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Central Sleep Disordered Breathing Predicts Incident Atrial Fibrillation in Older Males

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Author Contributions

Drs. AMM and RM had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. AMM, TB, PHS, PHS, KLS, PMC, PDV, SR, and RM made substantial contributions to the design and analysis plan of the study. TB conducted the statistical analysis and editing of the manuscript. AMM was involved in the data analysis and interpretation of results and drafted the manuscript. All authors revised the draft critically and gave final approval of the manuscript version to be published.

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Running Head: Central sleep apnea predicts incident AF

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At a Glance Commentary

Scientific Knowledge on the Subject: Obstructive sleep apnea has been linked with atrial fibrillation in clinic-based cross-sectional and retrospective studies.

What this Study Adds to the Field: In a large population-based, multicenter, prospective study with careful collection of sleep measures involving a cohort of older men vulnerable to AF development, central sleep apnea and Cheyne Stokes respiration were associated with incident atrial fibrillation. In the older (76 years or older) but not the younger subgroup, all sleep disordered breathing indices including both obstructive and central measures were associated with incident atrial fibrillation.

This article has an online data supplement, which is accessible from this issue's table of contents online at www.atsjournals.org

ABSTRACT

Rationale: Although research supports a sleep disordered breathing and atrial fibrillation association, prospective data examining sleep disordered breathing predicting incident atrial fibrillation are lacking.

Objectives: To investigate sleep disordered breathing indices as predictors of incident atrial fibrillation.

Methods: A cohort (n=843) of ambulatory older men without prevalent atrial fibrillation was assessed for baseline sleep indices: apnea hypopnea index, central sleep apnea (central apnea index≥5 vs. <5), central sleep apnea or Cheyne Stokes Respiration, obstructive apnea hypopnea index, and percentage sleep time with <90% oxygen saturation. Incident clinically-symptomatic adjudicated or self-reported atrial fibrillation outcome was ascertained (mean follow-up 6.5±0.7 years). Logistic regression models adjusted for age, race, body mass index, cardiopulmonary disease, alcohol use, pacemaker, cholesterol, cardiac medications, and alternate apnea type for obstructive and central apnea; age interaction terms and median age-stratified analyses were performed.

Measurements and main results: Central sleep apnea (OR=2.58, 1.18-5.66) and central sleep apnea-Cheyne Stokes respiration (OR=2.27, 1.13-4.56), but not obstructive apnea or hypoxemia, predicted incident atrial fibrillation. Central apnea, Cheyne Stokes, and sleep disordered breathing-age interaction terms were significant ($p<0.05$). Unlike younger participants, among participants ≥ 76 years (albeit with small atrial fibrillation counts), atrial fibrillation was related to central apnea (OR=9.97, 2.72-36.50), central apnea-Cheyne Stokes respiration (OR 6.31, 1.94-20.51), and apnea hypopnea index (OR=1.22, 1.08-1.39 per 5 unit increase).

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Conclusions: In older men central apnea and Cheyne Stokes respiration predicted increased atrial fibrillation risk with findings strongest in older participants in whom overall sleep disordered breathing also increased atrial fibrillation risk.

Abstract Word Count: 247

Key words: sleep disordered breathing; atrial fibrillation; cohort study

INTRODUCTION

Sleep disordered breathing (SDB) is a highly prevalent physiologic stressor which has been implicated in the burden of atrial fibrillation (AF).(1–3) SDB is characterized by repetitive breathing cessation accompanied by physiologic stressors including intermittent hypoxia, hypercapnia, autonomic nervous system fluctuations, and intrathoracic pressure swings, which can predispose to enhanced arrhythmogenicity. AF is highly prevalent, particularly with increasing age as evidenced by a 3-fold increase between the 6th and 8th decades of life.(4) The large population burden of AF is highlighted by progressive increased incidence with estimated prevalence of 10 million Americans by 2050 and contribution to substantial health care costs and morbidity.(4–7)

Cross-sectional epidemiologic data have identified a strong association between AF and SDB.(8, 9) Plausibility of a causal relationship is supported by data from a case crossover study that identified an increase in paroxysmal AF events immediately following SDB events, suggesting that respiratory disturbances may trigger AF events.(10) However, an important limitation of existing community-based epidemiologic studies is their cross-sectional nature which precludes understanding of the temporal relationship between the exposure (SDB and its subtypes) and outcome (AF), thereby limiting ability to inform causality.(8, 8, 9) Large retrospective clinic-based studies with a focus on obstructive sleep apnea (OSA), identified an association of nocturnal oxygen desaturation and incident AF only in participants less than 65 years old (11) and a dose-response relationship of OSA severity and hypoxemia with incident AF.(12) Existing data also suggest that central events may more significantly associate with atrial arrhythmogenesis, while obstructive respiratory events may more strongly contribute to ventricular arrhythmogenesis.(9) Although rigorously conducted randomized controlled trials

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are lacking, data from retrospective studies identify the impact of primarily OSA (but not CSA) treatment on reduction of the recurrence of AF after cardioversion or ablation and allude to a potential causal relationship.(13–17)

Although existing studies support an association of SDB and AF, it remains unclear whether SDB serves as a causal risk factor in the development of AF or vice versa. Gaining insight into the role of initiators of AF such as SDB is key to the development of AF prevention strategies and has been identified as a critical knowledge gap by several national AF prevention and treatment expert working groups.(18, 19) Furthermore, understanding the SDB characteristics (i.e. obstructive, central, and hypoxemic) that contribute to atrial arrhythmogenesis may hone prevention and treatment to target the specific physiologic determinants of abnormal sleep-related breathing leading to AF development.

