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Obstructive Sleep Apnea, Obesity, and the Risk of Incident Atrial Fibrillation

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Objectives This study sought to identify whether obesity and obstructive sleep apnea (OSA) independently predict incident atrial fibrillation/flutter (AF).

Background Obesity is a risk factor for AF, and OSA is highly prevalent in obesity. Obstructive sleep apnea is associated with AF, but it is unknown whether OSA predicts new-onset AF independently of obesity.

Methods We conducted a retrospective cohort study of 3,542 Olmsted County adults without past or current AF who were referred for an initial diagnostic polysomnogram from 1987 to 2003. New-onset AF was assessed and confirmed by electrocardiography during a mean follow-up of 4.7 years.

Results Incident AF occurred in 133 subjects (cumulative probability 14%, 95% confidence interval [CI] 9% to 19%). Univariate predictors of AF were age, male gender, hypertension, coronary artery disease, heart failure, smoking, body mass index, OSA (hazard ratio 2.18, 95% CI 1.34 to 3.54) and multiple measures of OSA severity. In subjects <65 years old, independent predictors of incident AF were age, male gender, coronary artery disease, body mass index (per 1 kg/m^2, hazard ratio 1.07, 95% CI 1.05 to 1.10), and the decrease in nocturnal oxygen saturation (per 0.5 U log change, hazard ratio 3.29, 95% CI 1.35 to 8.04). Heart failure, but neither obesity nor OSA, predicted incident AF in subjects ≥65 years of age.

Conclusions Obesity and the magnitude of nocturnal oxygen desaturation, which is an important pathophysiological consequence of OSA, are independent risk factors for incident AF in individuals <65 years of age. (J Am Coll Cardiol 2007;49:565–71) © 2007 by the American College of Cardiology Foundation

Atrial fibrillation/flutter (AF) is the most prevalent sustained cardiac arrhythmia in the U.S. (1) and is associated with significant morbidity and mortality (2,3). In the U.S., the major clinical risk factors for AF include age, diabetes, hypertension, heart failure, and coronary artery disease (4). Long-term follow-up data of over 5,000 subjects in the Framingham Heart Study (5) and nearly 48,000 subjects in the Danish Diet, Cancer and Health Study (6) showed that obesity predicts AF independently of other clinical characteristics. In the context of the growing obesity epidemic, these data have important implications for the population burden of AF. They also raise the important question of how obesity leads to AF.

In a recent cross-sectional study, we showed a strong association between AF and obstructive sleep apnea (OSA), independently of age, gender, hypertension, heart failure and, importantly, body mass index (7). No prior study, including the Framingham study and the Danish study, has assessed the potential contributions of OSA to the risk of AF associated with obesity. For several reasons, OSA may have an important role in clarifying the relationship between obesity and AF (8). First, obesity and OSA are powerfully and causally related (9). Second, pathophysiological characteristics traditionally attributed to obesity have been shown to be linked to occult OSA (10–14). Third, OSA is associated with multiple pathophysiological mechanisms that may be directly implicated in the pathogenesis of AF either by triggering its initiation or by affecting the myocardial substrate to promote or maintain the arrhythmia. These mechanisms include repetitive and prolonged hypoxemia, exaggerated intrathoracic pressure oscillations with increased cardiac wall stress (15–17), sympathetic and parasympathetic imbalances (18), systemic inflammation (14), and diastolic dysfunction (19–22). It is unknown, however, whether OSA increases the risk of

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Abbreviations and Acronyms

AF = atrial fibrillation/flutter
CI = confidence interval
HR = hazard ratio
OSA = obstructive sleep apnea

incident AF and how comorbid conditions, including obesity, may affect this relationship.

Methods

Study population. The Institutional Review Board of the Mayo Foundation approved the study, and we only included individuals who authorized their records to be used for research. Data were collected from subjects' medical records by dedicated and specifically trained personnel in a cardiovascular research studies unit. Quality control of data collection was maintained by supervision and feedback to the research personnel by a study physician. A validation series found excellent agreement between data of a subgroup of subjects collected blindly by both a study physician and the trained research personnel (Cohen kappa 0.91) (23).

