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Sex-based differences in obstructive sleep apnea and atrial fibrillation: Implication of atrial fibrillation burden

Chou-Han Lin [a], Yen-Bin Liu [b], Lian-Yu Lin [b,c], Hui-Chun Huang [b], Li-Ting Ho [b,d], Yen-Wen Wu [e,f], Ling-Ping Lai [b,c], Wen-Jone Chen [b,c], Yi-Lwun Ho [b,c], Chih-Chieh Yu [b,*]

[a] Division of Respiratory Medicine, Department of Internal Medicine, Far Eastern Memorial Hospital, New Taipei City, Taiwan
[b] Division of Cardiology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
[c] Department of Internal Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan
[d] Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan
[e] Division of Cardiology, Cardiovascular Medical Center, Far Eastern Memorial Hospital, New Taipei City, Taiwan
[f] School of Medicine, National Yang Ming Chao Tung University, Taipei, Taiwan

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ABSTRACT

Background: Obstructive sleep apnea (OSA) is a risk factor for atrial fibrillation (AF); however, it is unclear whether AF increases the risk of OSA. Furthermore, sex differences among patients with both AF and OSA remain unclear. We aimed to determine the association between an increased AF burden and OSA and investigate the differences in clinical characteristics between women and men with AF and OSA.

Methods: This was a descriptive, cross-sectional analysis from a prospective cohort study. Patients with non-valvular AF were recruited from the cardiac electrophysiology clinic of a tertiary center; they underwent a home sleep apnea test and 14-day ambulatory electrocardiography. Moderate-to-severe OSA was defined as an apnea-hypopnea index of ≥15.

Results: Of 320 patients with AF, 53.4% had moderate-to-severe OSA, and the mean body mass index (BMI) was 25.6 kg/m^2. Less women (38.2%) had moderate-to-severe OSA than men (59.3%) ($p < 0.001$). In the multivariate analysis, age, being a man, and BMI were significantly associated with moderate-to-severe OSA. AF burden was associated with moderate-to-severe OSA only in men (odds ratio: 1.008; 95% confidence interval: 1.001–1.014). Women and men with OSA had similar BMI ($p = 0.526$) and OSA severity ($p = 0.754$), but women were older than men (70.1 ± 1.3 vs. 63.1 ± 0.9 years, $p < 0.001$). Women with moderate-to-severe OSA had a lower AF burden than men did (27.6 ± 7.1 vs. 49.5 ± 3.9%, $p = 0.009$).

Conclusions: AF burden is a sex-specific risk factor for OSA and is limited to men. In contrast, women with both AF and OSA have a lower AF burden than men, despite being older and having similar OSA severity and body habitus. Thus, AF may develop later in women with OSA than in men.

1. Introduction

Atrial fibrillation (AF) is associated with a 1.5- to 3.5-fold increase in mortality and increases the risk of stroke by approximately five times [1,2]. More than 60% of the patients with AF report impaired quality of life, and related healthcare expenses impose a substantial socioeconomic burden [3–5]. Despite advances in pharmacological and ablative treatments, mortality has not improved [6], and the prevalence of AF is projected to increase 2.5-fold by 2050 [7]. The lifetime risk of AF has increased from one in four to one in three individuals, highlighting the need for novel approaches to curtail the AF epidemic [8]. Risk factor modification has been suggested as a key strategy for AF management, along with anticoagulation, rhythm control, and rate control [1,9].

Obstructive sleep apnea (OSA) is a risk factor for AF [10,11], and recently updated guidelines recommend screening for and treating OSA in patients with AF [1]. Therefore, risk factor assessment is important to identify OSA in these patients. Observational studies have shown a higher prevalence of OSA in patients with persistent AF than in those with paroxysmal AF [12,13]; therefore, it is conceivable that AF severity could be a risk factor for OSA. Although the risk of AF increases with OSA severity, it is unclear whether AF severity contributes to the risk of OSA [14]. Studies involving paroxysmal or non-paroxysmal AF and their

* Corresponding author.
E-mail address: ccyu2014@ntu.edu.tw (C.-C. Yu).

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associations with OSA have yielded mixed results. A study by Tanaka et al. revealed that non-paroxysmal AF is a predictor of OSA [15], while another study failed to reveal a significant association between the two [16]. This conflicting result may be partly attributed to the binary approach used to evaluate AF, which focuses on the presence of AF or the distinction between paroxysmal and nonparoxysmal AF. This approach may not capture the complexity of AF completely, especially regarding the AF burden. The American Heart Association has suggested incorporating long-term electrocardiogram (ECG) monitoring to provide a structured characterization of the AF burden [17]. This monitoring can provide detailed information on the frequency, duration, and severity of AF episodes as well as the response to treatment. This nuanced approach may help improve our understanding of the relationship between AF and OSA and lead to better management of both conditions.

In addition, previous studies have highlighted the importance of sex differences in patients with OSA and cardiovascular conditions, such as heart failure [18]. However, researchers have not investigated the impact of differences between sexes on the clinical features in patients with both AF and OSA. AF may pose a greater risk of cardiovascular morbidity and mortality in women than in men, thus warranting exploring potential sex differences in this population [19]. Indeed, a knowledge gap exists regarding sex-specific risk factors for AF and their management [1]. Such investigations could emphasize the sex-specific risk factors and treatment strategies for AF and OSA management.

Therefore, the purpose of our study was twofold. First, we aimed to determine whether an increased AF burden is associated with the presence of OSA; second, we aimed to explore differences in the clinical characteristics between women and men with AF and OSA.

2. Methods

This was a cross-sectional analysis of baseline data from the single-center, prospective, and ongoing "Atrial Fibrillation Trial To Eliminate Risk-factors" (AFTTER) registered at ClinicalTrials.gov (identifier: NCT05718336), which has been designed to reduce complications in patients with AF. All patients provided written informed consent prior to their enrollment in AFTTER. Furthermore, this study was approved by the National Taiwan University Hospital (NTUH) Institutional Committee on Human Research (202003090RINA).