To further characterize the relationship of SDB and its subtypes with AF, we examined SDB and AF development in a prospective large-scale, multicenter, community-based study of older men – a group particularly vulnerable to AF and its morbidity – utilizing systematic collection of polysomnographic data and standardized methods of clinically symptomatic AF identification as well as self-reported AF data.(20) We hypothesize that SDB will predict incident AF and postulate that central apnea will represent the strongest SDB determinant to predict future AF.(8, 11) Some of the results of these studies have been previously reported in the form of an abstract.(21)

METHODS

PARTICIPANTS AND STUDY DESIGN

This prospective observational study involved participants of the Outcomes of Sleep Disorders in Older Men Study (MrOS Sleep Study), an ancillary study of the Osteoporotic Fractures in Men Study (MrOS study). The MrOS study enrolled 5994 community-living men aged 65 and older, able to ambulate without assistance, and without history of bilateral hip replacement. Six centers (Birmingham, Alabama; Minneapolis, Minnesota; Monongahela Valley near Pittsburgh, Pennsylvania; Palo Alto, California; Portland, Oregon; San Diego, California) recruited participants.(22, 23) The MrOS study design, methods, and demographics were previously published (see **Supplement**).(9, 22, 23)

The MrOS Sleep Study recruited 3,135 participants December 2003-March 2005 for a comprehensive sleep assessment. Of the 3135 MrOS Sleep Study participants recruited, 179 did not participate in polysomnography (PSG) secondary to refusal or contemporaneous treatment of SDB and 45 men had failed sleep studies (1.5%), resulting in 2,911 participants. Of these, 2,316 did not have PSG-identified or self-reported prevalent AF at the first sleep visit. A subgroup of men (n=852) participated in a second sleep visit (November 2009 – March 2012). The analytic cohort consisted of study participants with acceptable PSG from the initial sleep visit with data on incident adjudicated and self-reported atrial fibrillation (n=843) and mean follow-up time of 6.5 ± 0.7 years (**Figure 1**). Additional recruitment information in **Supplement**.

Each site and the study coordinating center received ethics approval from their institutional review board. Written informed consent was obtained from all participants.

POLYSOMNOGRAPHY DATA

An unattended home PSG (Safiro, Compumedics, Inc.®, Melbourne, Australia) was performed consisting of recording of C_3/A_2 and C_4/A_1 electroencephalograms, bilateral electrooculograms,

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a bipolar submental electromyogram, thoracic and abdominal inductance plethysmography, airflow (oronasal thermocouple and nasal pressure cannula), finger pulse oximetry, lead I EKG, body position, and bilateral leg movements.(9) Indices per hour of sleep included the apnea hypopnea index (AHI, number of obstructive and central apneas and hypopneas with a ≥3% oxygen desaturation)(24), obstructive apnea hypopnea index (OAHI, number of obstructive apneas and hypopneas with ≥3% desaturation), central apnea index (CAI, number of central apneas). Cheyne Stokes Respiration (CSR) was characterized by a minimum consecutive 10-minute period of crescendo-decrescendo respiratory pattern culminating in a nadir of central apneas with typical cycle length. Percentage of sleep time spent below an oxygen saturation of 90% (TST<90%) defined sleep related hypoxemia.

OUTCOME MEASURE

AF was defined as either incident adjudicated AF or self-reported AF.(25–27) Adjudicated clinically-symptomatic AF – defined by symptoms, hospitalization, prolongation of hospitalization, or requiring invasive procedure –was identified by surveying for incident events followed by central adjudication using a standard protocol (**Supplement**). Self-reported AF was ascertained at each sleep visit by asking participants if they had ever been diagnosed with atrial fibrillation or atrial flutter.

COVARIATE MEASURES

Covariate measures including demographics, medical history, alcohol use, cardiovascular disease (CVD) medications (calcium channel blockers, non-ophthalmic beta-blockers, cardiac glycosides, or anti-arrhythmic medications – cardiac sodium channel blockers and potassium channel blockers), body mass index (BMI), cholesterol, and pacemaker presence were

assessed.(28) CVD was defined by history of myocardial infarction, angina, angioplasty, congestive heart failure (CHF), and/or coronary artery bypass graft surgery. A full description of covariate collection is located in **Supplement**.

STATISTICAL ANALYSIS

PSG parameters were expressed as continuous and/or categorical variables, the latter informed by standard cutoffs (29) or distributional characteristics. SDB was defined per 5-unit AHI increase and alternatively as AHI ≥15 vs. <15 based upon clinical convention(29) and obstructive sleep apnea (OSA) per 5-unit OAHI increase. Central sleep apnea (CSA) was defined as CAI≥5 vs. CAI<5 and CSA-CSR as CAI≥5 or CSR.TST<90 was defined per category given its skewed nature: <1%, 1 to <3.5%, 3.5 to <10%, ≥10%.