We identified adult residents of Olmsted County, Minnesota, who underwent their first diagnostic polysomnography at the Mayo Clinic Sleep Disorders Center from July 1, 1987, to July 31, 2003. During these years, the Mayo Clinic was the sole provider, in Olmsted County, of a comprehensive sleep disorders evaluation, with initial consultation by a sleep specialist, complete overnight polysomnography, study review with the sleep specialist, and long-term management of treatment when necessary. We excluded people with AF or a previous history of AF at the time of their first-ever polysomnogram because we wished to assess the risk of incident AF after the initial diagnosis of OSA. Data were collected regarding demographics, anthropomorphic measurements, and relevant comorbid conditions at the time of polysomnography for each subject.

Classification of OSA. All subjects' sleep evaluations were performed at the Mayo Clinic Sleep Disorders Center, an American Academy of Sleep Medicine-accredited sleep center with real-time monitoring of polysomnography by certified sleep technicians and supervision by board-certified sleep specialists. Each evaluation consisted of consultation with a board-certified sleep physician and split-night polysomnography, in which the first half of the night is a diagnostic study consisting of measurements of the electroencephalogram, electro-oculogram, electromyogram, electrocardiogram, thoracoabdominal excursions, pulse oximetry, and naso-oral airflow. Physiological variables collected from the polysomnograms included sleep efficiency; arousal index; the number of central apneas, obstructive or mixed apneas, and hypopneas per hour of rapid eye movement and non-rapid eye movement sleep; oxygen saturation during wakefulness; mean oxygen saturation during sleep; and the lowest oxygen saturation during sleep. Apneas and hypopneas were defined as obstructive events if occurring in the presence of thoracoabdominal excursions representing ventilatory efforts, and the apnea-hypopnea index was calculated as the average number of obstructive apneas and hypopneas per hour of sleep. We defined OSA as an apnea-hypopnea index ≥ 5 (24).

We ascertained the use of continuous positive airway pressure therapy during follow-up. We considered that continuous positive airway pressure had been used if it was prescribed during the consultation with the sleep specialist after the sleep study and if a subsequent note in the medical record stated that continuous positive airway pressure was being used.

Classification of AF. The occurrence of incident AF was ascertained from the date of polysomnography to the date of death or last follow-up (which was the date of the last clinic visit, nursing home visit, emergency department visit, surgical procedure, hospitalization, or laboratory evaluation) by querying the Mayo Clinic electronic medical index. The Mayo Clinic uses a unified medical record that includes the details of all inpatient and outpatient encounters, laboratory reports, and correspondence for every patient (25). Diagnoses made during office visits, clinic consultations, nursing home care, emergency department visits, surgical procedures, hospitalizations, and autopsy examinations are listed on a master sheet, assigned a modified hospital International Classification of Disease adaptation code, and included in a central, electronic, searchable diagnostic index (25). We cross-referenced our study sample with all medical index diagnostic codes for acute, paroxysmal, and chronic atrial fibrillation; atrial fibrillation-flutter; and atrial flutter. For quality assurance, we also manually reviewed the full medical record of each subject with AF identified by the above methods. We established the occurrence of AF only when a study physician confirmed the diagnosis by review of an electrocardiogram. We were interested in the occurrence of incident AF, and thus did not assess the duration of AF and made no distinction between paroxysmal, persistent, or permanent AF. The collection of follow-up data and confirmation of AF were performed in a blinded fashion to the collection of polysomnographic data and the classification of OSA.

Statistical analysis. Characteristics of the study population were described by counts (with percentages) and means (with standard deviations) or medians (with interquartile ranges).

Time-to-event analyses were performed using Kaplan-Meier methods to identify univariate predictors of incident AF. The parameters included subject age, gender, body mass index, relevant comorbidities, OSA status and severity, and physiological sleep variables. Multivariate time-to-event analyses were performed using Cox proportional hazards regression methods. A stepwise selection technique was used to construct a clinical model with parameters that are well-established clinical predictors of AF, including age, gender, smoking history, hypertension, diabetes, coronary artery disease, and heart failure. We also included body mass index as a potential predictor in this model.

