ORIGINAL RESEARCH

Obstructive and Central Sleep Apnea and the Risk of Incident Atrial Fibrillation in a Community Cohort of Men and Women

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***Background*—**Previous studies have documented a high prevalence of atrial fibrillation (AF) in individuals with obstructive sleep apnea (OSA). Central sleep apnea (CSA) has been associated with AF in patients with heart failure. However, data from prospective cohorts are sparse and few studies have distinguished the associations of obstructive sleep apnea from CSA with AF in population studies.

***Methods and Results*—**We assessed the association of obstructive sleep apnea and CSA with incident AF among 2912 individuals without a history of AF in the SHHS (Sleep Heart Health Study), a prospective, community-based study of existing ("parent") cohort studies designed to evaluate the cardiovascular consequences of sleep disordered breathing. Incident AF was documented by 12-lead ECG or assessed by the parent cohort. obstructive sleep apnea was defined by the obstructive apnea-hypopnea index (OAHI). CSA was defined by a central apnea index ≥5 or the presence of Cheyne Stokes Respiration. Logistic regression was used to assess the association between sleep disordered breathing and incident AF. Over a mean of 5.3 years of follow-up, 338 cases of incident AF were observed. CSA was a predictor of incident AF in all adjusted models and was associated with 2- to 3-fold increased odds of developing AF (central apnea index ≥5 odds ratio [OR], 3.00, 1.40–6.44; Cheyne–Stokes respiration OR, 1.83, 0.95–3.54; CSA or Cheyne–Stokes respiration OR, 2.00, 1.16–3.44). In contrast, OAHI was not associated with incident AF (OAHI per 5 unit increase OR, 0.97, 0.91–1.03; OAHI 5 to <15 OR, 0.84, 0.59–1.17; OAHI 15 to <30 OR, 0.93, 0.60–1.45; OAHI ≥30 OR, 0.76, 0.42–1.36).

***Conclusions*—**In a prospective, community-based cohort, CSA was associated with incident AF, even after adjustment for cardiovascular risk factors. **(*J Am Heart Assoc*. 2017;6:e004500. DOI: 10.1161/JAHA.116.004500.)**

Key Words: arrhythmia • atrial fibrillation • cohort • obstructive sleep apnea • sleep apnea

Atrial fibrillation (AF) is the most common cardiac arrhythmia encountered in clinical practice. Although incidence rates vary among studies, the lifetime risk for individuals aged 40 to 55 years has been estimated at 22% to 26%, with a clear age-related increase in incidence.[1,2] In addition to the symptomatic effects of AF, the associated sequelae of stroke and heart failure represent a significant burden on the healthcare system. Multiple common clinical conditions, such as diabetes mellitus, hypertension, and valvular heart disease, have been associated with AF. There is increasing evidence that obstructive sleep apnea (OSA), is also linked to AF. OSA is characterized by recurrent partial or complete collapse of the upper airway during sleep, shares many of the same risk factors as AF, and is thought to affect up to one quarter of the adult population.[3] Multiple studies have documented a higher prevalence of

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Accompanying Tables S1 and S2 are available at http://jaha.ahajournals.org/content/6/7/e004500/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Our study represents the largest, community-based prospective analysis of sleep disordered breathing and incident atrial fibrillation (AF) reported to date. Our findings signify the importance of central apnea in risk for AF, which may be based on several possible mechanisms, and suggest that individuals with central sleep apnea (CSA) or CSA/Cheyne Stokes Respiration constitute a phenotype with high risk for AF.

What Are the Clinical Implications?

- The association of CSA and AF risk suggests a role for screening and comprehensive management of both conditions. Given that nearly one quarter of those with CSA and 30% with CSA/Cheyne Stokes Respiration developed AF, the presence of CSA or Cheyne Stokes Respiration may be used to target individual patients for AF risk reduction.

AF in those with sleep apnea as compared with those without sleep apnea,[4–6] and sleep apnea has been associated with higher rates of recurrent AF following cardioversion and ablation.[7–10] However, much of the data documenting this association have come from cross-sectional and retrospective studies and have included individuals with preexisting AF. Furthermore, few studies have analyzed the respective relations of OSA and central sleep apnea (CSA), a condition characterized by cyclical changes in respiratory drive during sleep, to AF. There is emerging evidence linking CSA and AF, and CSA may be a marker of abnormal autonomic function, respiratory chemoreflex sensitivity, and cardiac function. Although studies performed to date have provided some insight into the connection underlying these conditions, more investigation is needed to understand the clinical overlap between these common clinical entities. Therefore, in our study, we sought to examine the association of OSA and CSA with incident AF in a large, prospective, community-based cohort.