2.1. Participants

All patients aged $\geq$ 18 years who were referred to the Cardiac Electrophysiology Clinic of NTUH for AF management were enrolled prospectively in AFTTER. All patients had a documented diagnosis of AF on a 12-lead ECG or single-lead strip reviewed by an electrophysiologist. The study patients were recruited by the cardiac electrophysiologists at the clinic. Prior to their enrollment, all patients underwent preliminary testing, which included blood sampling and echocardiography. They also underwent a sleep assessment that was performed using the Epworth Sleepiness Scale (ESS). The inclusion criterion was as follows: patients with AF aged $\geq$ 18 years (irrespective of their OSA symptoms or ESS scores). The exclusion criteria were as follows: (1) unwillingness or the inability to provide informed consent, (2) receiving treatment for OSA, (3) physical or cognitive impairment that restricted the ability to undergo the home sleep apnea test (HSAT), (4) heart failure with a reduced ejection fraction (<45%), (5) end-stage renal disease (ESRD), (6) history of abnormal thyroid function, and (7) primary valvular heart disease.

2.2. Measurements of AF burden

All patients underwent a 14-day ambulatory ECG (EZYPRO; Sigknow Biomedical Co., Ltd., Taipei, Taiwan) using a single lead positioned on the left upper chest to evaluate AF. We instructed them to maintain their daily activities, including work and exercise. They were allowed to bathe because ECG patch was waterproof and firmly attached to their chest. Furthermore, the patients could report any subjective symptoms experienced during the 14-day period using a recorder button. After that period, the patients or research assistants removed the patch, and the recorder was sent to the technicians for a preliminary analysis and signal interpretation by an electrophysiologist. The AF burden was defined as the percentage of time spent in AF.

2.3. Sleep study

OSA was detected using ApneaLink Plus (ResMed, San Diego, CA, USA) (HSAT), a three-channel device consisting of a digital pulse oximeter, nasal cannula with a pressure transducer, and chest belt to measure the respiratory effort. The patients, guided by a research assistant who is a nurse, were instructed to complete the test at home. Raw data were initially processed using the AUTO AASM scoring system provided by ApneaLink Plus and manually reviewed by a board-certified sleep physician blinded to the patient characteristics. AUTO AASM and manual scoring methods accurately identify sleep apnea, as demonstrated by in-laboratory polysomnography (PSG) [20] and in people with AF [21]. Apnea was scored as a $\geq$ 90% decrease in the peak signal excursion from the baseline lasting for at least 10 s. Conversely, hypopnea was scored as a $\geq$ 30% decrease in the peak signal excursion from the baseline for at least 10 s, followed by a $\geq$ 3% reduction in oxygen saturation. Central apnea or hypopnea was scored in the absence of respiratory effort or Cheyne-Stokes respiration. We did not include raw data in the final analysis if > 50% of the respiratory events were central. The apnea-hypopnea index (AHI) was calculated by dividing the sum of apneic and hypopneic events by the total recording time. Sleep studies with recording time < 4 h were deemed inadequate and repeated for the analysis. The OSA severity was classified according to AHI (mild OSA, $\geq$5 and < 15; moderate, $\geq$15 and < 30; and severe, AHI $\geq$ 30). Moderate-to-severe OSA was considered "significant OSA" based on a previous randomized control trial that used this criterion to recruit the patients [22].

2.4. Statistical analysis

Patient characteristics are presented as mean $\pm$ standard error or percentage. We performed the Student's *t*-test and Pearson's chi-square test for continuous and categorical variables, respectively. We compared the baseline characteristics between patients with and without moderate-to-severe OSA and between women and men. Additionally, we also compared the clinical characteristics between both women and men with and without moderate-to-severe OSA. Then, we conducted a multivariate logistic regression analysis to identify the independent risk factors for moderate-to-severe OSA using patients with no or mild OSA as the reference group. Subsequently, we further analyzed women and men separately using a multivariate logistic regression analysis to identify the independent risk factors for moderate-to-severe OSA. We evaluated sex, age, body mass index (BMI), hypertension (based on previously reported factors associated with OSA [13,15,16]), and AF burden as candidate risk factors using SPSS software (version 25; IBM Corp., Armonk, NY, USA). Statistical significance was defined as $p < 0.05$.

3. Results

3.1. Patient characteristics

From May 2020 to March 2023, 327 eligible patients visited the Cardiac Electrophysiology Clinic of NTUH and used ApneaLink Plus at home after receiving respective instructions at the hospital. All of them undertook the HSAT. Five patients failed to complete the HSAT after multiple attempts and withdrew from the study. Furthermore, two patients were excluded because of Cheyne-Stokes respiration. A total of

320 patients were included in the final analysis.

The mean age of the cohort was 62.0 ± 0.6 years, which comprised 72.2% of men and 70.0% patients with paroxysmal AF. The mean BMI was 25.6 ± 0.2 kg/m^2, and the mean CHA_2DS_2-VASc score was 1.6 ± 0.1. The majority of patients (82.8%) did not have excessive daytime sleepiness (ESS ≤ 10), with a mean ESS of 7.1 ± 0.2. The mean AHI was 18.9 ± 0.8. A total of 262 (81.9%) patients had AHI > 5, and 53.4% had moderate-to-severe OSA. Table 1 summarizes the clinical characteristics of the study population stratified by moderate-to-severe OSA. Compared with patients who had no or had mild OSA, those with moderate-to-severe OSA were characterized by advanced age, were predominantly men, had a higher BMI, and greater prevalence of comorbidities. Furthermore, patients with moderate-to-severe OSA demonstrated a higher AF burden and an increased left atrial diameter.

3.2. Sex-based patient characteristics

Table 2 summarizes the sex-specific clinical characteristics of the patients. Women were older ($p = 0.003$) and had lower BMI ($p = 0.01$) than men. We observed no significant differences in the underlying comorbidities or ESS values between the sexes, except for a lower percentage of coronary artery disease in women ($p = 0.014$). On echocardiography, women had a smaller left atrial diameter ($p = 0.009$) and higher left ventricular ejection fraction ($p = 0.046$) than men did. In addition, women had a lower OSA severity ($p = 0.001$) and AF burden ($p = 0.018$) than men did.

We compared the clinical characteristics among women with and without moderate-to-severe OSA, men with and without moderate-to-severe OSA, and women and men with moderate-to-severe OSA (Fig. 1). The degree of OSA severity was similar between men and women (28.8 ± 2.0 vs. 29.5 ± 1.0, $p = 0.754$). Women with moderate-to-severe OSA were older than those without moderate-to-severe OSA (70.1 ± 1.3 vs. 61.7 ± 1.4 years, $p < 0.001$) and men with moderate-to-severe OSA (70.1 ± 1.3 vs. 63.1 ± 0.9 years, $p < 0.001$). Both women and men with moderate-to-severe OSA had significantly higher BMI than those without moderate-to-severe OSA (26.1 ± 0.9 vs. 23.9 ± 0.5 kg/m^2 [$p = 0.022$] and 26.6 ± 0.3 vs. 25.0 ± 0.3 kg/m^2 [$p < 0.001$], respectively). Notably, women and men with moderate-to-severe OSA had similar BMI (26.1 ± 0.9 vs. 26.6 ± 0.3 kg/m^2, $p = 0.526$). We observed no differences in the ESS values and presence of hypertension, or diabetes mellitus between the sexes.