To assess the risk of AF posed by OSA and its related sleep parameters, we included these variables into the model independently of one another: OSA status, OSA severity, the apnea-hypopnea index, arousal index, awake oxygen saturation, lowest nocturnal oxygen saturation, mean nocturnal oxygen saturation, and decrease in nocturnal oxygen saturation (defined as the awake oxygen saturation minus mean nocturnal oxygen saturation). Continuous variables with a non-Gaussian distribution were logarithmically transformed for analysis.

We tested for effect modification of the dependent variable by interactions between OSA and gender or age by incorporating multiplicative interaction terms (OSA × gender and OSA × age) into the regression models. The rationale for this was the established increase of risk in men for both OSA (26) and AF (4), and the recognized nonmonotonic association between OSA and cardiovascular morbidity and mortality across the adult ages (27,28). Prior studies found that significant relationships between OSA and cardiovascular morbidity and mortality existed in adults through age 60 or 65 years, and then became nonsignificant in older patients (27,28). Thus, we performed multivariate analyses using Cox proportional hazards regression methods, as described above, to create additional models incorporating clinical predictors and physiological sleep parameters for subjects <65 years of age and for subjects ≥65 years of age.

We performed an analysis that included only subjects with OSA to identify the effect of continuous positive airway pressure use on the risk of incident AF. The use of continuous positive airway pressure was introduced into a multivariate model, which was created as described above to include the clinical predictors and sleep measurements. We performed an additional analysis to assess the simultaneous effects of both obesity and OSA, regardless of other comorbidities, on incident AF by comparing the cumulative probability of incident AF across 9 groups of subjects characterized by their apnea-hypopnea index (<5, 5 to 40, and ≥40) and body mass index (<25, 25 to 30, and ≥30 kg/m^2). Also, to evaluate whether greater follow-up in patients with OSA could account for increased identification of AF in these patients, we performed linear regression analyses to identify an association between follow-up duration and the apnea-hypopnea index, and to compare follow-up duration in patients without OSA and patients with increasing severities of OSA.

Analyses were performed using SAS Proprietary Software Release 8.2 (1999 to 2000, SAS Institute, Cary, North Carolina). A 2-sided p value <0.05 was considered statistically significant for all analyses. The authors had full access to the data and take responsibility for its integrity; all authors have read and agree to the article as written.

Results

Study population. The study population consisted of 3,542 subjects, and their baseline characteristics are described in Table 1. Obstructive sleep apnea (defined by an apnea-hypopnea index ≥5) was present in 2,626 subjects (74%), and their mean apnea-hypopnea index was 36 (±32), mean awake oxygen saturation was 96% (±3%), mean nocturnal oxygen saturation was 93% (±4%), and lowest nocturnal oxygen saturation was 81% (±11%). Use of continuous positive airway pressure was reported for 123 of 695 (18%), 190 of 636 (30%), 253 of 648 (39%), and 338 of 647 (52%) subjects with increasing severity of OSA based on quartiles of the apnea-hypopnea index. Bivariate linear regression showed no association between follow-up time and the apnea-hypopnea index (p = 0.87). Follow-up duration was similar for patients without OSA (4.76 years) and for patients with increasing severities of OSA based on quartiles of the apnea-hypopnea index (4.66 vs. 4.79 vs. 4.50 vs. 4.59 years; analysis of variance p = 0.58).

Table 1 Baseline Characteristics of Patients

Characteristic	Value
Age, mean (SD), yrs	49 (14)
Male gender, n (%)	2,349 (66)
Body mass index, mean (SD), kg/m^2	33 (9)
Coronary artery disease, n (%)	342 (10)
Heart failure, n (%)	89 (3)
Hypertension, n (%)	1,178 (33)
Diabetes mellitus, n (%)	397 (11)
History of smoking, n (%)	1,798 (56)
Obstructive sleep apnea, n (%)	2,626 (74)
Lowest nocturnal oxygen saturation, %	
Mean (SD)	83 (10)
Median	87
Mean nocturnal oxygen saturation, %	
Mean (SD)	93 (5)
Median	94
Decrease in nocturnal oxygen saturation,* %	
Mean (SD)	12 (10)
Median	9
Apnea–hypopnea index, events/h	
Mean (SD)	26.7 (31.3)
Median	15.0
Arousal index, events/h	
Mean (SD)	35.4 (26.1)
Median	28.0

*This variable is defined as the difference between awake oxygen saturation and mean nocturnal oxygen saturation.