Methods

Cohort and Study Design

The SHHS (Sleep Heart Health Study) is a community-based, prospective, cohort study designed to evaluate the cardiovascular consequences of sleep disordered breathing (SDB). Briefly, adults aged 40 years and older were recruited from existing community-based cohorts, including the ARIC (Atherosclerosis Risk in Communities Study),[11] CHS (Cardiovascular Health Study)[12], FHS (Framingham Heart Study),[13] Strong Heart Study,[14] Tucson Epidemiologic Study of Obstructive Lung Disease,[15] Tucson Health and Environment Study,[16] and the New York University-Cornell Worksite and Hypertension Study.[17] The SHHS study design and methods have been published previously.[18] A total of 6441 individuals were enrolled in the SHHS between 1995 and 1998 and completed an overnight polysomnogram (SHHS1 visit). A SHHS second exam (SHHS2), including a 12-lead ECG, was conducted ≈4 years after the initial exam in 3346 individuals. After excluding 388 subjects from the Strong Heart Study because of tribal restriction on data use, 46 subjects with prevalent AF, and individuals with missing data on key variables, 2912 individuals with 12-lead ECGs from the first and second SHHS visits (SHHS1 and SHHS2) were included in this analysis (Figure). Prevalent AF was defined by any of the following: a positive response to the question "Has a doctor ever told you that you have or had atrial fibrillation"; AF identified on resting 12-lead ECG at the baseline SHHS exam; or if the parent study identified AF documented in the medical record before the SHHS baseline exam. In addition, those taking any antiarrhythmic medications at baseline, including Class I and Class III antiarrhythmic medications, were excluded from the analysis.

The study protocol was approved by the institutional review board of each participating center, and each participant signed informed consent.

Definition of OSA and CSA

SHHS participants underwent in-home PSG using the Compumedics P-series portable monitor (Abbotsford, Victoria, Australia). The following channels were recorded: EEG, EOG, ECG, chin EMG, pulse oximetry, chest and abdominal excursion by inductance plethysmography, airflow by thermal sensor, and body position. PSGs were scored centrally as described previously.[19,20] Apnea was defined by complete or near-complete cessation in airflow for ≥10 seconds. Obstructive apneas were identified when there was evidence of respiratory effort on the inductance plethysmography bands during the apnea, and central apneas were identified when there was an absence of effort during the apnea. Hypopneas were defined by clearly discernible decrease in airflow or chest or abdominal plethysmograph amplitude (<30% baseline), lasting for at least 10 seconds, and associated with a 4% or greater oxyhemoglobin desaturation. The obstructive apnea-hypopnea index (OAHI) was defined as the average number of obstructive apneas plus hypopneas per hour of sleep. OAHI was divided into the following categories: Normal (OAHI <5), mild (OAHI 5<15), moderate (OAHI 15<30), and severe (OAHI ≥30) based on clinically accepted cut points. The central apnea index (CAI) was defined as the number of