Participant characteristics were summarized as mean ± SD or n (%) and were compared by AHI category using chi-square tests for categorical variables, t-tests for normally distributed continuous variables, and Wilcoxon rank sum tests for continuous variables with skewed distributions. SDB or nocturnal hypoxemia and subsequent AF risk associations were assessed by logistic regression. Results are presented as odds ratios (OR) with 95% CI. Models are presented as minimally adjusted (age, clinic, race) and multivariable adjusted (age; clinic; race; BMI; total cholesterol; self-reported history of CVD, hypertension, diabetes, stroke, alcohol use, chronic obstructive pulmonary disease; pacemaker placement; use of CVD medications; and also included OAHI in the CSA and CSA-CSR models and CAI in the OSA model. We assessed the SDB by age interaction (significant if p<0.10) and stratified by median age (<76 yrs, ≥76 yrs).(8) Sensitivity analyses included separate analyses excluding participants with a history of CHF or incident CHF.

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All significance levels reported are two-sided and all analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

STUDY POPULATION

Of 843 participants in the final analytic study sample, 86% were Caucasian with an average BMI of 27±4 kg/m^2. Compared to those in our analysis subset, the 390 men who died before sleep visit 2 had higher rates of CAI>=5 (6% vs. 8%, p=0.13) and CSA-CSR (8% vs. 11%, p=0.07) although differences did not reach statistical significance. As expected for this age range, 45% had hypertension (45%). Although 25% had some form of cardiovascular disease, only 3% of participants had a self-reported history of heart failure (**Table 1**). Compared to those with AHI<15, those with AHI≥15 (42% of participants) had a significantly higher BMI, more prevalent hypertension and higher percent total sleep time with hypoxemia (**Table 1**). Compared to the 843 men in our analytic cohort, those 1473 men with PSG data without a history of AF who did not participate in the second exam were similar on average in SDB indices and BMI, and had similar rates of chronic obstructive lung disease, stroke, diabetes and pacemaker placement (p>0.05). However, these men were on average older by 2.5 years and had a higher percentage of hypertension, CVD, CHF, cardiac medication use and lower alcohol intake (p<0.05).

SLEEP DISORDERED BREATHING INDICES AND INCIDENCE OF ATRIAL FIBRILLATION

There were 99 cases of AF (12%) reported over the follow-up period. SDB variables were analyzed in relation to AF incidence (**Table 2**). Overall, SDB defined by AHI level was not a significant predictor of incident AF when considered as a continuous or dichotomous variable.

Alternatively, CSA and CSA-CSR (OR=2.58, 95% CI 1.18-5.66 and OR=2.27, 95% CI 1.13-4.56, respectively) were significantly related to incident AF in the multivariable model including heart failure and obstructive sleep apnea severity. Hypoxemia as defined by percent total sleep time with saturation <90% was a significant predictor of AF in minimally adjusted (3.5% to <10% vs. <1%: OR=1.97, 95% CI 1.07-3.63), but not in fully adjusted analyses. Indices of OSA were not significantly related to incident AF.

SECONDARY ANALYSES

There was a statistically significant interaction of CSA, CSA-CSR and AHI indices and age for the incident AF outcome ($p<0.05$). In multivariable adjusted stratified analyses (**Table 3**), for men 76 years old or older, SDB was significantly associated with AF development– AHI per 5 unit increase: OR=1.22 (95% CI 1.08-1.39) and AHI≥15: OR=2.64 (95% CI 1.16-6.00). Similar to primary analyses, CSA indices remained significant predictors of incident AF in adjusted analyses with an observed stronger magnitude of association: CAI≥5 OR=9.97 (95% CI 2.72-36.50) and CSA-CSR OR=6.31 (95% CI 1.94-20.51) but suffered from low participant counts in the category. Although in minimally adjusted models, OSA defined using OAHI as a continuous variable was a significant predictor of incident AF, this association lost significance in the fully adjusted model. Consistent with findings from the primary analyses, hypoxemia was not significantly associated with incident AF. After excluding those men who had a history of CHF or developed CHF during the follow-up (, results remained significant in multivariable models for CSA-CSR (OR=2.56, 95% CI 1.17-5.58) and were similar in magnitude and marginally significant for CSA (OR=2.42, 95% CI 0.98-5.96, p=0.05).

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DISCUSSION

In this prospective, multicenter study of community-dwelling older men; indices of CSA, including CSR, were significantly associated with incident AF even after accounting for confounders including cardiovascular risk and disease. Additionally, there was effect

modification by age such that all SDB indices were significant predictors of incident AF. Overall, SDB defined by AHI as well central SDB defined by CSA and CSA-CSR significantly predicted AF in participants above the median age (≥76 years) even after consideration of cardiopulmonary risk. The robustness of these findings persisted in sensitivity analyses excluding those with self-reported heart failure. Although these prospective findings do not prove a causal relationship of CSA and AF, they highlight the potential role of CSA as a marker of AF development.(19)

