52
CHF	10.3	8.5	9.2	9.7	13.8	0.05
Cardiac Procedure	0.3	0.2	0.0	0.4	0.5	0.57

COPD, chronic obstructive pulmonary disease; HTN, hypertension; MI, myocardial infarction; CVA, cerebral vascular accident; PE, pulmonary embolus; CHF, congestive heart failure. ^aContinuous data is summarized as mean ± standard deviation. Comparison testing was performed using analysis of variance.

^bCategorical data are summarized as PERCENT. Comparison testing was performed using χ^2 . ^cHistory of this diagnosis or event. Same for all subsequent rows.

al outcome was calculated allowing a given patient to be identified for multiple outcomes. If a patient died during the course of the study, his/her data prior to death contributed to the non-fatal outcome analyses. Cox analysis was repeated for the 2 gender subgroups (males and female) and 2 age subgroups (< 50 and ≥ 50 years of age). This age division was chosen because it had been used previously by other investigators at our center.¹

CPAP Adherence

Since CPAP therapy was not offered to snorers, Cox regression analysis was used to evaluate the association of CPAP adherence with the mortality outcome within each separate OSA severity level (insufficient power to analyze other outcomes).

Interaction Analysis

Additional Cox regression modeling was performed with covariates included for the potentially influential interactions between apnea status and the other regression variables for the mortality and MI outcomes.

P-value ≤ 0.05 was considered significant. Due to the large number of regression models evaluated in this study, p-values between 0.01 and 0.05 indicated borderline significance.

The study was approved by the Henry Ford Health System Institutional Review Board.

RESULTS

Study Population

The baseline demographic characteristics and disease history data of the population studied obtained from EMR at the time of the initial Sleep Center evaluation are shown in

Table 1. Also, the number of individuals in each snorer and OSA severity patient group, as well as the number of patients in each age and gender subgroup used in the Cox analysis is shown. There was nearly an equivalent number of subjects < or ≥ 50 yo in the study group. There were significant differences in age, body mass index (BMI), and proportion of males across the study groups of snorers, mild, moderate, and severe OSA patients (all $p < 0.01$) (**Table 1**). Forty-two percent of the OSA population had severe OSA (AHI ≥ 30). Fifty-three percent of the severe OSA patients were under 50 years old; therefore, it was not the oldest group. Twenty-four percent of this group were female; 51% of snorers were females. The highest proportion of males ($p < 0.01$), the highest mean BMI ($p < 0.01$), the highest proportion of African Americans (AA) ($p = 0.06$), the highest prevalence of congestive heart failure (CHF) ($p = 0.05$) and the lowest prevalence of asthma ($p = 0.03$) was found in the severe OSA group. There was no significant difference in prevalence of other pulmonary/cardiovascular disease histories or cardiovascular procedure histories across the apnea/snorer groups (**Table 1**).

Outcomes

The mean follow-up duration was 5.3 ± 2.3 (SD) years, with a median time of 6.3 years. The rates of outcome occurrences per 1000 patient days for the study population are shown in **Table 2**. For all outcomes except CVA, severe OSA patients experienced the greatest number of adverse events—a total of 42/1000 patient days in the severe OSA group vs. 30 events/1000 patient days in the mild OSA group. The number of adverse events within the gender and age subgroups is shown in **Table 3**. Ninety-five deaths (6.3% of the population) were recorded; nearly 10% of the ≥ 50 OSA age group died. Although

Table 2—Whole population outcome rates (events per 1000 person-years)

Outcome	Snorers N = 494	Mild Apnea N = 371	Moderate Apnea N = 226	Severe Apnea N = 428
Death	9.36	10.81	11.33	15.25
MI ^a	9.61	7.34	8.34	10.43
CVA ^a	10.10	7.93	11.70	7.82
PE ^a	5.58	4.18	4.93	8.25

^aMI, myocardial infarction; CVA, cerebral vascular accident; PE, pulmonary embolus.

there were nearly twice as many male deaths as female deaths, the proportion of deaths in each gender was similar, 6.5% in males and 5.8% in females. The majority of non-fatal cardiovascular event outcomes occurred in males and in the ≥ 50 age group, except there was a nearly equivalent incidence of CVA in the male and female OSA patients (**Table 3**). Approximately one-fourth of deaths and MIs and one-third or more of CVAs and PEs occurred in the < 50 yo age group (**Table 3**). Event occurrences on a time basis are shown in the Kaplan-Meier plots (**Figure 1**).