Incidence of AF. After an average follow-up of 4.7 years (up to 15 years), incident AF occurred in 133 subjects (cumulative frequency 14%, 95% confidence interval [CI] 9% to 19%). Clinical characteristics and sleep measurements that predicted incident AF are listed in Table 2. These included established risk factors for AF, such as male gender, age, hypertension, coronary artery disease, heart failure, and smoking. In addition, body mass index strongly predicted incident AF (per 1 kg/m^2, hazard ratio [HR] 1.03, 95% CI 1.02 to 1.05, p < 0.001). Furthermore, OSA (defined by an apnea-hypopnea index ≥5) was a strong predictor of incident AF (HR 2.18, 95% CI

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Table 2 Risk of Incident Atrial Fibrillation, Univariate Model

	HR	95% CI	p Value
Age (per 10 yrs)	2.11	1.85–2.41	<0.001
Male gender	1.86	1.22–2.85	0.004
Hypertension	2.85	2.02–4.02	<0.001
Coronary artery disease	5.15	3.56–7.44	<0.001
Heart failure	11.76	7.6–18.20	<0.001
History of smoking	1.82	1.24–2.66	0.002
Diabetes mellitus	2.50	1.66–3.78	<0.001
Body mass index (per 1 kg/m^2)	1.03	1.02–1.05	<0.001
Obstructive sleep apnea (apnea–hypopnea index ≥5)	2.18	1.34–3.54	0.002
Apnea–hypopnea index (per 1 event/h)*	1.31	1.14–1.50	0.0001
Tertiles of apnea–hypopnea index distribution	1.36	1.13–1.64	0.001
Arousal index (per 1 event/h)*	1.65	1.29–2.10	<0.001
Lowest nocturnal oxygen saturation (per −1%)*	3.08	1.72–5.54	<0.001
Mean nocturnal oxygen saturation (per −1%)†	1.30	2.82–4.77	0.05

*For a 1-U change in the logarithm. †For a 0.1-U decrease in the logarithm.
CI = confidence interval; HR = hazard ratio.

1.34 to 3.54, p = 0.002). Atrial fibrillation occurred in 114 of 2,626 patients (4.3%) with OSA and in 19 of 916 patients (2.1%) without OSA. Measures of OSA severity were also strong predictors of incident AF: the log of the apnea-hypopnea index (p < 0.001), tertiles of the apnea-hypopnea index (p = 0.001), log of the arousal index (p < 0.001), log of the lowest nocturnal oxygen saturation (p < 0.001), and log of the mean nocturnal oxygen saturation (p = 0.05).

Age-stratified, multivariate analyses. The regression models showed a significant interaction between OSA and age (p = 0.04). This was consistent with previous data showing that age modifies the effect of OSA on cardiovascular outcomes, such that cardiovascular effects of OSA manifest in individuals younger than about age 65, but not in those who are older (27,28). These considerations provided the rationale for stratified analyses for subjects younger than 65 years (3,053 of 3,542, 86%) and 65 years or older (489 of 3,542, 14%). The cumulative probability of incident AF was significantly greater for subjects <65 years of age with OSA compared with those without OSA (Fig. 1). The results of multivariate Cox proportional hazards regression for subjects <65 years of age and for subjects ≥65 years of age are shown in Table 3. In subjects <65 years of age, established risk factors for AF (age, male gender, and coronary artery disease) independently predicted incident AF, as did body mass index (per 1 kg/m^2, HR 1.07, 95% CI 1.05 to 1.10, p < 0.001). The decrease in nocturnal oxygen saturation also was an independent predictor of incident AF (for each 0.5-U change in the log, HR 3.29, 95% CI 1.35 to 8.04, p = 0.009). For subjects ≥65 years old, only heart failure independently predicted incident AF (HR 7.68, 95% CI 4.32 to 13.66, p < 0.001). In a multivariate regression model that included only subjects with OSA, use of continuous positive airway pressure did not positively or negatively affect the incidence of AF. In multivariate regression models that directly compared the effects of OSA and obesity on incident AF, the conditions significantly predicted incident AF independently of each other (Fig. 2).