Our finding of a stronger relationship of central apnea compared to obstructive sleep apnea with AF is consistent with previously published cross-sectional results and identifies CSA as a predictor of AF development.(9) Unlike the prior cross-sectional epidemiologic work, AF ascertainment in the current study was based on incident events identified either through adjudication or by self-report and not exclusively based on AF identified by ECG monitoring during the sleep study. A preponderance of data elucidates specific underlying mechanisms related to SDB that contribute to atrial arrhythmogenicity. Autonomic dysfunction, a well-recognized corollary of SDB characterized by enhanced vagal activity during and sympathetic activation subsequent to the respiratory events, increases the likelihood of AF by shortening the atrial effective refractory period and predisposes to focal atrial firing (“adrenergic AF”), respectively.(30, 31) SDB-related intermittent hypoxia represents a potent stimulus of autonomic function activation creating regions of heterogeneous myocyte excitability, thereby increasing

AF propensity.(32) Substantial negative intrathoracic pressure alterations observed in OSA may lead to an abrupt decrease in left atrial volume and reduction in left ventricular systolic performance augmenting AF development.(33) On the other hand, there are some data to suggest that the reverse may be true (i.e. AF may lead to SDB). Paroxysms of AF have been described to occur subsequent to discrete apneic events plausibly due to immediate effects of tachycardia-induced left ventricular dysfunction and diastolic dysfunction leading to reduction of cardiac output and increased pulmonary vascular pressure hence resulting in breathing instability.(34, 35) The findings of this study provide further evidence to support the importance of central apnea pathophysiology leading to AF.

Mechanistically, CSA is characterized by ventilatory system instability resulting in hypocapnia, which may contribute to cardiac electrical instability(36). An underlying increase in central and peripheral chemoresponsiveness may contribute to augmented sympathetic activity and autonomic imbalance, predisposing factors for AF.(37–39) It is possible that CSA is a marker of augmented respiratory chemoreflexes and autonomic nervous system dysfunction rather than the primary impetus for AF development. However, heart failure is associated with autonomic dysfunction and altered chemosensitivity; so, the causal directionality of these associations are unclear. (40) Furthermore, as chemoresponsiveness wanes with age the extent that it plays a role in atrial fibrillation in the older population is unclear.(41) Our observation of a relationship of CSA and AF independent of heart failure is corroborated by findings from clinical studies reporting increased AF in those with central apnea compared to obstructive apnea even in the absence of heart failure.(42) Previous work suggesting that central apnea events directly trigger AF paroxysms also supports a role for CSA in AF development.(43) Further evidence implicating CSA as a true pathogenic factor and not simply a marker of underlying cardiac dysfunction is provided by improvement in heart transplant-free survival in heart failure patients

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whose CSA was effectively suppressed with positive airway pressure treatment.(44) These benefits did not appear to be due to direct positive airway pressure-related improvement in hemodynamics, but rather the reversal of central apnea pathophysiology, i.e. sympathetic nervous system activation secondary to apneas and arousals from sleep.(44, 45) We, however, recognize that we cannot definitively exclude the possibility that CSA may represent a marker of a diseased heart leading to AF.(46, 47) Recent data demonstrate increased mortality in reduced ejection fraction heart failure with CSA treatment by adaptive servoventilation, an advanced positive airway pressure modality. (48) However, given the contrasting pathophysiologic states of heart failure and AF, implications of the reversal of CSA and associated hypoxia/sympathetic activation via positive pressure or non-positive pressure modalities in AF remain unclear and warrant further investigation.

In the current study, stronger associations of SDB with AF were observed in the older study participants. This contrasts with several prior epidemiologic studies demonstrating weaker associations of adverse cardiac outcomes and SDB in older compared to younger individuals.(8, 11) Differences among studies in relationship to age modification relate to differences in age ranges compared. In the current study, the older cohort was a mean age of 76, a group in whom the effects of advanced age and SDB may be multiplicative. For example, the pathophysiologic insults of SDB including intermittent hypoxia, autonomic imbalance, and intrathoracic pressure swings may have more pronounced effects on atrial arrhythmogenesis when superimposed on the aged heart which has a different electrophysiological substrate compared to younger individuals.(49–53) Enhanced impulse generation due to increased automaticity, triggered activity, and reentrant circuits within the atria and pulmonary veins are considered to be responsible for AF initiation and maintenance in the elderly and at a specific age threshold may

be more likely to occur as a pathophysiologic response to SDB-induced physiologic stress.(50, 52, 54)

Unlike prior studies, this work does not show an association with OSA except for the oldest of the old subgroup. This difference may be secondary to different susceptibilities in the very aged (mean age 75 years) compared to cohorts that include significant numbers of middle-aged adults (mean age 49 years).(11)

This study did not show a relationship between hypoxemia and AF development which is somewhat unanticipated. A large single-center clinic-based study showed that degree of hypoxemia was associated with development of AF in individuals younger than 65 but not those 65 or older in fully adjusted models.(11) Another retrospective cohort study (mean age 59 years) affirmed the link between incident AF and hypoxemia, but did not find effect modification by age.(12) In our cohort (all aged >65 years), even the younger subgroup did not show a statistically significant relationship of hypoxemia with the development of AF. This may be secondary to different mechanisms for AF development in the elderly compared to younger individuals and potentially due to limited power as an association of hypoxemia and AF was observed in minimally, but not fully adjusted models.