The effect of elimination of patients because of missing data was minor. The largest group of patients eliminated from the

Table 3—Number of adverse events in the sleep clinic population sampled

Outcome	Male N = 948	Female N = 571	< 50 yo N = 782	≥ 50 yo N = 737	Whole Group N = 1519
Death	62 (6.5 ^c) (65.3 ^d)	33 (5.8) (34.7)	23 (2.9) (24.2)	72 (9.8) (75.8)	95 (6.3 ^b)
MI ^a	44 (4.6) (61.1)	28 (4.9) (38.9)	17 (2.2) (23.6)	55 (7.5) (76.4)	72 (4.7)
CVA ^a	38 (4.0) (52.8)	34 (6.0) (47.2)	24 (3.1) (33.3)	48 (6.5) (66.7)	72 (4.7)
PE ^a	31 (3.3) (66.0)	16 (2.8) (34.0)	19 (2.4) (40.4)	28 (3.8) (59.6)	47 (3.1)

^aMI, myocardial infarction; CVA, cerebral vascular accident; PE, pulmonary embolus. ^b% of total population, 1519. ^cNumbers in () are the % of each group, whole group or subgroups: males, females, < 50 yo, ≥ 50 yo. For instance, 6.5% of males and 5.8% of females died. ^dItalicized numbers in () are the % of the outcome, such as death, within each of the gender or age subgroups. For instance, 65.3% of deaths occurred in males and 34.7% of the deaths occurred in females, etc.

Figure 1—Kaplan-Meier plot of all-cause mortality, myocardial infarction, cerebral vascular accident, and pulmonary embolism data for snorers, mild OSA, moderate OSA, and severe OSA

Probability is plotted from 0.90 to 1.00.

Table 4—Cox regression analysis for predicting all-cause mortality in the 1519 study patients

Variable	Hazard Ratio	95% Hazard Ratio Confidence Limits		p-value
Mild apnea (vs. snorer)	0.96	0.52	1.74	0.88
Moderate apnea (vs. snorer)	1.08	0.54	2.15	0.83
Severe apnea (vs. snorer)	1.27	0.70	2.33	0.43
BMI ^a	1.01	0.99	1.04	0.23
Age ^a	1.06	1.04	1.08	< 0.01
Male	1.81	1.10	2.97	0.02
Race	1.37	0.89	2.11	0.16
AA vs. non-AA				
Hx DM	1.17	0.72	1.91	0.53
Hx Asthma	0.84	0.47	1.53	0.58
Hx COPD	1.60	0.90	2.84	0.11
Hx HTN	0.77	0.47	1.28	0.31
Hx MI	1.77	0.62	5.03	0.29
Hx CVA	2.14	0.93	4.91	0.07
Hx PE	0.93	0.39	2.23	0.87
Hx CHF	3.55	2.10	5.99	< 0.01
Hx Cardiac Procedure	1.33	0.14	12.81	0.81

^aContinuous variables. HR's are for 1 unit change in for BMI (kg/m²) and for 1 year change in age.

final grouping lacked height information needed for the calculation of BMI. In the 33 patients within this group, the prevalence of the following variables relative to the prevalence of these variables in the final study group was: history of DM (33% vs. 17%), history of asthma (27% vs. 12%) and history of CHF (30% vs. 10%). These exclusions accounted for 7%, 5%, and 6% fewer patients in each of those diagnostic categories within the final grouping, respectively. The level of OSA severity (snorers, mild, moderate, and severe OSA) did not differ, nor did demographic data or the prevalence of histories of HTN, COPD, MI, CVA, or PE differ between the excluded and included patients.