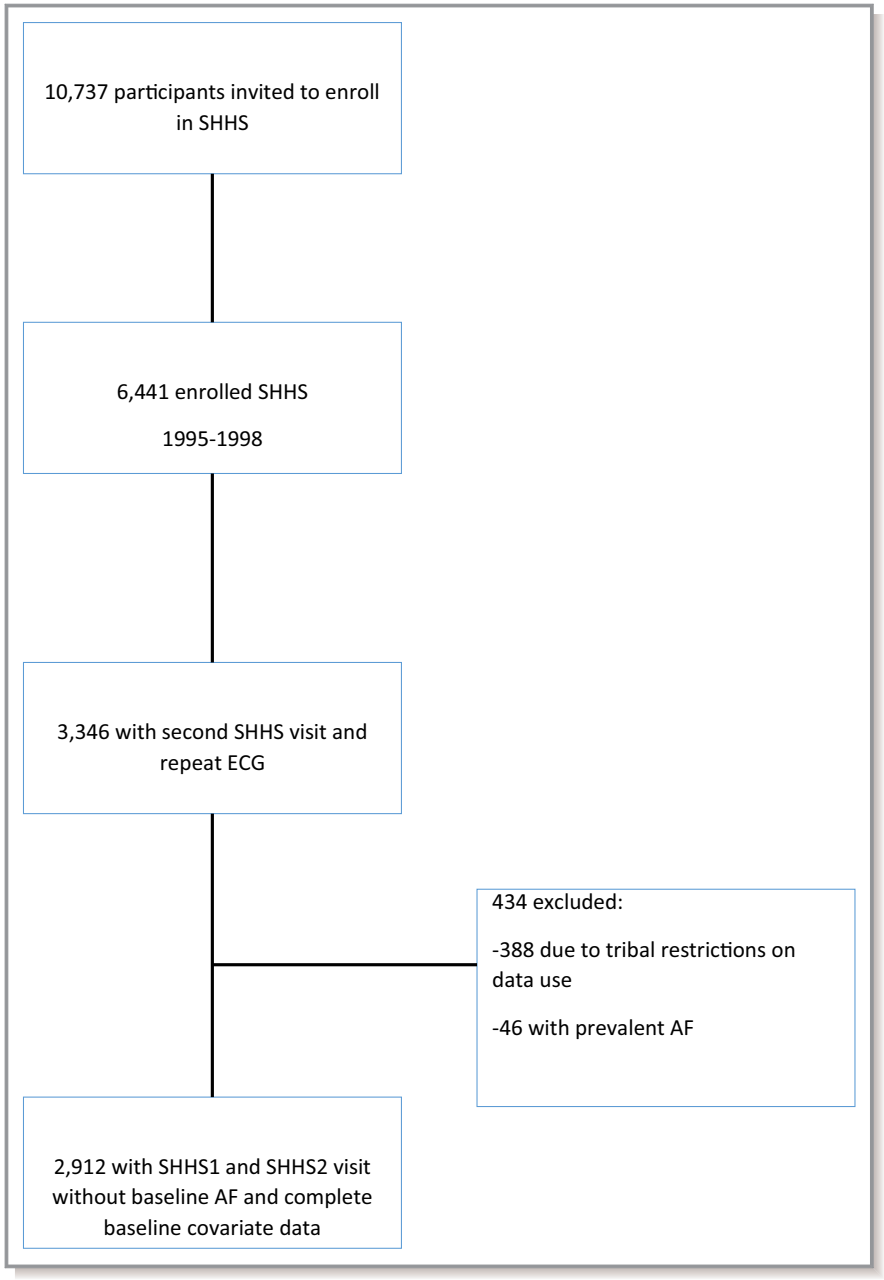

Figure. Study recruitment and enrollment. Sixty-four patients were excluded because of antiarrhythmic medication use and 293 were excluded because of incomplete covariate data. Given some overlap between excluded participants, a total of 295 of 2912 participants were excluded. AF indicates atrial fibrillation; SHHS, Sleep Heart Health Study.

central apneic episodes per hour of sleep. Similarly, CAI was divided into CAI ≥5 and CAI <5, based on accepted clinical categories.[21]

Cheyne–Stokes respiration (CSR) was identified as the occurrence of characteristic cycles of a crescendo-decrescendo pattern of breathing during sleep, typically associated with central apnea, and occurring for at least 5 minutes as consecutive cycles. Secondarily, we examined the composite CSA-CSR (CSA or CSR). Other PSG indices included the proportion of sleep time with oxygen saturation <90%.

Definition of AF Outcome

Incident AF was considered present if AF was identified on a 12-lead ECG obtained at the second SHHS exam or was adjudicated by the parent cohorts at any time between the baseline PSG and the final follow-up date for AF ascertainment of June 30, 2006. Ongoing surveillance for incident AF was performed by parent cohorts using periodic participant surveys querying for a diagnosis of AF and cardiovascular events by telephone and letter, as well as review of hospital

and medical records. The adjudication protocol used in the CHS, from which the majority of incident AF events were derived, relied on annual resting 12-lead ECGs and hospital discharge diagnoses (International Classification of Diseases, Ninth Revision, codes 427.3, 427.31, or 427.3). Determination of AF cases was conducted by individuals who did not have knowledge of the PSG findings. Ascertainment of AF in the other cohorts followed a similar protocol to that used in the CHS. Review of medical records in a subset of cases demonstrated that hospital discharge diagnoses provides an accuracy (positive predictive value) ranging from 89% to 98.6% for diagnosing AF in the ARIC and CHS.[22,23] In previous studies in the CHS to evaluate for potential missed outcomes, the results of 24-hour Holter monitoring performed at year 5 were evaluated in a subset of 819 participants.[24] Fifteen individuals demonstrated sustained AF, all of whom were identified by the above criteria, and 4 individuals demonstrated paroxysmal AF, 3 of whom were identified by the above criteria.

Covariates

During the baseline SHHS home visit, preceding the PSG, a study technician collected health history using a standardized questionnaire that included questions regarding sleep habits. The selection of covariates used in our analysis was based on the CHARGE-AF consortium findings, which developed and validated a risk prediction model for AF based on 3 large, prospective cohorts.[25] Blood pressure, height, and weight were measured using a standardized protocol.[26] Hypertension was defined as a systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of hypertension medications. Diabetes mellitus was considered present if the participant was taking insulin or an oral hypoglycemic agent. Cigarette smoking status was classified as never, former, or current. Information on smoking, alcohol use, and medications was by participant self-report. Left ventricular hypertrophy was assessed using the 12-lead ECG and was defined according to the Estes or Cornell voltage criteria.[27] Information on race, and total cholesterol, was obtained from the parent cohorts. Cardiovascular disease was defined as myocardial infarction, angina, heart failure, coronary bypass surgery, and angioplasty. Previous heart failure was ascertained both by participant questionnaire as well as from the parent cohorts. All covariate data from the parent cohorts were ascertained before the time of initial SHHS1 visit.

Statistical Analysis

Measures of SDB obtained from the PSG were expressed as continuous and categorical variables. Boundaries for categorical variables were based on frequently used clinical cut points and by the data distribution. OSA was modeled using the OAHI both as a continuous exposure (expressed as 5-unit increases in OAHI), as well as categorical exposure using categories of mild (OAHI 5 to <15), moderate (OAHI 15 to <30), and severe (OAHI ≥30) as compared to no OSA (OAHI <5). Central sleep apnea (CSA) was modeled using the CAI as CAI ≥5 compared to CAI <5, or a combined term indicating the presence of either CSA or Cheyne–Stokes respiration (CSA-CSR). Total sleep time with oxygen saturation <90% was defined according to the following categories: <1%, 1% to <3.5%, 3.5% to <10%, and ≥10% based on the distribution of the data.

Multivariable logistic regression modeling was used to examine the association of indices of baseline SDB and incident AF. A minimally adjusted model accounting for age, sex, clinic site, race, and body mass index (BMI) was initially constructed. Subsequently, a model adjusting for age, race, sex, BMI, total cholesterol, a history of cardiovascular disease, hypertension, diabetes mellitus, heart failure, stroke, ECG left ventricular hypertrophy, chronic obstructive pulmonary disease, alcohol use, and beta-blocker or calcium-channel blocker use was created. Additional models were created that included multiple measures of SDB (ie, OAHI and CAI).