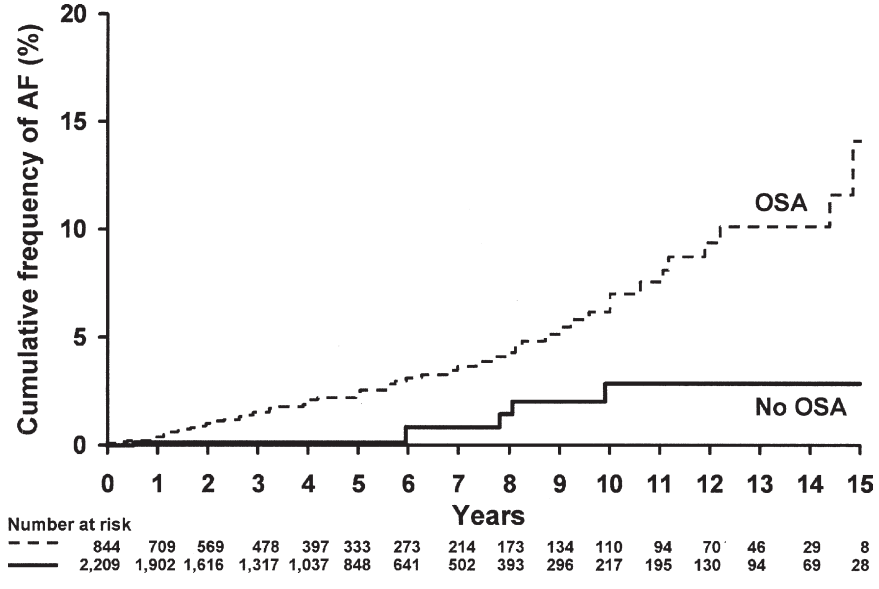

Figure 1 Incidence of AF Based on Presence or Absence of OSA

Cumulative frequency curves for incident atrial fibrillation (AF) for subjects <65 years of age with and without obstructive sleep apnea (OSA) during an average 4.7 years of follow-up. p = 0.002.

Table 3 Risk of Incident Atrial Fibrillation, Multivariate Models

	HR	95% CI	p Value
<65 yrs old			
Age (per 10 yrs)	2.04	1.48–2.80	<0.001
Male gender	2.66	1.33–5.30	0.006
Coronary artery disease	2.66	1.46–4.83	0.001
Body mass index (per 1 kg/m^2)	1.07	1.05–1.10	<0.001
Decrease in nocturnal oxygen saturation (per −1%)*	3.29	1.35–8.04	0.009
≥65 yrs old			
Heart failure	7.68	4.32–13.66	<0.001

*For a 0.5-U change in the logarithm of the difference between awake oxygen saturation and mean nocturnal oxygen saturation.
CI = confidence interval; HR = hazard ratio.

Discussion

This large cohort study provides important insights into the relationships between obesity, OSA, and AF. First, it confirms recent data showing that obesity is an independent risk factor for incident AF (5,6). It extends this information with the novel finding that body mass index predicts incident AF independently of OSA. Furthermore, the study has shown for the first time that in individuals <65 years of age, OSA strongly predicts the incidence of AF within about 5 years of its diagnosis, and that the degree of nocturnal oxygen desaturation, which is an important pathophysiological consequence of OSA, independently correlates with the risk of incident AF.

Although recent studies showed an independent role of obesity in predicting AF (5,6), other data suggest that this relationship may not be evident in older patients (i.e., those ≥65 years of age) (29,30). In this context, the findings in our select population suggest that the mechanisms by which obesity confers risk of AF may be more significant during younger adult ages. In these individuals, for every increase of 5 kg/m^2 (e.g., moving from normal weight to overweight, or from overweight to mild obesity), the risk of incident AF increased by 15%.

Similar differential effects of age on incident AF risk were evident for OSA. The limitation of the predictive power of OSA to adults <65 years of age is consistent with previous studies of OSA and cardiovascular morbidity and mortality (27,28), which together suggest that the pathophysiological consequences of OSA are less striking in older adults, in whom other factors may have greater prognostic significance. Why OSA and obesity may be accompanied by an increased risk of incident AF in individuals <65 years of age but not in older persons is unclear. Obesity and OSA are likely to be present and established by middle age. It is possible that when obesity and/or OSA are diagnosed at age 65 years or older, both conditions would already have been present for many years before diagnosis, and any effect on the incidence of AF already would be manifest. Subjects with AF at the time of diagnosis of OSA were excluded from our study—it is possible that if the effects of obesity and OSA had not already led to AF by the age of 65, then they were unlikely to do so as these older patients aged.