Adjusted Cox Model Results

Continuous Variables, Age, and BMI as Predictors of Outcomes

For the fully adjusted Cox regression model, advancing age predicted all-cause mortality, MI, and CVA (Tables 4, 5). The association between BMI and outcome variables was low (Tables 4, 5). In the gender subgroup analysis, age predicted all-cause mortality, MI, CVA, and PE in males, and PE in females. BMI also was a significant predictor of PE in males and all-cause mortality in females.

Categorical Variable Predictors of Outcomes

WHOLE GROUP ANALYSIS

In the fully adjusted Cox regression model for all-cause mortality, MI, and PE, there was a stepwise increase in hazard ratio (HR) as OSA severity increased (Table 4). However, all correla-

Table 5—Cox regression analysis for predicting cardiovascular diseases in the 1519 study patients

Variable	Hazard Ratio	95% Hazard Ratio Confidence Limits		p-value
Myocardial Infarction ^b				
Mild apnea (vs. snorer)	0.66	0.33	1.30	0.23
Moderate apnea (vs. snorer)	0.95	0.44	2.06	0.89
Severe apnea (vs. snorer)	1.07	0.55	2.08	0.85
BMI ^a	1.00	0.97	1.03	0.97
Age ^a	1.03	1.01	1.05	0.01
Male	1.53	0.88	2.65	0.13
Hx HTN	1.79	0.98	3.26	0.06
Hx MI	1.22	0.29	5.11	0.79
Hx CVA	2.99	1.23	7.25	0.02
Hx CHF	2.72	1.49	4.98	< 0.01
Cerebral Vascular Accident ^b				
Mild apnea (vs. snorer)	0.93	0.48	1.79	0.82
Moderate apnea (vs. snorer)	1.23	0.61	2.48	0.56
Severe apnea (vs. snorer)	0.73	0.36	1.46	0.37
BMI ^a	0.97	0.94	1.00	0.03
Age ^a	1.03	1.01	1.06	0.01
Male	0.86	0.51	1.45	0.56
Hx HTN	0.83	0.47	1.47	0.52
Hx CVA	4.98	2.22	11.19	< 0.01
Hx CHF	2.31	1.20	4.45	0.01
Hx Cardiac Procedure	12.83	1.91	85.97	0.01
Pulmonary Embolus ^b				
Mild apnea (vs. snorer)	0.59	0.24	1.43	0.24
Moderate apnea (vs. snorer)	0.74	0.27	2.06	0.56
Severe apnea (vs. snorer)	0.92	0.39	2.16	0.84
BMI ^a	1.03	1.00	1.07	0.03
Age ^a	1.02	1.00	1.05	0.09
Male	1.94	0.96	3.94	0.07
Hx MI	2.27	0.51	10.16	0.29
Hx PE	2.65	0.90	7.79	0.08
Hx CHF	2.50	1.13	5.55	0.02
Hx Cardiac Procedure	3.02	0.24	37.49	0.39

^aContinuous variables. HRs are for 1 unit change in for BMI (kg/m²) and for 1 year change in age. ^bCardiovascular diseases = HR < C.S. not presented.

tions between any level of OSA severity and any outcome were not significant. The highest HR for any outcome and OSA severity was the HR of severe OSA related to mortality, 1.27 (95% CI = 0.70–2.33). The predictive factor with the highest HR for all-cause mortality was a history of CHF, (HR 3.55 [95% CI =

2.10–5.99], **Table 4** and **5**). The most common predictors of MI were histories of CVA (HR = 2.99 [95% CI = 1.23–7.25]) and CHF (HR = 2.72 [95% CI = 1.49–4.98]; **Table 5**). CVA incidence was most prominently associated with histories of a cardiac procedure (HR = 12.83 [95% CI = 1.91–85.97]), CVA (HR = 4.98 [95% CI = 2.22–11.19]), and CHF (HR = 2.31 [95% CI = 1.20–4.50]; **Table 5**). PE was most accurately predicted by a histories of PE (HR = 2.67 [95% CI = 0.90–7.79]) and CHF (HR = 2.50 [95% CI = 1.13–5.55]), but most commonly by a history of a cardiac procedure (HR = 3.02 [95% CI = 0.24–37.49]; **Table 5**).