Regarding cardiovascular characteristics, the left atrial diameter was significantly larger in men with moderate-to-severe OSA than in those without moderate-to-severe OSA (4.3 ± 0.1 cm vs. 4.1 ± 0.1 cm, $p = 0.009$). Conversely, the left atrial diameter was similar between women with and without moderate-to-severe OSA (4.1 ± 0.1 vs. 3.9 ± 0.1 cm, $p = 0.137$). The AF burden did not differ significantly between women with and without moderate-to-severe OSA (27.6 ± 7.1 vs. 30.8 ± 5.6%, $p = 0.727$), whereas it was significantly higher in men with moderate-to-severe OSA than in those without moderate-to-severe OSA (49.5 ± 3.9 vs. 31.7 ± 4.2%, $p = 0.002$). Notably, women with moderate-to-severe OSA had a lower AF burden than men with moderate-to-severe OSA did (27.6 ± 7.1 vs. 49.5 ± 3.9%, $p = 0.009$).

Table 1
Clinical characteristics of patients with AF with and without moderate-to-severe OSA.

	All patients (n = 320)	Mild or no OSA (n = 149)	Moderate-to-severe OSA (n = 171)	*p*-value
Male, n (%)	231 (72.2%)	94 (63.1%)	137 (80.1%)	<0.001
Age, years	62.0 ± 0.6	59.1 ± 0.9	64.5 ± 0.8	<0.001
BMI, kg/m^2	25.6 ± 0.2	24.6 ± 0.2	26.4 ± 0.3	<0.001
Hypertension, n (%)	117 (36.6%)	43 (28.9%)	74 (43.3%)	0.008
Diabetes mellitus, n (%)	49 (15.3%)	13 (8.7%)	36 (21.1%)	0.002
Heart failure, n (%)	17 (5.3%)	3 (2.0%)	14 (8.2%)	0.014
Stroke, n (%)	17 (5.3%)	5 (3.4%)	12 (7.0%)	0.145
Coronary artery disease, n (%)	37 (11.6%)	12 (8.1%)	25 (14.6%)	0.067
Paroxysmal AF, n (%)	224 (70.0%)	116 (77.9%)	108 (63.2%)	0.004
Ablation, n (%)	58 (18.1%)	27 (18.1%)	31 (18.1%)	0.999
AF burden (%)	38.7 ± 2.5	31.4 ± 3.4	45.1 ± 3.5	0.005
ESS	7.2 ± 0.2	6.9 ± 0.3	7.4 ± 0.3	0.181
Left atrial diameter (cm)	4.1 ± 0.0	4.0 ± 0.1	4.3 ± 0.1	0.001
LVEF (%)	69.6 ± 0.5	70.0 ± 0.7	69.3 ± 0.7	0.431
AHI, event/h	18.9 ± 0.8	7.0 ± 0.4	29.4 ± 0.9	<0.001

AF, atrial fibrillation; AHI, apnea-hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale; LVEF, left ventricular ejection fraction; and OSA, obstructive sleep apnea.

Table 2
Sex-based comparison of the clinical characteristics in patients with AF.

	Women (n = 89)	Men (n = 231)	*p*-value
Age, years	64.9 ± 1.1	60.9 ± 0.7	0.003
BMI, kg/m^2	24.7 ± 0.5	25.9 ± 0.2	0.010
Hypertension, n (%)	26 (29.2%)	91 (39.4%)	0.090
Diabetes mellitus, n (%)	13 (14.6%)	36 (15.6%)	0.828
Heart failure, n (%)	4 (4.5%)	13 (5.6%)	0.685
Stroke, n (%)	6 (6.7%)	11 (4.8%)	0.479
Coronary artery disease, n (%)	4 (4.5%)	33 (14.3%)	0.014
Paroxysmal AF, n (%)	68 (76.4%)	156 (67.5%)	0.121
AF burden (%)	29.6 ± 4.4	42.3 ± 2.9	0.018
Ablation, n (%)	14 (15.7%)	44 (19.0%)	0.490
ESS	6.8 ± 0.4	7.3 ± 0.3	0.281
Left atrial diameter (cm)	4.0 ± 0.1	4.2 ± 0.0	0.009
LVEF (%)	71.2 ± 1.0	69.0 ± 0.6	0.046
OSA	34 (38.2%)	137 (59.3%)	0.001
AHI, event/h	14.8 ± 1.4	20.5 ± 0.9	0.001

AF, atrial fibrillation; AHI, apnea-hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale; LVEF, left ventricular ejection fraction; and OSA, obstructive sleep apnea.

3.3. Sex-based risk factors for moderate-to-severe OSA

We performed the multivariate analysis to evaluate risk factors associated with moderate-to-severe OSA. After adjusting for hypertension, BMI, sex, age, and AF burden, we found that age, being a man, and BMI were associated with moderate-to-severe OSA (Table 3). To examine the influence of sex on the risk factors for moderate-to-severe OSA, separate analyses were conducted in women and men. The dependent variable was moderate-to-severe OSA, and independent variables were hypertension, BMI, age, and AF burden. The AF burden was independently associated with moderate-to-severe OSA only in men (Table 4).