It is crucial for studies of obesity and cardiovascular risk to identify OSA in the study populations because several cardiovascular disease mechanisms in obese people can also be attributable to occult OSA (10–14). Although relationships between obesity and AF have been explored, no prior study incorporated the presence or absence of OSA into predictive models for AF during long-term follow-up. Therefore, it remained unclear whether OSA was confounding relationships between obesity and AF. In the present study, we were able to classify the presence or absence of OSA based on the gold standard diagnostic test, polysomnography, in a large study population. That obesity remains a powerful predictor of incident AF, even after controlling for OSA, in people <65 years of age clarifies an important question raised by previous studies (8).

Our finding that the magnitude of the decrease in nocturnal oxygen saturation was independently predictive of incident AF may provide insight into the putative mechanisms that link OSA to the development of AF. The primary consequence of an apnea is hypoxemia, which directly or indirectly (by promoting ischemia, sympathetic activation, and inflammation) may be an important mechanistic link to cardiovascular complications. Indeed, previous investigations have implicated measures of oxygen desaturation as likely mediators of the interaction between OSA and AF. One study found a direct relationship between incident AF and the oxygen desaturation index, but not the apnea-hypopnea index, before hospital discharge in patients undergoing coronary bypass surgery (31). A second study found that a very high rate of recurrent AF after electrical cardioversion in patients with untreated OSA was

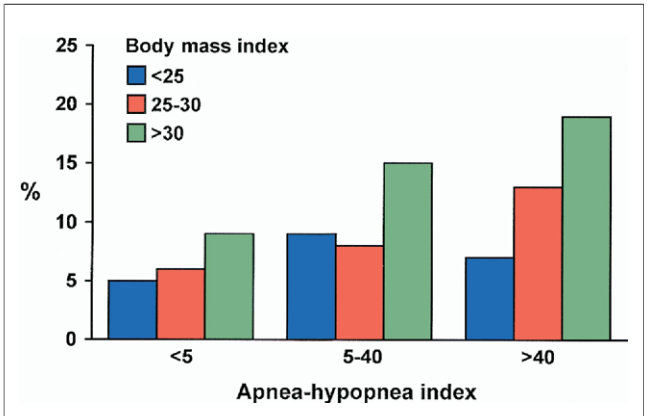

Figure 2 Incidence of AF Based on the Severity of OSA and Obesity

Cumulative frequency of incident atrial fibrillation (AF) during an average 4.7 years of follow-up, based on interactions between the body mass index (BMI) and the apnea-hypopnea index (AHI). An AHI <5 represents no obstructive sleep apnea (OSA), an AHI 5 to 40 represents mild to moderate OSA, and an AHI >40 represents severe OSA. A BMI <25 represents normal weight, a BMI 25 to 30 kg/m^2 represents overweight, and a BMI >30 kg/m^2 represents obesity.

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directly related to the magnitude and duration of nocturnal oxygen desaturation (32). Our findings are consistent with this literature. Identification of the specific mechanisms that initiate or promote AF in OSA patients may have implications for targeted intervention strategies.

Multiple studies have described the independent association of OSA with diastolic dysfunction (19–22). The pattern of mitral early and late inflow velocities (E-A ratio) and the duration of mitral early inflow (deceleration time) were both shown to correlate with the magnitude and duration of oxygen desaturation during sleep in OSA patients (19–22). Diastolic dysfunction may lead to increases in left atrial size, which has been shown to powerfully predict incident AF (29). Left atrial size also may be increased in OSA patients because of stretch of the thin-walled atria during the repetitive Mueller maneuvers (attempted inspirations against the obstructed airway) that characterize obstructive apneic sleep. These obstructed inspirations generate wide fluctuations in negative intrathoracic pressure, which elicit changes in cardiac transmural pressures and increased cardiac wall stress (15–17). Thus, mechanisms by which OSA increases the risk of AF may include diastolic dysfunction and increased left atrial size. However, the present study cannot address this directly.