SUBGROUP ANALYSIS

The best predictors of outcomes for the subgroups were:

1. Age < 50 yo. All cause-mortality for OSA patients < 50 years was predicted by the presence of severe OSA (HR = 2.76 [95% CI = 1.00–7.57]; $p = 0.05$), and also significantly by histories of CVA, MI, and CHF. MI was predicted by AA race (HR = 3.04 [95% CI = 1.04–8.91]; $p = 0.04$). CVA was predicted by histories of CVA (HR = 7.44 [95% CI = 1.35–41.07]; $p = 0.02$) and CHF (HR = 6.07 [95% CI = 1.79–20.59]; $p < 0.01$). PE was predicted by CHF

(HR = 5.30 [95% CI = 1.48–19.05]; $p = 0.01$) and maleness (HR = 4.34 [95% CI = 1.00–18.76]; $p = 0.05$). Other than its effect on mortality, OSA severity was not associated with MI, CVA, or PE in these younger OSA patients.

2. Age ≥ 50 yo. CHF, CVA, COPD and maleness were associated with mortality, MI and CVA outcomes. There were no significant predictors of PE in this older cohort. OSA severity was not associated with outcomes in these older OSA patients.
3. Males. All-cause mortality was predicted by OSA severity (HR = 3.28 [95% CI = 1.40–7.66]; $p < 0.01$) and a history of CHF (HR = 3.65 [95% CI = 1.80–7.40]; $p < 0.01$). AA race and cardiovascular disease histories were predictors of MI, CVA, and PE. OSA severity was not associated with these latter outcomes.
4. Females. All-cause mortality was predicted by histories of CHF (HR = 4.92 [95% CI = 2.12–11.41]; $p < 0.01$) and CVA (HR = 3.61 [95% CI = 1.22–10.70]; $p = 0.02$). MI was predicted by histories of HTN and CVA. CVA and PE were predicted by histories of CVA and PE, respectively, and both by a history of CHF. OSA severity was not predictive of any outcome in female OSA patients.

Table 6—Interactions of independent variables with severe OSA versus non-severe apnea/snorer to predict outcome

Outcome/Interaction	Hazard Ratio	95% Hazard Ratio Confidence Limits		p-value
All-cause Mortality				
BMI	0.43	0.17	1.07	0.07
Age	0.54	0.22	1.30	0.17
Male	5.15	1.38	19.20	0.02
Race AA	1.48	0.61	3.63	0.39
Hx of COPD	2.01	0.65	6.22	0.23
Hx of CVA	0.18	0.02	2.02	0.17
Hx of CHF	0.90	0.33	2.46	0.84
Myocardial Infarction				
Age	3.61	1.03	12.63	0.04
Male	1.92	0.56	6.62	0.30
Race AA	1.91	0.67	5.40	0.22
Hx DM	0.97	0.29	3.32	0.97
Hx HTN	0.13	0.04	0.45	0.01
Hx CVA	5.79	0.91	36.76	0.06
Hx CHF	1.58	0.48	5.16	0.45

Interactions (Table 6)

In the whole OSA sample, there were no significant interactions between OSA severity and any of the independent variables examined. Within the severe OSA patient group alone, severe OSA interacted with male gender to predict mortality. Age and a history of HTN interacted with severe OSA to predict MI.

CPAP Benefit (Table 7)

There were significant adjusted inverse correlations between all-cause mortality and CPAP use ≥ 4 h/night for (1) severe OSA patients, (2) severe OSA patients ≥ 50 yo, and (3) severe OSA male patients. No significant correlation existed between mortality and CPAP use in other OSA severity groups.

