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Cross-ethnic comparison of the association between central sleep apnea and atrial fibrillation/flutter: The Kuakini Honolulu-Asia Aging Study and the Osteoporotic Fractures in Men (Mr.OS) study

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ABSTRACT

Introduction: Few studies indicated the impact of ethnicity on an association between central sleep apnea (CSA) and atrial fibrillation/flutter (AF) in older populations. We assessed possible ethnic differences in the association among elderly Japanese-American and White-American men.
Methods: We performed a cross-sectional analysis using two population studies of Japanese-American and White-American men. The Kuakini Honolulu-Asia Aging Study is a longitudinal cohort study of Japanese-American men living in Hawaii. Sleep data were collected between 1999 and 2000. The Osteoporotic Fractures in Men (Mr.OS) Sleep Study was conducted between 2003 and 2005 on the continental U.S. The majority of Mr.OS participants were White-American. We selected 79–90 year old males, who had overnight polysomnography from both studies. Total participants were 690 Japanese-American and 871 White-American men. The central apnea index (CAI) was the measure of the number of central apneas. CSA was defined by CAI>=5. Cheyne-Stokes breathing (CSB) was defined as a minimum consecutive 5–10 min period of a crescendo-decrescendo respiratory pattern associated with CSA.
Results: The prevalence of AF was 5.7% in Japanese-American men and 9.0% in White-American men. The prevalence of CSA and CSB in White-Americans were higher than in Japanese-Americans (11.5% vs 6.5% and 5.7% vs 3.3%, respectively). In multivariable-adjusted logistic regression models, CSA was associated with higher odds of AF, and the association was stronger in Japanese-Americans [Odds Ratio (OR) = 4.77, 95% confidence interval (CI): 1.95–11.67] than in White-Americans (OR = 2.09, 95 %CI: 1.09–4.01). CSB showed similar trends as CSA.
Conclusions: After adjustment, CSA and CSB were significantly associated with AF in both Japanese-American and White-American men.

1. Introduction

Atrial fibrillation/flutter (AF) is characterized by temporally and chronically rapid disorganized atrial electrical activation and contraction. AF is the most common cardiac arrhythmia, especially in the elderly population. AF is also associated with several high mortality diseases such as congestive heart failure (CHF) and stroke.

Therefore, it is very important to prevent AF. Epidemiological studies have indicated several risk factors for AF, such as aging, hypertension, hyperlipidemia, type-2 diabetes, cardiac disease, obesity, heavy alcohol intake, intensive physical activity, and sleep apnea [1]. There are two main types of sleep apnea: obstructive sleep apnea (OSA) which is the most common type due to an obstruction of the airway; and central sleep apnea (CSA) which is the lack of proper signals from the brain to the muscles that control breathing. In addition, CSA was often observed with Cheyne-Stokes Breathing (CSB): characteristic cycles of a crescendo-decrescendo respiratory pattern during sleep.

Many studies show an association between OSA and AF [2]. Moreover, several studies recently have indicated there was an

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association between CSA/CSB and AF in the general population [3–7]. However, few studies focused on the impact on ethnicity on the association between CSA and AF even though the prevalence and characteristics of CSA vary among ethnic groups. Therefore, we conducted a cross-sectional analysis to investigate the association between CSA and prevalence of AF among elderly Japanese-American and White-American men.

2. Methods

A cross-sectional analysis was conducted to estimate the associations between AF and sleep apnea.

We compared the prevalence of sleep apnea in community-based studies between Japanese-American men (The Kuakini HAASSA) and White-American men (Mr.OS sleep study) aged 79–90 years. The polysomnography (PSG) data of the two studies were obtained through the National Sleep Research Resource database (NSRR) [8].

2.1. The Kuakini HAASSA (1999–2000) [4,9]

The Kuakini Honolulu Heart Program (HHP) is a longitudinal cohort study of Japanese-American men in Hawaii that began in 1965. The Kuakini Honolulu-Asia Aging Study (HAAS) was originally conducted in 1991 to study dementia and other diseases of aging in survivors of the HHP. The Kuakini HAASSA was held between 1999 and 2000 during the Kuakini HHP-HAAS seventh examination. A total 1523 participants were examined at the Kuakini HHP-HAAS seventh examination. Details of the selection algorism have been published in a previous paper [4]. Briefly, a total of 718 Japanese-American men between 79 and 97 years old had overnight PSG in their homes using criteria established by the large multicenter Sleep Heart Health Study (SHHS) [6,9], which was a community-based prospective cohort study conducted in 1995–2006. PSG data for 9 electrocardiograms (ECG) had lead errors and were excluded. Nineteen of 709 participants did not meet the inclusion criteria (age 79–90 years) of this study. As a result, 690 participants' PSG data were analyzed from 709 participants (Fig. 1).