4. Discussion

In this prospective study, the patients with AF were recruited from the cardiac electrophysiology clinic. We used HSAT to diagnose OSA. Increased AF burden was significantly associated with OSA only in men, highlighting the importance of considering sex-specific risk factors when evaluating patients with AF. Moreover, this novel study compared sex differences in patients with AF, including their age, BMI, left atrial size,

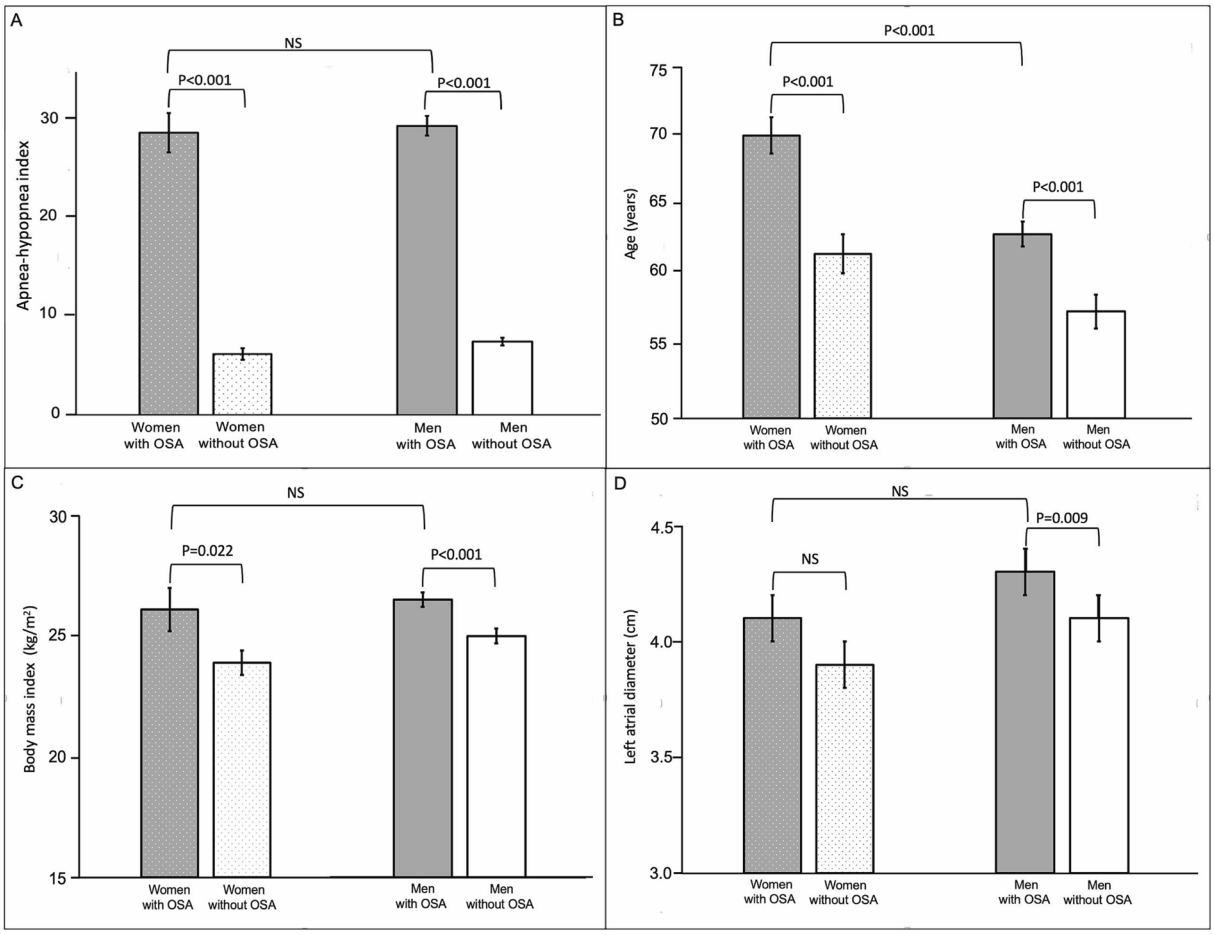

Fig. 1. Intra- and inter-sex comparisons among patients with AF, with and without OSA (A) The severity of OSA does not differ between women and men ($p = 0.754$). (B) Women with OSA have a higher mean age than those without OSA ($p < 0.001$) and men with OSA ($p < 0.001$). (C) The BMI is similar in men and women with OSA ($p = 0.526$). Women with OSA have a significantly higher BMI than those without OSA ($p = 0.022$). Men with OSA have higher BMI than those without OSA ($p < 0.001$). (D) Men with OSA have a larger left atrial diameter than those without OSA ($p = 0.009$). Conversely, the left atrial diameter is similar in women with and without OSA ($p = 0.137$) and in men with OSA ($p = 0.144$). AF, atrial fibrillation; BMI, body mass index; OSA, obstructive sleep apnea.

Table 3
Multivariate logistic regression analysis of risk factors for moderate-to-severe OSA in patients with AF.

	Moderate-to-severe OSA Adjusted odds ratio (95% CI)	*p*-value
BMI, 1-unit increase	1.169 (1.085–1.259)	<0.001
AF burden, 1% increase	1.004 (0.998–1.010)	0.160
Hypertension, yes vs. no	1.147 (0.676–1.946)	0.611
Sex, male vs. female	2.699 (1.516–4.804)	0.001
Age, 1-year increase	1.063 (1.037–1.090)	<0.001

AF, atrial fibrillation; BMI, body mass index; CI, confidence interval; OSA, obstructive sleep apnea.

Table 4
Sex-specific multivariate logistic regression analysis of risk factors for OSA in patients with AF.

	Moderate-to-severe OSA in women with AF,Adjusted odds ratio (95% CI)	*p*-value	Moderate-to-severe OSA in men with AF,Adjusted odds ratio (95% CI)	*p*-value
BMI, 1-unit increase	1.147 (1.012–1.301)	0.032	1.173 (1.066–1.290)	0.001
AF burden, 1% increase	0.995 (0.982–1.008)	0.438	1.008 (1.001–1.014)	0.027
Hypertension, yes vs. no	0.500 (0.152–1.650)	0.255	1.563 (0.840–2.909)	0.159
Age, 1-year increase	1.121 (1.052–1.194)	<0.001	1.051 (1.022–1.081)	0.001

AF, atrial fibrillation; BMI, body mass index; CI, confidence interval; OSA, obstructive sleep apnea.

and AF burden. Our findings have implications for the diagnosis and management of AF and OSA in clinical practice.

In our study, we found no significant correlation between the AF burden and OSA. However, we observed a sex difference in this association, with a significant correlation between the AF burden and OSA only in men. One possible explanation for this disparity is the sex-based difference in the phenomenon of rostral fluid shifting, which has been suggested as a factor for "AF begets OSA." [23] Men are more susceptible to upper airway collapse caused by overnight fluid shifting from the lower extremities than women [24]. This condition can increase the neck circumference and OSA severity and has been documented in non-obese healthy individuals [25] and in patients with heart failure or renal failure, primarily in men [26,27]. This sex-based disparity in OSA severity may be attributed to the redistribution of fluid from the legs to the neck or peripharyngeal space in men. Conversely, fluid is redistributed to the gonadal venous system in women [28].