DISCUSSION

Findings Summary

OSA patients and non-apneic snorers were followed for up to eight years after their initial diagnosis. Within the apnea popula-

Table 7—Cox regression analysis to predict mortality outcome by CPAP use, controlled for OSA severity

Group	Variable	Hazard Ratio	95% Hazard Ratio Confidence Limits		p-value
All Mild Apnea Patients	CPAP ≥ 4 h/night	1.61	0.48	5.44	0.44
All Moderate Apnea Patients	CPAP ≥ 4 h/night	0.83	0.30	2.28	0.71
All Severe Apnea Patients	CPAP ≥ 4 h/night	0.37	0.19	0.73	0.01
Mild Apnea Patients ≥ 50 Years of Age	CPAP ≥ 4 h/night	1.52	0.45	5.13	0.50
Moderate Apnea Patients ≥ 50 Years of Age	CPAP ≥ 4 h/night	1.24	0.38	4.06	0.72
Severe Apnea Patients ≥ 50 Years of Age	CPAP ≥ 4 h/night	0.29	0.13	0.66	0.01
Mild Apnea Patients of Male Gender	CPAP ≥ 4 h/night	0.95	0.12	7.39	0.96
Moderate Apnea Patients of Male Gender	CPAP ≥ 4 h/night	0.45	0.09	2.16	0.32
Severe Apnea Patients of Male Gender	CPAP ≥ 4 h/night	0.42	0.21	0.83	0.01

tion there was a high concentration of those with severe disease. The population was relatively young, obese, predominately males, with a large contingent of African American patients.

1. All-cause mortality and the cardiovascular outcomes of MI, CVA, and PE were predicted by age and gender, as would be expected.
2. In the overall analysis mortality and cardiovascular disease outcomes were predicted by histories of CVD, not by OSA severity.
3. In the age and gender subgroup analysis, severe OSA (AHI ≥ 30) was a significant independent predictor of mortality for two groups: younger OSA patients (< 50 yo), and male OSA patients.
4. Use of CPAP > 4 hours per night was associated with a lower mortality incidence in the severe OSA group, as well as within the male and older age subgroups with severe OSA.
5. Severe OSA interacted with male gender to predict mortality and with age and a hypertensive history to predict MI.

Findings Related to Previous Investigations

A comprehensive review of previous publications examining the association between mortality and cardiovascular outcomes is beyond the scope of this manuscript, but comparison of our methodology and findings with population- and clinic-based studies is appropriate.

Mortality

Our findings of an association between severe OSA and all-cause mortality in younger males is consistent with the findings of other studies. In the Sleep Heart Health Study (SHHS), a community-based study of volunteers, Punjabi et al. evaluated 1047 deaths in 6441 individuals that occurred over 8.2 years.⁸ Although an older sample than ours, these investigators identified age, severe OSA, and arterial oxygen desaturation index as predictors of all-cause and cardiovascular mortality in males under the age of 70 years relative to community dwellers with AHI < 5 (HR = 2.09 [95% CI = 1.31–3.33]). This result was similar to our mortality risk for male OSA patients (HR = 3.28 [95% CI = 1.40–7.66]) and for the younger severe OSA patients (HR = 2.76 [95% CI = 1.00–7.57]) relative to patients with an AHI < 5 . In another study of 1620 male OSA patients, there was an increased death rate in the 30–60 age range, associated with BMI but not with OSA severity, HR = 3.33 and 3.23 (p-values < 0.01 , no CI's provided) for those 30–40 yo and 40–50 yo, respectively.¹³ Again, these values are very similar to our results. Further work from this group showed that the respiratory disturbance index (RDI) obtained with home monitoring was associated with all-cause mortality, especially in male OSA patients < 50 yo.²¹ In a subsequent study of predictors of mortality in male OSA patients, these investigators found that severe OSA predicted mortality only by an interaction with obesity (RDI > 40 and BMI > 30 kg/m², HR = 11.85 [95% CI = 1.21–115.67]).²⁵ In this case-control study of more than 10,000 male OSA patients with 331 deaths over a 10-year span, significant predictors of mortality were COPD, CHF, DM, and BMI, with HR's ranging from 1.44 to 7.07. In a largely male OSA patient group, Marti et al. found a significant association between untreated OSA and mortality, especially in those < 50 yo after adjustment for