2.2. Mr.OS sleep study [10,11]

This study involved participants of the Mr.OS sleep study, which was an outgrowth of the Mr.OS study. The original Mr.OS study was conducted from 2000 to 2002 and included 5,994 men from the continental US. Participants were primarily White men over the age of 65 who were able to live independently and had no history of bilateral hip replacement. Participants were examined at six centers (Birmingham, AL; Minneapolis, MN; the Monongahela Valley, near Pittsburgh, PA; Palo Alto, CA; Portland, OR; and San Diego, CA) [10,11]. The Mr.OS sleep study was conducted from 2003 to 2005. A total 3,135 of the original 5,994 participants were included in the Mr.OS sleep study. Of the 3,135 participants, 179 did not participate in the sleep studies due to refusal or previous treatment for sleep apnea, 45 had failed ECG recordings. Therefore, PSG data were not available for 224 participants. The analytic sample for the MR.OS sleep study included 2,911 participants, for whom PSG data were not available for 35 participants due to ECG lead error, and an additional 2,005 participants did not meet the age inclusion criteria (79–90 years). As a result, 871 participants' PSG data were analyzed in the current study (Fig. 1).

Written informed consent for participation was received from all participants involved. All protocols were in accordance with the Institutional Review Board of the Kuakini Medical Center and University of Hawai'i at Mānoa.

2.3. Ascertainment of AF

The ascertainment method of AF was as described in our previous study [4]. In brief, AF was confirmed by a Japanese Circulation Society board-certified physician using single lead ECG of the PSG interpretation software. The software was developed for the analysis of large numbers of sleep studies from NSRR [8]. AF was diagnosed according to the ACC/AHA/ESC guidelines [12]. A validation analysis to assess the accuracy of our physician's ECG interpretations, using the 12-lead ECG data from SHHS as the gold standard, revealed the specificity and sensitivity to be 97.5% (154/158) and 93.3% (14/15) respectively [4]. Mehra et al. indicated that when ECG of PSG data from the Mr.OS sleep study, which was a random

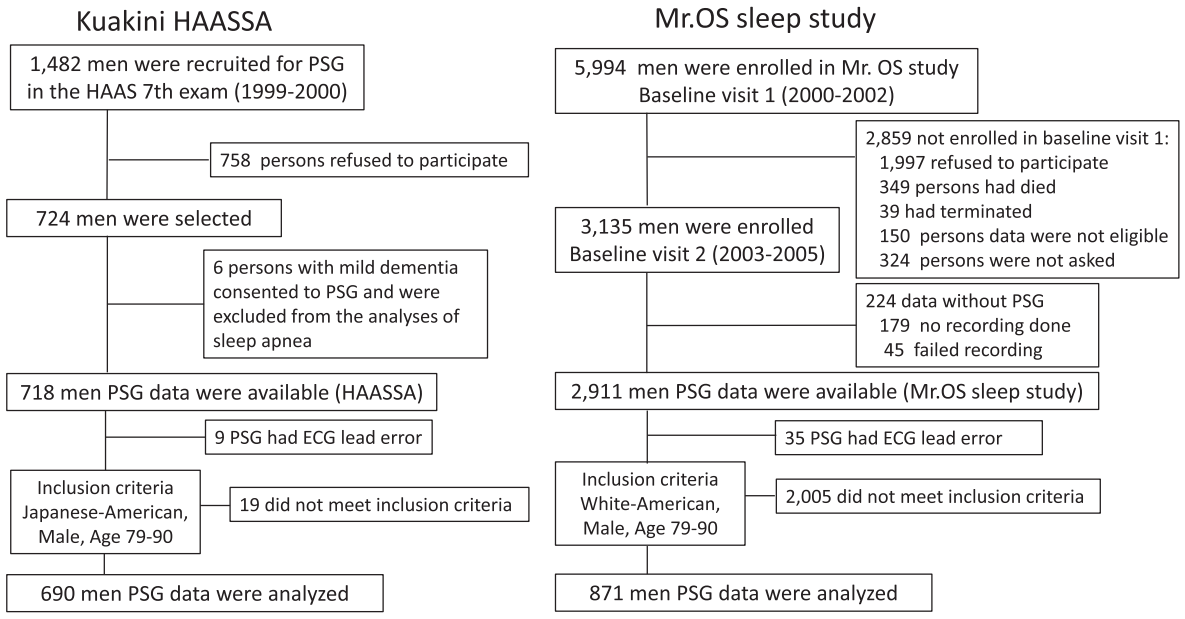

Fig. 1. Study's recruitment and enrollment. The Kuakini HAASSA 1999–2000[4,9] and Mr.OS Sleep Study 2003–2005[10,11]. ECG, Electrocardiogram; HAASSA, Honolulu-Asia Aging Study of Sleep; HAAS, Honolulu Asia Aging Study; Mr. OS, the Osteoporotic Fractures in Men Sleep Study; PSG, polysomnography.

sample of 20 sleep studies, were manually reviewed by two blinded electrophysiologists, the estimated correlation coefficient was 0.98 for supraventricular beats [7].