Because we did not measure the fluid status of the patients, we could not confirm the theory of rostral fluid shifting as an explanation for the

sex-based differences in the association between the AF burden and OSA. However, men with moderate-to-severe OSA had greater left atrial enlargement than those without moderate-to-severe OSA, which may have contributed to the association between the AF burden and OSA in men. Respiratory chemosensitivity supposedly increases with an enlarged left atrium, which may be attributed to stretch receptors in the left atrium or pulmonary vein or indirectly through pulmonary edema via the juxtacapillary receptors or pulmonary C-fibers [29,30]. In addition, left atrial enlargement is a common consequence of AF, and this relationship, apart from rostral fluid shift theory, may mediate the correlation between AF burden and OSA severity. This increased ventilatory response may create a positive feedback loop, predisposing men to a higher degree of AHI severity. This is because loop gain is one of the major mechanisms underlying OSA development [31]. Supporting this finding, Lyons et al. demonstrated a positive correlation between the left atrial size and AHI in only male patients with ESRD, providing further evidence for the correlation between left atrial enlargement and AHI, suggesting that this relationship may be sex-specific [32].

Women generally exhibit a lower OSA severity than men do. In contrast, we demonstrated that OSA severity was similar in men and women with both AF and OSA. One explanation for this finding is that women with moderate-to-severe OSA were on average 7 years older than men with moderate-to-severe OSA. This is because OSA severity increases with age. The age difference between men and women may explain why women typically develop OSA later in life than men. The anatomy in women is typically more protective against OSA owing to a greater gynoid distribution of fat. Thus, this protection is attenuated after menopause, which shifts fat accumulation to the neck, chest, and abdomen, thereby increasing the risk of OSA by causing pharyngeal narrowing and airway collapse [33]. Specifically, the odds of developing OSA increase by 7% each year after menopause [34]. Notably, women typically experience a later onset of OSA. However, they exhibit a greater increase in the AHI every 5 years than men, which may account for the reduction in the severity gap of the AHI between women and men after the age of 60 years [35,36].

Furthermore, a comparable body habitus may contribute to the similar OSA severity in women and men. Women typically have a lower average BMI than men do; however, in our study the BMI was similar in both men and women with moderate-to-severe OSA. This finding was consistent with a previous study indicating that older women with OSA had a BMI equivalent to that in men with OSA [37]. Moreover, it supports the theory that women develop OSA later in life because of increased BMI and central obesity that often occur after menopause [38], both of which are strongly associated with the development of OSA.

Our study demonstrated an intriguing finding regarding the relationship between AF and OSA in women and men. Despite similarities in OSA severity and body habitus, women with AF and moderate-to-severe OSA were approximately 7 years older than men, yet they exhibited a lower AF burden. This discrepancy suggests sex-based differences in the interplay between AF and OSA.

This lower AF burden in women with OSA contributes substantive evidence to suggest that AF has a later onset in women. Women received a diagnosis of AF or were referred for ablation at an older age; this may be attributed to factors such as under-referral, women's hesitancy to seek medical attention, or a delayed diagnosis of AF due to the more frequent presentation of atypical AF symptoms in women [1]. Given the temporal progression of AF from a paroxysmal to a persistent status, a higher AF burden in men with OSA could be indicative of a longer duration of AF. This inference is further substantiated by the comparable size of the left atrium between women with and without OSA in our study, which implies that the course of AF is not long enough to manifest an enlarged remodeled left atrium as is observed in men with OSA. This is further corroborated by the findings of a recent prospective study, which involved 7-day Holter ECG monitoring and revealed a positive association between the left atrial size and temporal evolution of the AF burden [39].

This potential temporal distinction in the onset of AF between women and men with OSA provides valuable insights that further our understanding of sex differences in the mechanism of AF development and its clinical impact. OSA onset occurs at a later time in women than in men, resulting in a shorter period of exposure to OSA in women than in men. It is plausible that this shorter exposure period leads to a later onset of AF and a lesser AF burden in women than in men. This mechanism further substantiates the pivotal role of risk factors in the development of AF and the AF burden, thereby supporting an integral approach to identifying and managing risk factors in patients with AF, as suggested by the guidelines [1]. Moreover, this sex-difference can also help understand the exact reason for a higher risk of stroke in women with AF aged $>$ 65 years than in similarly aged men with AF [1,40]. Given that OSA is an independent risk factor for stroke and mortality [41], our data reveal a plausible scenario wherein OSA assumes a greater relevance as an intrinsic sex-specific risk factor as the age of the patients with AF increases. Specifically, women over the age of 60 began to experience a pronounced increase in OSA severity [35,36]. As a result, the clinical impact of OSA is not yet evident in women under the age of 65. In contrast, men with OSA over the age of 60 may have suffered from end-stage complications of OSA (such as stroke and death), which is corroborated by the plateauing of the OSA prevalence after the age of 65 years [42].

Thus, the age-dependent significance of OSA as a sex-specific risk factor has crucial implications in clinical practice. This is particularly noteworthy because structured testing for OSA in patients with AF is infrequently performed [43], and the current screening tool prioritizes male sex as a key risk factor for OSA. In addition, the optimal testing time for patients with OSA remains unclear, as indicated by the guidelines [1]. Our data justify assessing the presence of OSA in older women with AF, who are at a higher risk for stroke than men. Moreover, repeated testing for OSA in younger women with AF may be necessary, considering the accelerated deterioration in OSA severity after the age of 60 years [35,36].

Therefore, given that current guidelines recommend equal diagnostic assessments in both sexes to prevent stroke or AF-related complications [1], future research should focus on a more proactive approach to screen for and diagnose OSA in women with AF. This is important because compared to men, women with OSA and AF are more likely to possess a less remodeled AF substrate; owing to this, such women may respond to OSA treatment more effectively, since they may have been exposed to OSA for a shorter period. Additionally, considering the poorer outcomes of ablation in women with AF [1], early detection and management of OSA would constitute a rational treatment strategy for this population. Interestingly, studies have demonstrated a reduced AF burden after implementing strategies for risk factor reduction (including OSA treatment); these studies enrolled a higher percentage of women than the usual female representation in general AF studies or populations [44,45]. This suggests that women may exhibit a more favorable response to treatment strategies aimed at risk factor reduction. Therefore, further studies are imperative to elucidate whether OSA treatment exerts different effects on AF in women and men.