Results

The study sample consisted of 2912 individuals followed for an average of 5.3 (median, 5.3; range, 4.6–7.3) years. Mean age was 62.8 years at baseline and 55% were female and 45% were male. With regards to race, 86% of the sample was white, whereas 14% was nonwhite (7% black, 12% American Indian, 5% Hispanic, and 1% Asian or Pacific Islander). Individuals excluded from the analytic sample because of missing follow-up ECG, prevalent AF, or data restrictions were compared to those in the analytical sample. The 2 groups were of similar age (62.9 years), but the latter had a small but significantly lower BMI (28.2+5.0 versus 28.8+5.6) and lower AHI (13.4+14.4 versus 14.4+15.5) and had a lower prevalence of hypertension (38.3% versus 46.0%), diabetes mellitus (6.2% versus 14.9%), and heart failure (1% versus 2.9%). Baseline characteristics of our cohort according to severity of OSA and presence of CSA are shown in Tables 1 and 2. Mild or greater OSA (OAHI ≥5) was present in 1440 or 49% of subjects. Moderate or greater OSA (OAHI ≥15) was present in 552 or 19% of the cohort. Severe OSA (OAHI ≥30) was present in 195 or 7% of the cohort. CSA (CAI ≥5) was present in 74 or 2.5%, 84 had CSR, and CSA-CSR was present in 135 or 4.6% of the cohort. There were 338 cases of incident AF among 2912 subjects (75 determined on the basis of follow-up 12-lead ECG) for an overall incidence of 11.6%, occurring at a median of 1817 days after the baseline assessment.

Table 1. Selected Baseline Characteristics by OSA Severity

Characteristic	SHHS Cohort N=2912	No OSA (OAHI <5) N=1472	Mild OSA (OAHI 5 to <15) N=888	Moderate OSA (OAHI 15 to <30) N=357	Severe OSA (OAHI ≥30) N=195	*P* Value*
Age, y	62.8 (11.2)	60.4 (11.2)	64.7 (10.9)	65.8 (10.1)	66.1 (10.8)	<0.0001
Men	1312, 45.1%	491, 33.4%	456, 51.4%	225, 63.0%	140, 71.8%	<0.001
Race/ethnicity						
White	2498, 85.8%	1246, 84.6%	774, 87.2%	311, 87.1%	167, 85.6%	0.32
Nonwhite	414, 14.2%	226, 15.4%	114, 12.8%	46, 12.9%	28, 14.4%	
Hypertension	1100, 37.8%	450, 30.6%	378, 42.6%	170, 47.6%	102, 52.3%	<0.0001
Diabetes mellitus	175, 6.1%	55, 3.8%	77, 8.8%	26, 7.4%	17, 8.9%	<0.0001
BMI, kg/m^2	28.2 (5.0)	26.7 (4.3)	29.2 (5.0)	30.0 (5.3)	31.4 (5.7)	<0.0001
Smoking						
Never	1366, 47.1%	729, 49.7%	395, 44.6%	163, 45.9%	79, 40.7%	<0.0001
Current	265, 9.1%	165, 11.2%	62, 7.0%	20, 5.6%	18, 9.3%	
Former	1270, 43.8%	573, 39.1%	428, 48.4%	172, 48.5%	97, 50.0%	
Cardiovascular disease†	308, 10.7%	117, 8.1%	113, 12.9%	52, 14.7%	26, 13.6%	<0.0001
Left ventricular hypertrophy	166, 5.7%	80, 5.4%	55, 6.2%	20, 5.6%	11, 5.6%	0.90
Heart failure	27, 0.9%	7, 0.5%	10, 1.1%	7, 2.0%	3, 1.6%	0.02
Stroke	88, 3.0%	28, 1.9%	32, 3.6%	13, 3.7%	15, 7.8%	0.0001
Total cholesterol, mg/dL	206.3 (37.2)	204.9 (37.8)	208.0 (38.7)	206.1 (31.9)	208.4 (34.4)	0.22
Chronic obstructive pulmonary disease	32, 1.1%	19, 1.3%	9, 1.0%	4, 1.1%	0, 0.0%	0.50
Cardiovascular medication	998, 34.3%	442, 30.0%	327, 36.8%	146, 40.9%	83, 42.6%	<0.0001
Alcohol use‡	2.5 (5.8)	2.1 (4.5)	2.6 (5.4)	3.7 (9.7)	2.8 (6.0)	0.24
CAI ≥5	74, 2.5%	12, 0.8%	30, 3.4%	16, 4.5%	16, 8.2%	<0.0001
CSA-CSR	135, 4.6%	28, 1.9%	46, 5.2%	37, 10.4%	24, 12.3%	<0.0001

For continuous variables, mean and SDs are presented and number and percentage in parentheses are presented for categorical variables. BMI indicates body mass index; CAI, central apnea index; CSA-CSR, central sleep apnea/Cheyne–Stokes respiration; OAHI, obstructive apnea hypopnea index; OSA, obstructive sleep apnea; SHHS, Sleep Heart Health Study.
**P* value derived from ANOVA or Kruskal–Wallis test, where appropriate, for continuous variables, chi-square test, or Fisher exact test, where appropriate, for categorical variables.
†Cardiovascular disease includes myocardial infarction, angina, heart failure, coronary bypass surgery, and angioplasty.
‡Units are mean number of drinks per week.