Strengths of this study include the prospective design and high rate of follow-up completers (99% for the adjudicated AF). Standardized protocols and procedures were used to maximize data integrity. A systematic consideration of several metrics of SDB, including central apnea and overnight hypoxemia, was conducted. Limitations of this study include possible residual confounding. Potentially representing overestimates of true risk, small AF event counts in age-stratified analyses led to large confidence intervals which may be secondary to small differences in AF incidence. A potential limitation is survivorship bias given the higher prevalence of central

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SDB in the subset who died (n=390) and did not participate in the second examination, however, exclusion of these participants would be expected to bias to the null. Because this study focused on a cohort of community-dwelling elderly men, findings may not be generalizable to younger individuals or women. Measures of cardiac function such as echocardiography were not included, which precludes examination of cardiac function mediation of SDB and AF relationships. Use of self-reported measures of cardiac co-morbidity including heart failure limited our ability to adjust for potential confounding related to undiagnosed heart disease. Interestingly, the overall higher percentage of participants with CSA-CSR relative to the percentage of participants with self-reported heart failure or stroke suggests the possibility of under-reporting of these co-morbidities versus central apnea physiology which is idiopathic or attributable to other factors. Future investigation focused on the underlying pathways which link SDB and AF should examine the role of cardiac function and structure through morphologic analysis, the interplay between CSA and respiratory chemoreflexes and autonomic dysfunction, and the role of biochemical mediators, i.e. systemic inflammation and oxidative stress. In addition, further characterization of phenotypes of central sleep apnea by analysis of apnea, ventilation, and overall cycle length may provide further insight into the mechanism of this phenomenon.(55, 56) Although we cannot exclude the possibility that CSA represents a marker of altered chemosensitivity and autonomic dysfunction mediating AF risk, these findings provide a basis to risk stratify and target individuals with CSA for AF risk reduction and potentially supports investigation of CSA pathophysiology reversal on AF development.

This study highlights the importance of CSA and Cheyne-Stokes respiration in the development of incident AF with results strengthened in the older subgroup of this elderly cohort of men. These findings suggest that CSA serves as an important potential prevention and therapeutic

target for AF particularly in older individuals, the latter representing a group particularly susceptible to AF development and accompanying morbidity.

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TABLES

Table 1. Baseline Characteristics of Participants*

Characteristic	Overall (N= 843)	AHI<15 (N= 491)	AHI≥15 (N= 352)	p-value
Age, yr	75 ± 5	74 ± 5	75 ± 5	0.50
Race/Ethnicity				0.89
Caucasian	726 (86)	419 (85)	307 (87)	
African American	36 (4)	22 (5)	14 (4)	
Asian	40 (5)	25 (5)	15 (4)	
Other	41 (5)	25 (5)	16 (4)	
Body mass index, kg/m^2	27 ± 4	27 ± 4	28 ± 4	<.0001
Diabetes	101 (12)	56 (11)	45 (13)	0.54
Hypertension	383 (45)	202 (41)	181 (51)	0.003
Cardiovascular disease†	208 (25)	115 (23)	93 (26)	0.32
Heart failure	25 (3)	12 (2)	13 (4)	0.29
Stroke	22 (3)	16 (3)	6 (2)	0.16
Chronic obstructive pulmonary disease or emphysema	33 (4)	18 (4)	15 (4)	0.66
Pacemaker placement	17 (2)	8 (2)	9 (3)	0.34
Total cholesterol, mg/dL	197 ± 34	196 ± 33	198 ± 36	0.45
Taking cardiovascular medications	272 (32)	150 (31)	122 (35)	0.21
Alcohol use, drinks per week				0.61
<1	384 (46)	229 (47)	155 (44)	
1-13	393 (47)	226 (46)	167 (48)	
≥14	60 (7)	32 (7)	28 (8)	
Obstructive apnea hypopnea index	16 ± 14	7 ± 4	29 ± 13	<.0001
Central apnea index ≥5	48 (6)	4 (1)	44 (13)	<.0001
Central sleep apnea-Cheyne Stokes respiration	68 (8)	12 (2)	56 (16)	<.0001
% Total Sleep Time with SaO_2<90%				<.0001
<1%	416 (49)	339 (69)	77 (22)	
1 to <3.5%	236 (28)	108 (22)	128 (36)	
3.5 to <10%	100 (12)	23 (5)	77 (22)	
≥10%	91 (11)	21 (4)	70 (20)	

* For continuous variables mean and standard deviations are presented and number and percentage in parentheses are presented for categorical variables.
†Cardiovascular disease includes myocardial infarction, angina, heart failure, coronary bypass surgery, and angioplasty.
P-values generated from T-test for normally distributed continuous variables, Wilcoxon rank sum test for skewed variables, and Chi-square test for categorical data.