Other mechanisms may also contribute to the increased risk of AF in people with OSA. Rapid swings in cardiac transmural pressures may activate atrial stretch-sensitive ion channels, particularly in anatomically vulnerable sites such as the pulmonary vein ostia, that are implicated in the initiation of AF. Another potential mechanism is the marked autonomic imbalance that occurs in OSA (18). The severe elevations of sympathetic activity during apneas may activate atrial catecholamine-sensitive ion channels and result in focal discharges that initiate AF. Furthermore, the marked vagal predominance at the end of apneas, which is associated with bradyarrhythmias, may change conduction properties of the atria to promote AF. Lastly, OSA is associated with systemic inflammation (14), which may increase the risk of AF via effects on atrial myocardial remodeling (33).

The finding that the use of continuous positive airway pressure did not reduce the risk of AF deserves mention. The method by which we classified use of continuous positive airway pressure was limited because of the retrospective nature of the study. The assessment relied on the subjective reporting of continuous positive airway pressure use and the documentation of such in the medical record. It could not account for its frequency (days per week or hours per night) of use, compliance, or effectiveness at abolishing apneas because the majority of subjects were cared for before the widespread use of continuous positive airway pressure devices that incorporate time-of-use counters. Intuitively, the use of continuous positive airway pressure, which decreases apneic events and reduces hypoxemia, would be expected to protect from incident AF. However, continuous positive airway pressure tends to be prescribed and used more often in patients with more severe OSA, as was also evident in our study. Thus, patients with more severe OSA were more likely to be using continuous positive airway pressure therapy, which may have confounded the association between its use and incident AF. This is especially true because compliance with and effectiveness of the treatment could not be assessed and accounted for in the predictive models.

A limitation of the study is that the sample consisted of patients referred to a sleep clinic because of a suspected sleep disorder. Extending the findings to the general population is limited by the fact that characteristics of OSA in the general population may differ from those in this referral population. However, there are major economic and logistic obstacles to confirming the diagnosis of OSA with the gold standard test, polysomnography, in large population studies. Thus, evaluating the questions assessed in the present study in the population at large is limited by resources and only rarely possible. In fact, over 80% of individuals with OSA in the general population remain undiagnosed (34). Another limitation is the method of ascertainment of AF during follow-up, which would fail to identify patients with asymptomatic AF who did not seek medical attention. This is a common limitation in studies of AF, even in prospective studies that use electrocardiographic monitoring. Ours was a retrospective cohort study, and thus active electrocardiographic monitoring of study patients to identify incident AF was not possible. We limited our study sample to individuals who were Olmsted County residents to form a geographically circumscribed group of patients whose medical follow-up would be limited mostly to our institution. The details of the Mayo Medical Index were described earlier, and this system should have been successful in including all *diagnosed* episodes of AF during follow-up. Another potential limitation of the study is that the presence of OSA may have resulted in greater follow-up, which could have led to increased identification of AF in OSA patients. To address this, we compared follow-up durations in these patients and found that follow-up duration was unrelated to the presence or severity of OSA. However, it remains possible that patients with OSA had more medical encounters than patients without OSA despite similar follow-up durations. Lastly, there is the consideration that the risk of AF was modified during follow-up by the progression of obesity and development of OSA after an initially negative polysomnogram. It is possible that individuals without OSA at the time of polysomnography gained weight during follow-up and developed OSA, which if true in a substantial proportion of study patients could have limited our ability to identify more robust associations between OSA and AF.

Conclusions. In this cohort of 3,542 people who underwent complete polysomnography, obesity, and the magnitude of nocturnal oxygen desaturation, which is an important pathophysiological consequence of OSA, were independent risk factors for incident AF over an average of about 5 years of follow-up. The risks conferred by obesity

and OSA were independent of one another and limited to people <65 years of age.

Our results have important implications, first, for understanding the pathophysiology of AF, and second, for the growing obesity epidemic, which is accompanied by a significant increase in the number of individuals with OSA. Based on our findings, both obesity and OSA may contribute to the looming epidemic of AF. Both conditions should be recognized as independent risk factors for incident AF. Treatments targeting obesity are imperative, and randomized controlled trials are required to evaluate the efficacy of the treatment of OSA for preventing or treating AF.

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