OSA was associated with advancing age, male sex, higher BMI, and increasing prevalence of hypertension, diabetes mellitus, cardiovascular disease, heart failure, stroke, cardiovascular medication use, and concomitant CSA (Table 1). CSA (CAI ≥5) was associated with older age, male sex, and a higher prevalence of diabetes mellitus as well as concomitant OSA (Table 2). Individuals with incident AF were older, more likely to have hypertension, diabetes mellitus, take cardiovascular medications, and to have a previous history of cardiovascular disease, heart failure, or stroke compared to those who did not develop AF. Baseline characteristics of the cohort according to incident AF are shown in Table S1. The breakdown of participants according to parent cohort as well as AF cases by cohort is shown in Table S2.

Among those with OSA, the proportion of those with incident AF increased with increasing severity of OSA; the incidence of AF among those with OAHI <5 was 142 (9.6%), OAHI 5 to <15 was 113 (12.7%), OAHI 15 to <30 was 51 (14.8%), and OAHI ≥30 was 32 (16.4%). Among those with CAI ≥5, 19 (25.7%) had incident AF, as compared with 319 (11.2%) of those with CAI <5.

Table 3 demonstrates the results of multivariable analyses addressing the association between OSA, CSA, and incident AF. After adjusting for multiple potential confounders, we found no significant associations between OSA, defined either as a continuous measure or by categorical levels of OSA based on the OAHI, and incident AF (Table 3). Results were consistent in all adjusted models. Sensitivity analyses, using alternative hypopnea definitions to calculate the OAHI (ie, defined if associated with 3% or more desaturation or evaluating only obstructive apneas without hypopneas) did not result in substantially different findings (data not shown).

Table 2. Selected Baseline Characteristics by Presence of CSA (Based on CAI)

Characteristic	SHHS Cohort (N=2912)	CAI <5 (N=2838)	CAI ≥5 (N=74)	*P* Value*
Age, y	62.8 (11.2)	62.6 (11.2)	67.5 (11.1)	0.0003
Men	1312, 45.1%	1253, 44.2%	59, 79.7%	<0.0001
Race/ethnicity				
White	2498, 85.8%	2431, 85.7%	67, 90.5%	0.24
Nonwhite	414, 14.2%	407, 14.3%	7, 9.5%	
Hypertension	1100, 37.8%	1069, 37.7%	31, 41.9%	0.46
Diabetes mellitus	175, 6.1%	165, 5.9%	10, 13.7%	0.01
BMI, kg/m^2	28.2±5.0	28.2±5.0	27.7±3.7	0.38
Smoking				
Never	1366, 47.1%	1329, 47.0%	37, 50.0%	0.85
Current	265, 9.1%	258, 9.1%	7, 9.5%	
Former	1270, 43.8%	1240, 43.9%	30, 40.5%	
Cardiovascular disease†	308, 10.7%	297, 10.6%	11, 14.9%	0.24
ECG left ventricular hypertrophy	166, 5.7%	161, 5.7%	5, 6.8%	0.61
Heart failure	27, 0.9%	26, 0.9%	1, 1.4%	0.50
Stroke	88, 3.0%	86, 3.0%	2, 2.7%	>0.99
Total cholesterol, mg/dL	206.3 (37.2)	206.4 (37.4)	201.5 (31.0)	0.27
Chronic obstructive pulmonary disease	32, 1.1%	31, 1.1%	1, 1.4%	0.83
Cardiovascular medication	998, 34.3%	971, 34.2%	27, 36.5%	0.68
Alcohol use‡	2.5 (5.8)	2.5 (5.8)	1.8 (4.2)	0.37
OAHI ≥5	1440, 49.5%	1378, 48.6%	62, 83.8%	<0.0001
OAHI ≥15	552, 19.0%	520, 18.3%	32, 43.2%	<0.0001

For continuous variables, mean and SDs are presented and number and percentage in parentheses are presented for categorical variables. BMI indicates body mass index; CAI, central apnea index; CSA, central sleep apnea; OAHI, obstructive apnea hypopnea index; SHHS, Sleep Heart Health Study.
**P* value derived from ANOVA or Wilcoxon rank-sum test, where appropriate, for continuous variables, chi-square test, or Fisher exact test, where appropriate, for categorical variables.
†Cardiovascular disease includes myocardial infarction, angina, heart failure, coronary bypass surgery, and angioplasty.
‡Units are mean number of drinks per week.

In contrast, CSA defined by CAI ≥5, by CSR, or by a combination of CSA-CSR, was significantly associated with a 2- to 3-fold increase in the odds of developing AF (CAI ≥5 odds ratio, 3.00, 1.40–6.44; CSR odds ratio, 1.83, 0.95–3.54; CSA or CSR odds ratio, 2.00, 1.16–3.44). These results were consistent in models with minimal adjustments as well as in models additionally adjusted for AF risk factors, as well as after adjusting for OAHI (Table 3). Hypoxemia, defined by amount of total sleep time with oxygen saturation <90%, was not associated with incident AF in any model.

Discussion

We found that indices of central, but not obstructive, sleep apnea were associated with incident AF in our large, prospective, and well-characterized cohort of middle-aged and elderly individuals who were free of a history of AF at baseline. Individuals with CSA, defined using the CAI as well as CSR, had a higher incidence of AF than individuals without CSA, and associations persisted after adjustment for a history of heart failure, BMI, hypertension, left ventricular hypertrophy, and other confounding variables. These associations were unchanged after further adjustment for OSA. The potential importance of CSA as a predictor of incident AF is further strengthened by the large effect estimates observed for the CSA-AF relationship. In contrast, neither indices of OSA nor sleep-related hypoxemia were associated with AF in models that adjusted for confounders.