Table 2. Adjusted Associations of Sleep Disordered Breathing Predictors and Incident Atrial Fibrillation or Flutter*

Predictor	N Event/ Total N	Minimally Adjusted† OR (95% CI)	Multivariable Adjusted‡ OR (95% CI)
AHI, per 5 increase	99/843	1.05 (0.98 - 1.13)	1.01 (0.94 - 1.10)
AHI<15	49/491	1.00 (reference)	1.00 (reference)
AHI≥15	50/352	1.47 (0.95 - 2.27)	1.15 (0.72 - 1.84)
OAHI, per 5 increase§	99/843	1.04 (0.97 - 1.12)	0.98 (0.91 - 1.07)
CAI<5	88/795	1.00 (reference)	1.00 (reference)
CAI≥5§	11/48	**2.34 (1.14 - 4.77)**	**2.58 (1.18 - 5.66)**
No CSA-CSR	85/775	1.00 (reference)	1.00 (reference)
CSA-CSR§	14/68	**2.10 (1.11 - 3.97)**	**2.27 (1.13 - 4.56)**
% Total Sleep Time with SaO2<90%			
<1%	43/416	1.00 (reference)	1.00 (reference)
1% to <3.5%	24/236	0.93 (0.55 - 1.60)	0.83 (0.47 - 1.47)
3.5% to <10%	19/100	**1.97 (1.07 - 3.63)**	1.64 (0.83 - 3.24)
≥ 10%	13/91	1.31 (0.65 - 2.64)	1.01 (0.46 - 2.24)

* Data presented as OR (95% Confidence interval); OAHI adjustment continuous, CAI adjustment CAI≥5

† Adjusted for age, clinic, and race

‡ Adjusted for age, clinic, race, body mass index, history of cardiovascular disease, hypertension, diabetes, stroke, chronic obstructive pulmonary disease, pacemaker placement, total cholesterol, use of cardiovascular medications, and alcohol use

§ Multivariable models further adjusted by alternate apnea type: models with CAI and CSA-CSR predictors are further adjusted by OAHI; the model with the OAHI predictor is further adjusted by CAI

Key: AHI: apnea hypopnea index, CAI: central apnea index, CSA-CSR: Cheyne Stokes respirations or central sleep apnea, OAHI: obstructive apnea hypopnea index

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Table 3. Age-Stratified Adjusted Associations of Sleep Disordered Breathing Predictors and Incident Atrial Fibrillation or Flutter*

Predictor	N Event/ Total N	Minimally Adjusted† OR (95% CI)	Multivariable Adjusted‡ OR (95% CI)
AGE < 76			
AHI, per 5 unit increase	57/529	0.95 (0.86 - 1.06)	0.92 (0.82 - 1.04)
AHI<15	33/308	1.00 (reference)	1.00 (reference)
AHI≥15	24/221	0.96 (0.54 - 1.70)	0.79 (0.42 - 1.49)
OAHI, per 5 unit increase§	57/529	0.95 (0.85 - 1.06)	0.92 (0.82 - 1.04)
CAI<5	53/500	1.00 (reference)	1.00 (reference)
CAI≥5§	4/29	1.33 (0.44 - 3.99)	1.22 (0.34 - 4.41)
No CSA-CSR	51/486		
CSA-CSR§	6/43	1.36 (0.55 - 3.40)	1.45 (0.52 - 4.07)
%Total Sleep Time with SaO_2< 90%			
<1%	29/276	1.00 (reference)	1.00 (reference)
1% to <3.5%	11/139	0.69 (0.33 - 1.45)	0.61 (0.28 - 1.35)
3.5% to <10%	12/61	2.13 (0.99 - 4.57)	1.74 (0.71 - 4.24)
≥ 10%529+	5/53	0.78 (0.27 - 2.23)	0.57 (0.18 - 1.82)
AGE ≥ 76			
AHI, per 5 unit increase	42/314	**1.20 (1.08 - 1.33)**	**1.22 (1.08 - 1.39)**
AHI<15	16/183	1.00 (reference)	1.00 (reference)
AHI≥15	26/131	**2.91 (1.43 - 5.90)**	**2.64 (1.16 – 6.00)**
OAHI, per 5 unit increase§	42/314	**1.17 (1.05 - 1.30)**	1.13 (0.98 - 1.29)
CAI<5	35/295	1.00 (reference)	1.00 (reference)
CAI ≥ 5§	7/19	**4.86 (1.72 - 13.72)**	**9.97 (2.72 - 36.50)**
No CSA-CSR	34/289	1.00 (reference)	1.00 (reference)
CSA-CSR§	8/25	**3.88 (1.50 - 10.07)**	**6.31 (1.94 - 20.51)**
%Total Sleep Time with SaO_2< 90%			
<1%	14/140	1.00 (reference)	1.00 (reference)
1% to <3.5%	13/97	1.34 (0.58 - 3.09)	1.69 (0.65 - 4.40)
3.5% to <10%	7/39	1.93 (0.67 - 5.51)	2.24 (0.69 - 7.30)
≥ 10%	8/38	2.38 (0.87 - 6.52)	2.68 (0.77 - 9.34)

* The p-value for interaction was significant for all variables (p<0.10). Interactions with age as a categorical variable (above/below median): AHI continuous, p=0.01; AHI≥15, p=0.04; OAHI, p=0.02). Interactions of age as a continuous variable: CAI>=5, p=0.04, CSA-CSR, p=0.02; %total sleep with SaO_2<90%, p=0.08). Data is presented as OR (95% Confidence interval)
† Adjusted for age, clinic, and race
‡ Adjusted for age, clinic, race, body mass index, history of cardiovascular disease, hypertension, diabetes, stroke, chronic obstructive pulmonary disease, pacemaker placement, total cholesterol, use of cardiovascular medications, and alcohol use