several demographic, lifestyle, and medical history variables.¹⁶ The HR for mortality in the male OSA patients was 4.58 (95% CI = 3.09–6.78), an HR slightly higher than we found in males. In general, these studies demonstrate an all-cause mortality risk of 200% to 500% in younger males with severe OSA. The above referenced clinic-based study groups demonstrated less mortality in those who were adherent with CPAP. We found that our patients with severe OSA, especially males and those ≥ 50 yo who used CPAP ≥ 4 h/night had a significantly lower mortality rate than patients who refused CPAP therapy or used it < 4 h/night. This beneficial effect of CPAP was not seen in the mild or moderately severe OSA patients (AHI < 30). In all these studies, as well as in the present investigation, the beneficial effects of CPAP were not based on a randomized study, which is needed to control for factors associated with CPAP adherence that may also contribute to an improved outcome in the treatment-adherent patients relative to the treatment-non-adherent individuals.

Cardiovascular Disease Outcomes

The impact of OSA severity on CV endpoints, such as MI or CVA, has been evaluated in different populations. In the SHHS population, Gottlieb et al. found a significantly elevated incidence of CHF in men, but not coronary heart disease in men or women with OSA when AHI was modeled as a continuous variable in their fully adjusted model.¹⁰ In men, the adjusted HR for incident CHF in those untreated OSA patients with an AHI ≥ 30 was 1.58 (95% CI = 0.93–2.66) relative to those with an AHI < 5 . In their case-control prospective study, Marin et al. found a higher CVD event rate in untreated severe OSA patients than in those with less severe OSA or in treated patients, adjusted HR = 3.17 (95% CI = 1.12–7.51).²² The impact of OSA on outcomes in CVD patient populations has also been studied. In an older CVD cohort, Takara et al. found a significantly lower adjusted survival in those patients with OSA, HR = 2.45 (95% CI = 1.26–5.08).²⁶

Regarding CVA, Redline et al. examined CVA incidence in yet another subset of the SHHS population after nearly nine years of follow-up and found that CVA prevalence was predicted by age, male gender, and OSA with an AHI > 19 ; the latter group having an adjusted HR = 2.86 (95% CI = 1.1–7.4) for CVA, relative to those with an AHI < 5 .⁹ Marin found an increased CVA incidence in untreated young moderate/severe OSA patients.²² Yaggi et al. found that OSA severity and age were significant predictors of CVA and transient ischemic attack (TIA), even in a CPAP-treated population, HR = 1.97 (95% CI = 1.12–3.48).²³ In a prospective observational study of 408 coronary artery disease patients, Moee et al. found that the significant predictors of a composite outcome (death, MI, and CVA) were left ventricular dysfunction, history of diabetes mellitus, and OSA (for AHI ≥ 10 , adjusted HR = 2.98 [95% CI = 1.43–6.20] for CVA).¹⁵ When outcomes were analyzed separately, OSA was not a predictor of death nor MI in this study. In a retrospective clinic cohort study, Doherty et al. did not find a higher incidence of CVA in CPAP intolerant OSA patients compared to CPAP adherent patients, the two groups not differing in BMI or initial CV risk status.²⁰ Thus, the predominance of data in these studies confirms that males with untreated severe OSA may be susceptible to fatal and non-fatal

CVD-related outcomes. Similar to our results, these studies demonstrate the significant impact of cardiovascular diseases on mortality and CV outcomes in OSA patients.

Pulmonary Embolus (PE)

Our examination of PE incidence in an OSA patient sample is unique. PE did not occur often, affecting 3.1% of our sample; however, it had a relatively high incidence in younger OSA patients, in that 40% of the PEs occurred in the < 50 yo age group. We found that PE incidence was associated with BMI, male-ness, and histories of cardiac procedure, previous PE, and CHF in our whole group analysis. Gender and cardiovascular disease histories were predictors of PE in the younger OSA patients. AA race in males and age in females were additional variables associated with PE incidence. Epstein et al. recently showed an increased prevalence of PE in OSA patients,²⁸ previously described in a small group of OSA patients.²⁹ As we found in OSA patients, PE is a comorbid condition of obesity in general.³⁰ OSA leads to heightened venous stasis.³¹ In addition, OSA has been associated with inflammation and hypercoagulability,³²⁻³⁶ damaged endothelium,³⁶ and sympathetic stimulation,³⁷ all factors predisposing one to PE, as well.