Our findings are consistent with previous cross-sectional evidence linking central apnea and AF. In a sample of 450 individuals with heart failure referred for evaluation of SDB, Sin et al found AF to be associated with CSA, but not OSA, in multivariable analysis.[28] Similarly, the prevalence of AF was significantly higher in a sample of 60 participants with CSA, but without heart failure, as compared with 120 participants with OSA or without symptoms of SDB.[29] Interestingly, in the Sin et al analysis, the prevalence of AF was lower among those with OSA than among the reference group without SDB.

Table 3. Adjusted Associations of Sleep Disordered Breathing and Incident Atrial Fibrillation

	SHHS Cohort			
Predictor	Minimally Adjusted*	Multivariable Adjusted†	Multivariable Adjusted†+OAHI	Multivariable Adjusted†+CAI
OAHI, per 5 increase	0.97 (0.91–1.02), 0.22	0.97 (0.91–1.03), 0.26	NA	0.96 (0.90–1.02), 0.21
OAHI <5 (reference)	1.00 (reference)	1.00 (reference)	NA	1.00 (reference)
OAHI 5 to <15	0.79 (0.58–1.08), 0.14	0.84 (0.59–1.17), 0.30	NA	0.81 (0.58–1.14), 0.23
OAHI 15 to <30	0.91 (0.61–1.36), 0.65	0.93 (0.60–1.45), 0.75	NA	0.91 (0.59–1.42), 0.69
OAHI ≥30	0.78 (0.47–1.32), 0.36	0.76 (0.42–1.36), 0.35	NA	0.72 (0.40–1.30), 0.28
CAI ≥5	1.71 (0.89–3.30), 0.11	3.00 (1.40–6.44), 0.005	3.15 (1.46–6.80), 0.003	NA
CSR	1.77 (0.99–3.16), 0.05	1.83 (0.95–3.54), 0.07	1.92 (0.99–3.73), 0.05	NA
CSA-CSR	1.63 (1.02–2.62), 0.04	2.00 (1.16–3.44), 0.01	2.13 (1.23–3.70), 0.007	NA
% total sleep time with SaO_2 <90%				
<1%	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1% to <3.5%	1.03 (0.70–1.50), 0.89	0.98 (0.64–1.50), 0.94	1.04 (0.67–1.61), 0.86	0.99 (0.65–1.51), 0.96
3.5% to <10%	0.92 (0.61–1.39), 0.69	0.98 (0.61–1.58), 0.94	1.10 (0.66–1.84), 0.72	0.99 (0.61–1.59), 0.95
≥10%	0.91 (0.58–1.44), 0.69	0.91 (0.55–1.50), 0.71	1.05 (0.60–1.82), 0.87	0.93 (0.56–1.53), 0.77

Beta (95% CI), *P* values are presented in each cell. CAI indicates central apnea index; CSA-CSR, central sleep apnea/Cheyne–Stokes respiration; NA, not applicable; OAHI, obstructive apnea hypopnea index; SHHS, Sleep Heart Health Study.

*Minimally adjusted for: age, sex, race, body mass index.

†Multivariable adjusted for: age, clinic, race, body mass index, history of cardiovascular disease, hypertension, diabetes mellitus, stroke, chronic obstructive pulmonary disease, pacemaker placement, total cholesterol, use of cardiovascular medications, and alcohol use.

Mehra et al also documented a stronger cross-sectional relationship of CSA than OSA to AF in an unselected community cohort of 2911 men.[30] Thus, our findings extend the previous work, in which CSA was more strongly associated with AF than OSA,[28–31] but which were limited by cross-sectional designs, which precluded assessment of the directional relationship between CSA and AF. More recently, a prospective analysis found that CSA and CSR predicted the risk of AF in a community-based sample of older men.[32] Our study extends these results by showing similar findings in both men and women across a wider age range, and further shows the persistence of findings even after adjusting for ECG-based indices of left ventricular hypertrophy. The consistency of findings across these different cohorts, as well as across all our models and the longitudinal design, strengthens the evidence linking CSA and AF. Our findings indicate that the presence of CSA (as noted by an elevated CAI or the presence of CSR) may identify individuals at increased risk of developing AF after adjusting for potential confounders.

Although we adjusted for prevalent heart disease, it is possible that CSA is a sensitive marker of subclinical cardiac dysfunction and that this explains the observed association of CSA with incident AF. However, there are several mechanisms by which CSA may increase the risk for developing AF. Intermittent fluctuations in $PaCO_2$ levels and periodic arousals, as occurs with CSA, may predispose to arrhythmia by enhancing sympathetic activation and, secondarily, through electrical and structural remodeling.[28] Although these physiological changes are observed with OSA, fluctuations in CO_2 may be greater in CSA than OSA and have been linked to changes in sympathetic tone.[33] Increased concentrations of plasma and urinary norepinephrine and epinephrine have been documented in patients with CSA and have been associated with left ventricular dysfunction.[34] There is also evidence from animal and human studies supporting the role of the autonomic nervous system in the initiation and maintenance of AF.[35,36]