§ Multivariable models further adjusted by alternate apnea type: models with CAI and CSA-CSR predictors are further adjusted by OAHI; the model with the OAHI predictor is further adjusted by CAI

Key: AHI: apnea hypopnea index, CAI: central apnea index, CSA-CSR: Cheyne Stokes respirations or central sleep apnea, OAHI: obstructive apnea hypopnea index

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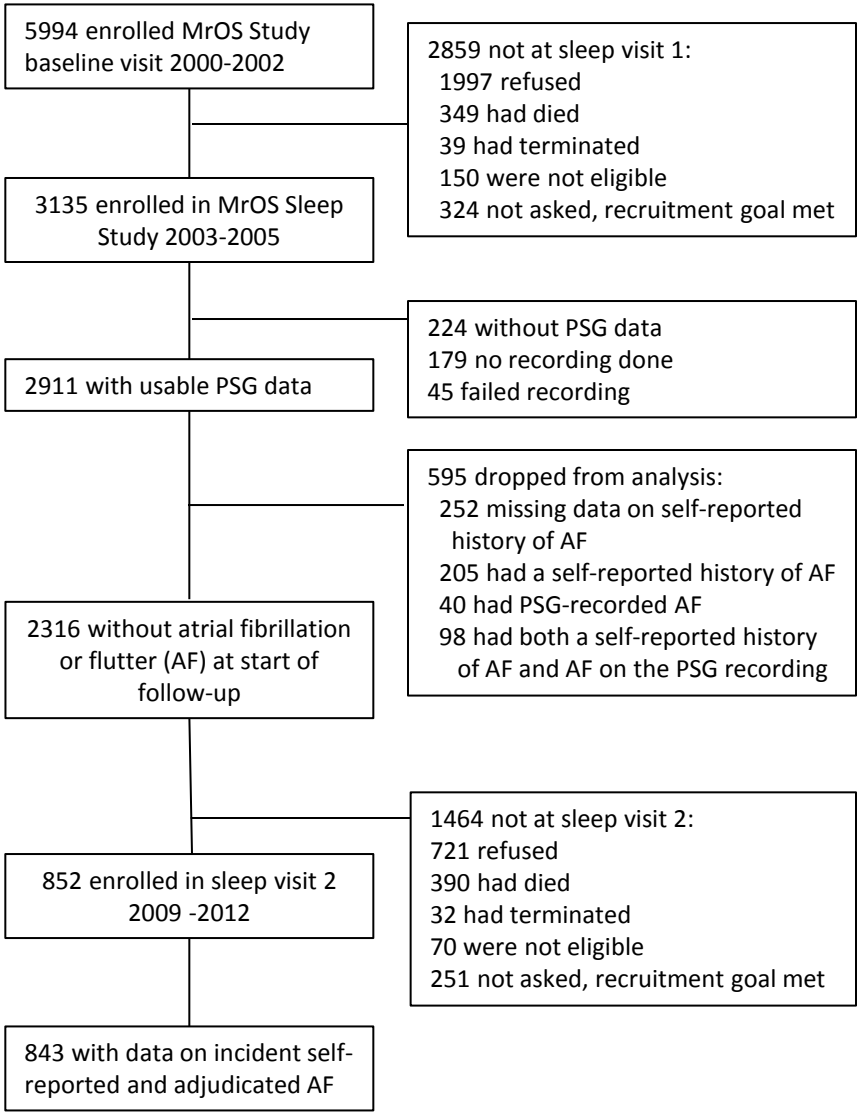
FIGURES

Figure 1. Study Design: Recruitment, Attrition, and Retention



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Online Supplement

Central Sleep Disordered Breathing Predicts Incident Atrial Fibrillation in Older Males

May AM, Blackwell T, Stone PH, Stone KL, Cawthon PM, Varosy PD, Redline S, Mehra R for the Osteoporotic Fractures in Men (MrOS) Study Group.

METHODS

PARTICIPANTS AND STUDY DESIGN

The MrOS Sleep Study, an ancillary study of the MrOS cohort, recruited 3,135 participants December 2003 - March 2005 for a comprehensive sleep assessment. MrOS Sleep Study participants were screened for nightly use of mechanical devices during sleep including pressure mask for sleep apnea (continuous positive airway pressure or bilevel positive airway pressure), mouthpiece for snoring or sleep apnea, or oxygen therapy and were excluded if they could not forgo use of these devices during a polysomnography (PSG) recording. Of the 2859 men who did not participate in the MrOS Sleep Study, 349 died before the sleep visit, 39 had already terminated the study, 324 were not asked because recruitment goals had already been met, 150 were ineligible, and 1997 refused. Of the 3135 MrOS Sleep Study participants recruited 179 did not participate in PSG secondary to refusal or contemporaneous treatment of SDB, and 45 men had a failed sleep study (1.5%), resulting in 2911 participants. Of these, 2316 did not have prevalent AF defined as either PSG-identified or self-reported AF at the first sleep visit.