CPAP Impact

Others have shown that CPAP therapy appears protective, associated with decreased incidence of mortality^{12,14,16,19,20} and cardiovascular disease.^{17,18,22,24} Of course, the application of CPAP was not randomized in these studies, including ours. This is a distinct limitation.

Limitations

There are important biases and assumptions that may affect our results or their interpretation:

Data Source and Abstraction

The first concern is the source and reliability of study data. In general, EMR data of large health care systems have been found to be reliable for research purposes. Yeh et al. identified a 90% agreement between external data sources and the EMR documented diagnosis of acute MI.³⁸ Specific to the Henry Ford EMR, preliminary unpublished data indicate a 91% agreement between external data and the EMR MI diagnosis (personal communication). The Henry Ford EMR, which was fully operational at the study initiation and remained so thereafter, is the primary repository of all demographic and clinical data. All clinic visit notes, all consultations, all specialty procedures, radiology and specimen laboratory results are fed into the EMR; and therefore, data are extractable from this single source, the structure and format of which did not change during the course of this investigation. Since all patient data came from the same source and had a standard structure, any errors of omission likely would be randomly distributed within our patient sample.

During our abstraction process, we discovered that some lifestyle variables were inconsistently recorded. Alcohol use, smoking history, waist and hip circumferences, and serum lipids were not consistently recorded. Therefore, these lifestyle variables could not be used in our analysis. However, rarely have these lifestyle variables affected the relationship between OSA severity and outcomes in other studies. For instance, the

addition of lipid levels to the Cox analysis did not alter the association between OSA severity and mortality in the SHHS.⁸ We used one chart abstractor so as to provide consistency in data acquisition. We verified this consistency by having this abstractor re-abstract 80 patient sleep records and EMRs after all the chart abstraction was completed. A relatively low error rate on re-abstraction occurred (see Methods above).

OSA Patient and Control Group Classification

The chance of misclassification of OSA severity based on AHI was small, since patients underwent all-night diagnostic polysomnograms, and all technologist polysomnographic scoring was reviewed by a staff physician twice, once at the time of the physician review of the polysomnogram and again at the time of the patient's clinic appointment. Technologist polysomnographic scoring skills were verified by participation in a scoring reliability program conducted on a quarterly basis. Although not controlled prospectively, it was the practice within the Sleep Center that if a given snorer patient's symptomatology suggested more severe OSA than identified, the diagnostic PSG was repeated. Of course, it is possible that some OSA patients, likely only those with mild OSA, were classified in the snoring control group. Since such misclassification would have been limited to a small number of patients and limited to those with mild OSA, the effect of this misclassification on outcome data, especially of the moderate and severe OSA groups, would be estimated to have been minimal.

Missing Data

The effect of not including a small group of patients for whom we did not have BMI data did not affect the distribution of diagnostic categorization or the prevalence of most independent variables. The higher prevalence of these disease histories within the absent-BMI patient group not included in the study population would have increased the prevalence data of these independent variables 5% to 7% in our study group. Histories of DM and asthma were not predictors of outcomes, and even without these additional patients with a history of CHF, a history of CHF was already a leading predictor of several outcomes. Therefore, we conclude that these exclusions were not likely to impact our results. Incomplete data because of drop-outs from our sample would have affected the results; however, our patient population was stable, in that they were members of a large health maintenance organization (HMO) that has been associated with the Henry Ford Health System for decades.