Fluctuating levels of CO_2 and intermittent arousal also have been proposed as risk factors for electrical remodeling. Two forms of CSA have been described; one in which $PaCO_2$ levels are normal or low and a second form in which they are elevated.[37,38] In heart failure patients, arousal events may precipitate hyperventilation and the resultant low $PaCO_2$ levels may trigger central apneas through a vagally mediated mechanism of hypersensitivity to $PaCO_2$ levels.[39] In these nonhypercapnic forms of CSA, sensitivity of the chemoreceptors is elevated, and repeated exposure over time may result in relative changes in parasympathetic and sympathetic tone, with resultant effects on atrial refractoriness and conduction. It has been shown that the ventilatory response to $PaCO_2$ is increased in patients with CSA and heart failure, but not in those with OSA and heart failure.[40] In contrast, in hypercapnic CSA, $PaCO_2$ levels are elevated and chemoreceptor sensitivity

to $PaCO_2$ levels is reduced.[37] These changes in end-tidal CO_2 levels and chemoreceptor sensitivity have been linked to autonomic imbalance and concomitant electrical remodeling that predisposes to AF. In a sheep model, Stevenson et al infused atropine and propranolol before inducing hypoxemia and hypercapnia in 2 groups of animals that were compared to a third, control group. The atrial effective refractory periods and conduction times of the left and right atria were both significantly increased during acute hypercapnia, but not during hypoxemia or among the control sheep.[41] Interestingly, AF was less easily induced with rapid pacing during periods of acute hypercapnia, but more easily induced on return to eucapnia and to baseline refractoriness. Additional research is needed to better define how baseline $PaCO_2$ and fluctuations in $PaCO_2$ levels over time may influence electrical substrate remodeling and risk of AF. CSA may also promote electrical remodeling through changes in the sensitivity of central chemoreceptors to $PaCO_2$ levels. It is also possible that CSA is a marker of augmented respiratory chemoreflexes or autonomic nervous system dysfunction, which may be the actual mediators of risk for developing AF.

Other physiological changes of SDB, including intermittent hypoxemia and fluctuations in intrathoracic pressure, also have been associated with development of AF, potentially through autonomic nervous system dysregulation and secondary electrical remodeling.[6,28,42,43] However, in our cohort, the proportion of sleep time spent at a saturation less than 90% was not associated with AF, which may reflect a lesser role for hypoxemia in the range observed, relative to the other physiological perturbations associated with CSA, in producing changes in the autonomic nervous system. Negative intrathoracic pressure also has been linked to altered autonomic system activation and a secondary increase in the ability to induce AF.[44] In a porcine model, autonomic blockade with atropine prevented the increased susceptibility to AF that was induced with negative intrathoracic pressure that was independent of hypoxemia or hypercapnia.[44] Although these physiological changes may be occasionally present in CSA, they are more prominent in OSA, and our strong associations with CSA as compared with OSA suggest that in a general community sample of mostly older adults without a high prevalence of severe OSA, negative intrathoracic pressure changes may not be a key mechanism for developing AF.

Left ventricular diastolic dysfunction is prevalent in individuals with SDB.[45–48] This results in elevated filling pressures, which may predispose to AF through a mechanism of left atrial stretch and increased left atrial size. Although there is some evidence that the presence of diastolic dysfunction may be elevated in those with CSA,[49] these mechanisms have been most clearly associated with OSA. Whether they are also operative in CSA, and secondarily increase the risk for AF through structural changes, needs to be determined.

It should be noted that our results diverge from some previous reports linking OSA to AF, despite similar incidence rates of AF.[10,42] There are several possible reasons for our lack of association. First, several of the previous analyses did not explicitly distinguish between central and obstructive apnea. In clinical practice, patients with SDB often exhibit features of both obstructive and central apnea. Most previous research analyzed exposure as the AHI, and did not specifically distinguish the contribution of central and obstructive apneic events in statistical models. Second, some of the previous data linking OSA and AF come from a tertiary referral center for sleep disorders, which may reflect a distinct referral subset of OSA individuals who may have more symptomatic and severe OSA than found in a community cohort, or who also may be at increased risk for CVD. A community-based sample with undiagnosed OSA may differ from patients referred to a tertiary care center for evaluation of SDB; the groups may vary in their risk for developing AF.[42,50] Third, it is possible that our results reflect a survival effect. That is, those with OSA most at risk for developing AF could have been excluded from analysis if they had prevalent AF at baseline. However, of the 46 subjects excluded because of baseline AF, only 16 had moderate or severe OSA (OAHI $\geq$15). Finally, it is possible that any association between OSA and incident AF was diminished by the treatment of OSA during the course of follow-up. However, in previous analyses of this cohort, fewer than 3% of those with OSA received treatment during the course of our study.[51] Therefore, treatment of OSA is unlikely to account for the lack of observed association between OSA and AF.