Our study had several limitations. First, we could not perform PSG, the gold standard diagnostic test; therefore, we could not accurately distinguish central sleep apnea from OSA. In addition, the current diagnostic guidelines do not provide strong recommendations for HSAT use in patients with AF. However, we excluded patients with heart failure and reduced ejection fraction or ESRD, suggesting that the percentage of patients with central sleep apnea was likely low. ApneaLink Plus is the only validated HSAT for patients with AF; therefore, PSG use was less likely to significantly alter the percentage of each category of sleep apnea severity or the prevalence of central sleep apnea. Furthermore, a single AHI measurement might be insufficient because previous research has demonstrated considerable night-to-night variability in the AHI scores among patients with AF [23]. However, nocturnal AHI

variability is generally less severe in patients with moderate or severe sleep apnea than in those with mild sleep apnea [23]. The patients had moderate-to-severe OSA with a mean AHI of 18.9, making a single sleep study less likely to exert a significant impact. Second, the study had a cross-sectional design, relied on a single assessment of 14-day ECG data, and involved a one-time sleep study; these may have limited our ability to infer causality between the AF burden and OSA.

5. Conclusions

An increased AF burden was associated with OSA only in men. In addition, women with OSA had a lower AF burden than men with OSA did, despite being older and having similar OSA severity and body habitus. Despite not being a longitudinal study, our study showed sex differences between women and men with AF and OSA, emphasizing the need for personalized approaches to evaluate and manage OSA in both sexes. In addition, this finding underscores the importance of considering the impact of sex on AF and OSA for future research.

CRediT authorship contribution statement

Chou-Han Lin: Conceptualization, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Methodology, Funding acquisition. **Yen-Bin Liu:** Investigation, Resources, Writing – review & editing. **Lian-Yu Lin:** Resources, Writing – review & editing, Conceptualization. **Hui-Chun Huang:** Data curation, Investigation, Resources, Writing – review & editing. **Li-Ting Ho:** Investigation, Resources, Writing – review & editing. **Yen-Wen Wu:** Investigation, Resources, Writing – review & editing. **Ling-Ping Lai:** Conceptualization, Resources, Supervision, Writing – review & editing. **Wen-Jone Chen:** Conceptualization, Funding acquisition, Resources, Supervision, Writing – review & editing. **Yi-Lwun Ho:** Conceptualization, Investigation, Resources, Supervision, Writing – review & editing, Funding acquisition. **Chih-Chieh Yu:** Conceptualization, Formal analysis, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing, Funding acquisition, Project administration, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] G. Hindricks, T. Potpara, N. Dagres, E. Arbelo, J.J. Bax, C. Blomström-Lundqvist, G. Boriani, M. Castella, G.A. Dan, P.E. Dilaveris, L. Fauchier, G. Filippatos, J. M. Kalman, M.L. Meir, D.A. Lane, J.P. Lebeau, M. Lettino, G.Y.H. Lip, F.J. Pinto, G. N. Thomas, M. Valgimigli, I.C.V. Gelder, B.P.V. Putte, C.L. Watkins, ESC Scientific Document Group, ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC, Eur. Heart J. 373 (2020) 42, https://doi.org/10.1093/eurheartj/ehaa612.

[2] H. Kamel, P.M. Okin, M.S. Elkind, C. Iadecola, Atrial fibrillation and mechanisms of stroke: time for a new model, Stroke. 47 (2016) 895–900, https://doi.org/10.1161/STROKEAHA.115.012004.

[3] S.P. Johnsen, L.W. Dalby, T. Täckström, J. Olsen, A. Fraschke, Cost of illness of atrial fibrillation: a nationwide study of societal impact, BMC Health Serv. Res. 17 (2017) 714, https://doi.org/10.1186/s12913-017-2652-y.

[4] G. Rozen, S.M. Hosseini, M.I. Kaadan, Y. Biton, E.K. Heist, M. Vangel, M. C. Mansour, J.N. Ruskin, Emergency department visits for atrial fibrillation in the United States: trends in admission rates and economic burden from 2007 to 2014, J. Am. Heart Assoc. 7 (2018) e009024.

[5] T.E. Walters, K. Wick, G. Tan, M. Mearns, S.A. Joseph, J.B. Morton, P. Sanders, C. Bryant, P.M. Kistler, J.M. Kalman, Symptom severity and quality of life in patients with atrial fibrillation: psychological function outweighs clinical predictors, Int. J. Cardiol. 279 (2019) 84–89, https://doi.org/10.1016/j.ijcard.2018.10.101.

[6] S.M. Singh, H. Abdel-Qadir, A. Pang, J. Fang, M. Koh, P. Dorian, H. C. Wijeysundera, D.T. Ko, Population trends in all-cause mortality and cause specific-death with incident atrial fibrillation, J. Am. Heart Assoc. 9 (2020) e016810.

[7] G.V. Naccarelli, H. Varker, J. Lin, K.L. Schulman, Increasing prevalence of atrial fibrillation and flutter in the United States, Am. J. Cardiol. 104 (2009) 1534–1539, https://doi.org/10.1016/j.amjcard.2009.07.022.

[8] L. Staerk, B. Wang, S.R. Preis, M.G. Larson, S.A. Lubitz, P.T. Ellinor, D.D. McManus, D. Ko, L.C. Weng, K.L. Lunetta, L. Frost, E.J. Benjamin, L. Trinquart, Lifetime risk of atrial fibrillation according to optimal, borderline, or elevated levels of risk factors: cohort study based on longitudinal data from the Framingham Heart Study, BMJ. 361 (2018), k1453, https://doi.org/10.1136/bmj.k1453.

[9] M.K. Chung, L.L. Eckhardt, L.Y. Chen, H.M. Ahmed, R. Gopinathannair, J.A. Joglar, P.A. Noseworthy, Q.R. Pack, P. Sanders, K.M. Trulock, American Heart Association Electrocardiography and Arrhythmias Committee, Exercise, Cardiac Rehabilitation, and Secondary Prevention Committee of the Council on Clinical Cardiology; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; and Council on Lifestyle and Cardiometabolic Health, Lifestyle and risk factor modification for reduction of atrial fibrillation: A scientific statement from the American Heart Association, Circulation. 141 (2020) e750–e772, https://doi.org/10.1161/CIR.0000000000000748.