All participants who remained active in the study and had acceptable PSG and actigraphy data from the initial sleep visit were eligible to be contacted to participate in a second sleep visit. For the second sleep visit a special emphasis was placed on minority recruitment, so all available minority participants were contacted for participation. Non-minority participants were contacted in random order for enrollment until the study recruitment goal was met. Of the 2316 men with PSG data and no history

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of AF at the initial sleep visit, 852 participants were assessed at the second sleep visit, of which 843 had incident self-reported and adjudicated AF data (**Figure 1**).

POLYSOMNOGRAPHY DATA

An unattended home PSG (Safiro, Compumedics, Inc.®, Melbourne, Australia) was performed after the first sleep visit consisting of recording of C_3/A_2 and C_4/A_1 electroencephalograms, bilateral electrooculograms, a bipolar submental electromyogram, thoracic and abdominal respiratory inductance plethysmography, airflow (by nasal-oral thermocouple and nasal pressure cannula), finger pulse oximetry, lead I EKG (250Hz), body position, and bilateral leg movements. Trained, certified staff set up the units in the participant's homes for 1 night. Apnea was defined as complete or near complete cessation of airflow for 10 or more seconds. The event was categorized as obstructive if effort was evident on thoraco-abdominal inductance channels or as central if there was no effort detected. Hypopneas were scored if reductions in breathing amplitude (at least 30% below baseline breathing) occurred, and lasted 10 or more seconds with a drop in arterial saturation of 3% or more.(1) The inter-scorer reliability for AHI was high (ICC=0.99).

OUTCOME MEASURES

We defined AF based upon similar criteria used in prior studies as either incident adjudicated AF meeting stringent clinical criteria or self-reported AF.(2–4) Adjudicated AF was identified by surveying participants for incident cardiovascular events by postcard and/or phone every four months (>99% response rate) followed by central

adjudication by a board certified cardiologist using a standard protocol. Participants were asked if they had visited the emergency department or admitted to the hospital in the last 4 months, and if so, if the visit was due to cardiovascular causes. Medical records and supporting documentation from potential incident events were centrally adjudicated by a board-certified cardiologist using a pre-specified adjudication protocol. Specific documentation was required for adjudication of arrhythmias which were divided into subtypes. The following symptoms of arrhythmia were considered in adjudication: fatigue, palpitations, lightheadedness, pre-syncope, syncope, chest pain, or dyspnea. Documentation required for adjudicated AF event included one or more of the following: emergency medical services notes and/or rhythm strips, electrocardiography (including stress testing), in-hospital telemetry, ambulatory electrocardiography (Holter monitor and/or event monitor), pacemaker or defibrillator telemetry (for those patients with a device already implanted), or invasive cardiac electrophysiology testing. Atrial fibrillation and atrial flutter events specifically include the pre-excited forms of either of these tachycardias as well as any cardioversion procedures to restore normal sinus rhythm.

OTHER MEASURES

All participants completed questionnaires at the initial sleep visit, which included demographics, medical history, and alcohol use questions. Participants were asked to bring in all medications used within the preceding 30 days, which were recorded in an electronic database. All prescription and nonprescription medications were entered into an electronic database and each medication was matched to its ingredient(s) based on the Iowa Drug Information Service (IDIS) Drug Vocabulary (College of Pharmacy,

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University of Iowa, Iowa City, IA).(5) The use of cardiovascular medications was categorized by type and included calcium channel blockers, non-ophthalmic beta-blockers, cardiac glycosides, or anti-arrhythmic medications – cardiac sodium channel blockers and potassium channel blockers.(6) Body weight was measured with standard balance beam or digital scale calibrated with standard weights, and height was measured with a wall-mounted Harpenden stadiometer to calculate body mass index (BMI, kg/m^2). Presence of a pacemaker was determined by examination of the PSG ECG recording. Cholesterol was measured an average of 3.4 years earlier during the MrOS baseline visit using a Roche COBAS Integra 800 automated analyzer that was calibrated daily (Roche Diagnostics Corp., Indianapolis, IN). Total cholesterol (mg/dl) was calculated as: high-density lipoprotein (mg/dl) + low-density lipoprotein (mg/dl) + 0.5*triglycerides (mg/dl). Cardiovascular disease (CVD) was defined by self-reported history of myocardial infarction, angina, angioplasty, congestive heart failure (CHF), and/or coronary artery bypass graft surgery.

STATISTICAL ANALYSIS

Models are presented as minimally adjusted (age, clinic, race) and multivariable adjusted (adjusted for age, clinic, race, BMI, total cholesterol and self-reported history of CVD, hypertension, diabetes, stroke, alcohol use, chronic obstructive pulmonary disease [COPD], pacemaker placement, and use of CVD medications). The multivariable models with OSA as a predictor included adjustment for CAI>5 and the

models with CSA or CSA-CSR as predictors included adjustment for OAHI as a continuous variable.

Since age is associated with increasing prevalence of both SDB and AF and prior work has noted an SDB-age interaction with cardiac arrhythmia,(8) we examined the possible interaction between age and SDB parameters in secondary analyses and stratified by median age (<76 yrs., ≥76 yrs). Interaction terms were considered significant if $p<0.10$. Sensitivity analyses were performed excluding participants with a history of CHF or incident CHF

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