The strengths of our study include rigorous and standardized collection of sleep data, prospective design, and large sample size. However, there are also several limitations. Given the paroxysmal nature of the majority of AF cases, it is likely that AF is under-represented in our analysis and it is possible that individuals with unrecognized AF may have gone undetected in follow-up. We restricted analyses to individuals who participated in a follow-up SHHS exam that included a 12-lead ECG. We cannot exclude a selection bias given that individuals who were not followed had slightly higher baseline AHI levels and a higher prevalence d of diabetes mellitus and heart disease than those in the analytical sample. However, restricting our analysis allowed for a more constant period of follow-up. Furthermore, if our analytical sample was healthier than the original cohort, this would have biased our results toward the null, and thus may have underestimated the association with OSA. Dates of AF ascertainment were not uniformly available across the parent cohorts, precluding calculation of incidence rates. The number of individuals with CSA was modest. Electrophysiological data and echocardiographic data were not available. We cannot exclude the

possibility of residual confounding. Finally, it should be noted that because of scoring standards at the time of PSG, hypopneas were not differentiated as central or obstructive. Further characterization may have resulted in some reclassification of events. Therefore, our results should be replicated in future studies.

Conclusions

Our study represents the largest, community-based prospective analysis of SDB and incident AF reported to date. Our findings signify the importance of central apnea in risk for AF, which may be based on several possible mechanisms, and suggest that individuals with CSA or CSA-CSR constitute a phenotype with high risk for AF. The co-aggregation of CSA and AF risk suggest a role for screening and simultaneous management of both conditions. Notably, approximately one quarter of those with CSA and 30% with CSA-CSR developed AF, suggesting that the presence of CSA or CSR may be used to target individual patients for AF risk reduction. This is similar to estimates of AF and CSA from other cohorts.[32] Further study is needed to understand the specific mechanisms underlying the association of central apnea and AF, and to evaluate the efficacy of treatment of CSA on the development, treatment, and prognosis of AF.

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Disclosures

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SUPPLEMENTAL MATERIAL

Table S1. Selected Baseline Characteristics by Incident Atrial Fibrillation (AF)

Characteristic	SHHS Cohort N = 2912	No Incident AF N = 2574	Incident AF N = 338	P valueψ
Age, yr	62.8 (11.2)	61.3 (10.8)	73.9 (7.4)	<0.0001
Men	1312, 45.1 %	1159, 45.0 %	153, 45.3 %	0.93
Race/Ethnicity				
White	2498, 85.8 %	2203, 85.6 %	295, 87.3 %	0.46
Non-white	414, 14.2 %	371, 14.4 %	43, 12.7 %	
Hypertension	1100, 37.8 %	882, 34.3 %	218, 64.5 %	<0.0001
Diabetes	175, 6.1 %	134, 5.3 %	41, 12.2 %	<0.0001
Body mass index, kg/m^2	28.2 (5.0)	28.2 (5.0)	28.2 (4.8)	0.73
Smoking				
Never	1366, 47.1 %	1218, 47.5 %	148, 43.9 %	0.01
Current	265, 9.1 %	245, 9.6 %	20, 5.9 %	
Former	1270, 43.8 %	1101, 42.9 %	169, 50.1 %	
Cardiovascular disease†	308, 10.7 %	229, 9.0 %	79, 23.9 %	<0.0001
ECG Left ventricular hypertrophy	166, 5.7 %	141, 5.5 %	25, 7.4 %	0.15
Heart failure	27, 0.9 %	15, 0.6 %	12, 3.6 %	<0.0001
Stroke	88, 3.0 %	67, 2.6 %	21, 6.3 %	0.001
Total cholesterol, mg/dL	206.3 (37.2)	207.1 (37.5)	200.1 (35.0)	0.001
Chronic obstructive pulmonary disease	32, 1.1 %	25, 1.0 %	7, 2.1 %	0.09
Cardiovascular medication	998, 34.3 %	781, 30.3 %	217, 64.2 %	<0.0001
Alcohol use*	2.5(5.8)	2.5(5.4)	3.0(8.2)	0.66
Obstructive apnea hypopnea index ≥ 5	1440, 49.5 %	1244, 48.3 %	196, 58.0 %	<0.0001
Obstructive apnea hypopnea index ≥ 15	552, 19.0 %	469, 18.2 %	83, 24.6 %	<0.0001
Central Apnea Index ≥ 5	74, 2.5 %	55, 2.1 %	19, 5.6 %	<0.0001
CSA-CSR	135, 4.6 %	96, 3.7 %	39, 11.5 %	<0.0001

ψ For continuous variables mean and standard deviations are presented, p value is derived from ANOVA, or Wilcoxon Rank Sum test where appropriate.

For Categorical variables, count and column percentage are presented, values are derived from Chi square tests, or Fisher exact tests where appropriate.
†Cardiovascular disease includes myocardial infarction, angina, heart failure, coronary bypass surgery, and angioplasty
*units are mean number of drinks per week
Abbreviations: SHHS Sleep Heart Health Study, CSA-CSR central sleep apnea-cheyne stokes respiration

Table S2. Events by Parent Cohort

Parent Cohort	Number of Participants	No AF	Incident AF	Mean Age (yrs)
CHS	706	460, 65.2%	246, 34.8%	77
ARIC	858	826, 96.3%	32, 3.7%	65
Framingham	751	694, 92.4%	57, 7.6%	66
Tucson	597	594, 99.5%	3, 0.5%	65
Total	2912	2574, 88.4%	338, 11.6%	

Abbreviations: AF atrial fibrillation, CHS Cardiovascular Health Study, ARIC Atherosclerosis Risk in Communities Study

Obstructive and Central Sleep Apnea and the Risk of Incident Atrial Fibrillation in a Community Cohort of Men and Women

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