[10] R. Mehra, E.J. Benjamin, E. Shahar, D.J. Gottlieb, R. Nawabit, H.L. Kirchner, J. Sahadevan, S. Redline, Sleep Heart Health Study, Association of nocturnal arrhythmias with sleep-disordered breathing: the Sleep Heart Health Study, Am. J. Respir. Crit. Care Med. 173 (2006) 910–916, https://doi.org/10.1164/rccm.200509-1442OC.

[11] R. Mehra, K.L. Stone, P.D. Varosy, A.R. Hoffman, G.M. Marcus, T. Blackwell, O. A. Ibrahim, R. Salem, S. Redline, Nocturnal Arrhythmias across a spectrum of obstructive and central sleep-disordered breathing in older men: outcomes of sleep disorders in older men (MrOS sleep) study, Arch. Intern. Med. 169 (2009) 1147–1155, https://doi.org/10.1001/archinternmed.2009.138.

[12] B. Braga, D. Poyares, F. Cintra, C. Guilleminault, C. Cirenza, S. Horbach, D. Macedo, R. Silva, S. Tufik, A.A. De Paola, Sleep-disordered breathing and chronic atrial fibrillation, Sleep Med. 10 (2009) 212–216, https://doi.org/10.1016/j.sleep.2007.12.007.

[13] G.M. Traaen, B. Øverland, L. Aakerøy, T.E. Hunt, C. Bendz, L. Sande, S. Aakhus, H. Zaré, S. Steinshamn, O.G. Anfinsen, J.P. Loennechen, L. Gullestad, H. Akre, Prevalence, risk factors, and type of sleep apnea in patients with paroxysmal atrial fibrillation, Int. J. Cardiol. Heart Vasc. 26 (2020), 100447, https://doi.org/10.1016/j.ijcha.2019.100447.

[14] M. Gleeson, W.T. McNicholas, Bidirectional relationships of comorbidity with obstructive sleep apnoea, Eur. Respir. Rev. 31 (2022), 210256, https://doi.org/10.1183/16000617.0256-2021.

[15] N. Tanaka, K. Tanaka, Y. Hirao, M. Okada, Y. Ninomiya, I. Yoshimoto, T. Onishi, Y. Koyama, A. Okamura, K. Iwakura, K. Fujii, Y. Sakata, K. Inoue, Home sleep apnea test to screen patients with atrial fibrillation for sleep apnea prior to catheter ablation, Circ. J. 85 (2021) 252–260, https://doi.org/10.1253/circj.CJ-20-0782.

[16] A. Shapira-Daniels, S. Mohanty, F.M. Contreras-Valdes, H. Tieu, R.J. Thomas, A. Natale, E. Anter, Prevalence of undiagnosed sleep apnea in patients with atrial fibrillation and its impact on therapy, JACC Clin. Electrophysiol. 6 (2020) 1499–1506, https://doi.org/10.1016/j.jacep.2020.05.030.

[17] L.Y. Chen, M.K. Chung, L.A. Allen, M. Ezekowitz, K.L. Furie, P. McCabe, P. A. Noseworthy, M.V. Perez, M.P. Turakhia, American Heart Association Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; and Stroke Council, Atrial fibrillation burden: moving beyond atrial fibrillation as a binary entity: a scientific statement from the American Heart Association, Circulation 137 (2018) e623–e644, https://doi.org/10.1161/CIR.0000000000000568.

[18] D.D. Sin, F. Fitzgerald, J.D. Parker, G. Newton, J.S. Floras, T.D. Bradley, Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure, Am. J. Respir. Crit. Care Med. 160 (1999) 1101–1106, https://doi.org/10.1164/ajrccm.160.4.9903020.

[19] C.A. Emdin, C.X. Wong, A.J. Hsiao, D.G. Altman, S.A. Peters, M. Woodward, A. A. Odutayo, Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies, BMJ. 532 (2016), h7013, https://doi.org/10.1136/bmj.h7013.

[20] J.H. Cho, H.J. Kim, Validation of ApneaLink™ Plus for the diagnosis of sleep apnea, Sleep Breath. 21 (2017) 799–807, https://doi.org/10.1007/s11325-017-1532-3.

[21] A.M. Mohammadieh, K. Sutherland, L.B. Kanagaratnam, D.W. Whalley, M. J. Gillett, P.A. Cistulli, Clinical screening tools for obstructive sleep apnea in a population with atrial fibrillation: a diagnostic accuracy trial, J. Clin. Sleep Med. 17 (2021) 1015–1024, https://doi.org/10.5664/jcsm.9098.

[22] G.M. Traaen, L. Aakerøy, T.E. Hunt, B. Øverland, C. Bendz, L.Ø. Sande, S. Aakhus, M.W. Fagerland, S. Steinshamn, O.G. Anfinsen, R.J. Massey, K. Broch, T. Ueland, H. Akre, J.P. Loennechen, L. Gullestad, Effect of continuous positive airway pressure on arrhythmia in atrial fibrillation and sleep apnea: a randomized controlled trial, Am. J. Respir. Crit. Care Med. 204 (2021) 573–582, https://doi.org/10.1164/rccm.202011-4133OC.

[23] D. Linz, M. Baumert, L. Desteghe, K. Kadhim, K. Vernooy, J.M. Kalman, D. Dobrev, M. Arzt, M. Sastry, H.J.G.M. Crijns, U. Schotten, M.R. Cowie, R.D. McEvoy, H. Heidbuchel, J. Hendriks, P. Sanders, D.H. Lau, Nightly sleep apnea severity in patients with atrial fibrillation: potential applications of long-term sleep apnea monitoring, Int. J. Cardiol. Heart Vasc. 24 (2019), 100424, https://doi.org/10.1016/j.ijcha.2019.100424.

[24] M.C. Su, K.L. Chiu, P. Ruttanaumpawan, S. Shiota, D. Yumino, S. Redolfi, J. S. Haight, B. Yau, J. Lam, T.D. Bradley, Difference in upper airway collapsibility during wakefulness between men and women in response to lower-body positive pressure, Clin. Sci. (Lond.) 116 (2009) 713–720, https://doi.org/10.1042/CS20080321.

[25] S. Redolfi, D. Yumino, P. Ruttanaumpawan, B. Yau, M.C. Su, J. Lam, T.D. Bradley, Relationship between overnight rostral fluid shift and obstructive sleep apnea in nonobese men, Am. J. Respir. Crit. Care Med. 179 (2009) 241–246, https://doi.org/10.1164/rccm.200807-1076OC.