Referral Bias

Likely, our clinic patient population was affected by referral bias. Obese sleepy snorers seen by their primary care or specialty caregivers would be predictable referrals. The regression model we used was constructed to include all of the covariates combined together, accounting for the effect of each covariate when evaluating the ability of all independent variables to predict each outcome. Inclusion of all covariates in the model helped adjust for the comorbidity burden level these patients faced. In addition, our findings that younger and male OSA patients were at significant risks for outcomes such as all-cause mortality were similar to the results of population-based studies without such bias. This similarity may be due to one or a

combination of factors: (1) the influence of referral bias within our data set was minimal; (2) the referral bias was not strong enough to affect results; and/or (3) our findings were so robust that they were not affected by the referral bias.

Role of Preexisting Conditions

Our study was different methodologically from most studies of outcome incidence in OSA, in that we did not remove patients with histories of a particular disease when evaluating the incidence of that disease during the follow-up period. We purposely chose this methodology since we were interested in evaluating the impact of these medical histories on the outcomes. We also reasoned that such an analysis would be more generalizable with enhanced clinical relevance than if we had deleted patients with these medical histories from our analyses.

Interestingly, in our sample the preexisting history of a given CVD usually was not the most common predictor of that particular outcome. For instance, a history of MI was not a significant predictor of MI occurrence over the course of our study, and a history of CVA was not the most common predictor of CVA. These associations demonstrate that retention of preexisting conditions in our analyses did not overly bias the results.

Multiple Analyses and Power Adequacy

The multiple analyses performed in this study might be of concern, but each outcome event type was predetermined and independently evaluated in this study. Furthermore, due to the large number of regression models evaluated in this study, p-values between 0.01 and 0.05 are being viewed as borderline significant.

One might be concerned if our data set did not provide adequate power for our analyses; however, we propose that the number of deaths and CV events observed provided adequate power for the analyses performed. We did not have as many deaths as identified in the SHHS⁸ and the large clinical cohorts of Lavie et al.,^{13,21,25} but our patient population is equivalent to the size of the Wisconsin and Bussleton cohorts.^{7,8,39} Since our population was clinic-based, the concentration of outcome events, especially those related to severe OSA (42% of our OSA population), was higher than in a population-based study, as evidenced by the fact that our patient group experienced a higher death rate than either the Wisconsin or the Bussleton studies. In addition, given the number of snorers and apnea patients used in this study, an underlying five-year event rate difference for any particular outcome of about 5% in snorers versus 10% in apnea patients would be detectable with a log-rank test power of 0.80 when using a 2-sided α level of 0.05. However, effects smaller than what were powered may still be clinically significant.

Clinical Implications of the Findings

Data from this study have clinical utility. The younger male patient with severe OSA is highly susceptible to mortality and cardiovascular outcomes. Those severe OSA patients with histories of previous CV events are at risk of mortality or some future CV event, albeit not necessarily the one(s) identified by their medical history. By examining and identifying multiple predictors of mortality and life-changing cardiovascular comorbidities, we gained information about the relative importance of

those predictive variables. For the sample studied, cardiovascular risk factors were shown to be more frequent predictors of outcomes than was even severe OSA. It was apparent from our data that patients with severe OSA were at higher risk for mortality, MI, and PE, but not CVA. Specifically for male patients, OSA severity was an important independent predictor of all-cause mortality. The incidence of adverse outcomes in the mild and moderate OSA groups was similar to the incidence of these events in snorers, except for CVA. Although this finding is substantiated in the above-referenced community and clinic-based cohorts, study power limitations may affect conclusions regarding outcome data in these patient samples. From the perspective of mortality and most cardiovascular outcomes, treatment focus should primarily be on those with severe OSA. In our non-randomized evaluation of the therapeutic effect of CPAP on mortality incidence, we found that treated and CPAP adherent severe OSA patients had a significantly lower mortality rate than the untreated severe OSA patients. This benefit was not found in the moderate and mild OSA patient groups. In summary, our study results indicate that sleep medicine care providers, as well as generalists and specialists focusing on cardiovascular disease in OSA patients need to emphasize preventative, as well as ongoing care for active cardiovascular diseases, in addition to initiating care for OSA. Otherwise, mortality rate and future cardiovascular disease event occurrence may not be improved.

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