[26] D. Yumino, S. Redolfi, P. Ruttanaumpawan, M.C. Su, S. Smith, G.E. Newton, S. Mak, T.D. Bradley, Nocturnal rostral fluid shift: a unifying concept for the pathogenesis of obstructive and central sleep apnea in men with heart failure, Circulation. 121 (2010) 1598–1605, https://doi.org/10.1161/CIRCULATIONAHA.109.902452.

[27] R.M. Elias, T.D. Bradley, T. Kasai, S.S. Motwani, C.T. Chan, Rostral overnight fluid shift in end-stage renal disease: relationship with obstructive sleep apnea, Nephrol. Dial. Transplant. 27 (2012) 1569–1573, https://doi.org/10.1093/ndt/gfr605.

[28] D.D. White, L.D. Montgomery, Pelvic blood pooling of men and women during lower body negative pressure, Aviat. Space Environ. Med. 67 (1996) 555–559.

[29] T.C. Lloyd Jr, Breathing response to lung congestion with and without left heart distension, J. Appl. Physiol. 65 (1988) (1985) 131–136, https://doi.org/10.1152/jappl.1988.65.1.131.

[30] A.S. Paintal, Mechanism of stimulation of type J pulmonary receptors, J. Physiol. 203 (1969) 511–532, https://doi.org/10.1113/jphysiol.1969.sp008877.

[31] J.C. Carberry, J. Amatoury, D.J. Eckert, Personalized management approach for OSA, Chest 153 (2018) 744–755, https://doi.org/10.1016/j.chest.2017.06.011.

[32] O.D. Lyons, C.T. Chan, R.M. Elias, T.D. Bradley, Relationship of left atrial size to obstructive sleep apnea severity in end-stage renal disease, Sleep Med. 15 (2014) 1314–1318, https://doi.org/10.1016/j.sleep.2014.07.001.

[33] R.L. Horner, R.H. Mohiaddin, D.G. Lowell, S.A. Shea, E.D. Burman, D.B. Longmore, A. Guz, Sites and sizes of fat deposits around the pharynx in obese patients with obstructive sleep apnoea and weight matched controls, Eur. Respir. J. 2 (1989) 613–622, https://doi.org/10.1183/09031936.93.02070613.

[34] A.G. Mirer, T. Young, M. Palta, R.M. Benca, A. Rasmuson, P.E. Peppard, Sleep-disordered breathing and the menopausal transition among participants in the Sleep in Midlife Women Study, Menopause 24 (2017) 157–162, https://doi.org/10.1097/GME.0000000000000744.

[35] I.E. Gabbay, P. Lavie, Age- and gender-related characteristics of obstructive sleep apnea, Sleep Breath. 16 (2012) 453–460, https://doi.org/10.1007/s11325-011-0523-z.

[36] O.K. Basoglu, M.S. Tasbakan, Gender differences in clinical and polysomnographic features of obstructive sleep apnea: a clinical study of 2827 patients, Sleep Breath. 1 (2018) 241–249, https://doi.org/10.1007/s11325-017-1482-9.

[37] S. Redline, K. Kump, P.V. Tishler, I. Browner, V. Ferrette, Gender differences in sleep disordered breathing in a community-based sample, Am. J. Respir. Crit. Care Med. 149 (1994) 722–726, https://doi.org/10.1164/ajrccm.149.3.8118642.

[38] S.R. Davis, C. Castelo-Branco, P. Chedraui, M.A. Lumsden, R.E. Nappi, D. Shah, P. Villaseca, Writing Group of the International Menopause Society for World Menopause Day 2012, Understanding weight gain at menopause, Climacteric 15 (2012) 419–429. https://doi.org/10.3109/13697137.2012.707385.

[39] P. Krisai, S. Aeschbacher, M. Bossard, E. Herber, S. Blum, P. Meyre, T. Burkard, M. Kühne, S. Osswald, B.A. Kaufmann, D. Conen, Change in atrial fibrillation burden over time in patients with nonpermanent atrial fibrillation, Cardiol. Res. Pract. 17 (2020) 9583409, https://doi.org/10.1155/2020/9583409.

[40] M. Avgil Tsadok, C.A. Jackevicius, E. Rahme, K.H. Humphries, H. Behlouli, L. Pilote, Sex differences in stroke risk among older patients with recently diagnosed atrial fibrillation, JAMA. 307 (2012) 1952–1958, https://doi.org/10.1001/jama.2012.3490.

[41] H.K. Yaggi, J. Concato, W.N. Kernan, J.H. Lichtman, L.M. Brass, V. Mohsenin, Obstructive sleep apnea as a risk factor for stroke and death, N Engl J Med. 353 (2005) 2034–2041, https://doi.org/10.1056/nejmoa043104.

[42] T. Young, P.E. Peppard, D.J. Gottlieb, Epidemiology of obstructive sleep apnea: a population health perspective, Am. J. Respir. Crit. Care Med. 165 (2002) 1217–1239, https://doi.org/10.1164/rccm.2109080.

[43] L. Desteghe, J.M.L. Hendriks, H. Heidbuchel, T.S. Potpara, G.A. Lee, D. Linz, Obstructive sleep apnoea testing and management in atrial fibrillation patients: a joint survey by the European Heart Rhythm Association (EHRA) and the Association of Cardiovascular Nurses and Allied Professions (ACNAP), Europace. 23 (2021) 1677–1684, https://doi.org/10.1093/europace/euab109.

[44] R.K. Pathak, A. Elliott, M.E. Middeldorp, M. Meredith, A.B. Mehta, R. Mahajan, J. M. Hendriks, D. Twomey, J.M. Kalman, W.P. Abhayaratna, D.H. Lau, P. Sanders P, Impact of CARDIOrespiratory FITness on arrhythmia recurrence in obese individuals with atrial fibrillation: the CARDIO-FIT study, J. Am. Coll. Cardiol. 66 (2015) 985–996. https://doi.org/10.1016/j.jacc.2015.06.488.

[45] R.K. Pathak, M.E. Middeldorp, D.H. Lau, A.B. Mehta, R. Mahajan, D. Twomey, M. Alasady, L. Hanley, N.A. Antic, R.D. McEvoy, J.M. Kalman, W.P. Abhayaratna, P. Sanders, Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study, J. Am. Coll. Cardiol. 64 (2014) 2222–2231, https://doi.org/10.1016/j.jacc.2014.09.028.