2.4. Definition of Obstructive Apnea–Hypopnea Index (OAHI) and Central Apnea Index (CAI)

AHI (measure of the number of obstructive and central apneas and hypopneas with > 4% oxygen desaturation) was used for the definition of sleep apnea in this study. OAHI was defined as the measure of the number of obstructive apneas and hypopneas with > 4% desaturation, and CAI was defined as the measure of the number of central apneas episodes per hour of sleep.

2.5. Central Sleep Apnea (CSA), Obstructive Sleep Apnea (OSA) and Cheyne-Stokes Breathing (CSB)

OSA was categorized as none (OAHI < 5), mild (OAHI 5–14), moderate (OAHI 15–29) and severe (OAHI 30 or more). CSA was defined as CAI $\geq$ 5. In the Mr.OS sleep study, CSB was defined as a minimum consecutive **10-minute** period of a crescendo-decrescendo respiratory pattern during CSA; in the Kuakini HAASSA, CSB was defined as a minimum consecutive **5-minute** period of a crescendo-decrescendo respiratory pattern during CSA. Percentage of Total Sleep Time (TST) with SaO2 < 90% was measured as the percentage of time below an oxygen saturation of 90%.

2.6. Assessment of potential confounders

Potential confounding variables identified from previous studies included age, body mass index (BMI), hypertension, diabetes, smoking status, prevalent stroke, prevalent coronary heart disease (CHD), the Epworth Sleepiness Scale (ESS), and neck circumference [1,13]. Age was evaluated as a continuous variable. Prevalence of hypertension was defined as a measured systolic blood pressure >=140 mmHg, measured diastolic blood pressure >=90 mmHg, or the use of antihypertensive medications including β-adrenergic blocking agents or diuretics. Prevalence of diabetes mellitus was defined as the use of anti-diabetic medications, such as insulin or oral hypoglycemic medications. Prevalent stroke and CHD were based on hospital record surveillance by an expert morbidity and mortality committee in the Kuakini HAASSA and on the questionnaire about medical history in the Mr.OS sleep study. BMI was calculated from measured height and weight (kg/m^2). ESS is a self-administered questionnaire with eight questions. Participants scored their daily chances of dozing off in eight different activities on a four-point scale (0 to 3). Scores ranged from 0 to 24, and a score greater than 10 was categorized as excessive daytime sleepiness (EDS). Neck circumference was measured in centimeters.

2.7. Statistical analysis

Participant characteristics were summarized as mean ± standard deviation (SD) or percentage and count. $\chi 2$ tests or Fisher exact tests were used to examine the association between categorical variables and AF. T-tests or ANOVA were used for continuous variables. Multiple logistic regression analyses were performed to calculate adjusted odds ratios (ORs) of AF by sleep apnea with 95% confidence intervals (CIs) adjusting for potential confounders [1,13]. SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses. Statistical significance was set at 5% and all tests were 2-tailed.

3. Results

3.1. Sample size and population characteristics

The age distributions (mean, median, and tertiles of age) were similar between the two studies (Supplemental Fig. 1). AF prevalence in the elderly White-Americans was higher than the elderly Japanese-Americans (9.0% vs 5.7%) (Table 1). The prevalence of severe OSA in the elderly Japanese-Americans was higher than in the elderly White-Americans (20.7% vs 11.8%). On the other hand, CSA and CSB prevalence in the Japanese-Americans were lower than the White-Americans (6.5% vs 11.5% and 3.3% vs 5.7%, respectively).

Table 1
Characteristics of the Kuakini HAASSA (1999–2000) and Mr.OS Sleep Study (2003–2005).

Variable	Japanese-American Kuakini HAASSA	White-American Mr.OS Sleep Study	P-value
Participants (n)	690	871	N/A
Male %	100%	100%	N/A
Age, year	82.9 ± 2.7	82.9 ± 3.2	0.937
Min-Max Age, year	79–90	79–90	N/A
BMI, kg/m^2	23.2 ± 3.1	26.4 ± 3.5	<0.0001
AF			
AF prevalence %(n)	5.7% (39 of 690)	9.0% (78 of 871)	0.014
PSG			
Severe OSA %(n)	20.7% (143 of 690)	11.8% (103 of 871)	<0.0001
Moderate OSA %(n)	25.2% (174 of 690)	22.7% (198 of 871)	0.253
CSA %(n)	6.5% (43 of 657)	11.5% (100 of 871)	0.001
CSB % (n)	3.3% (22 of 657)	5.7% (50 of 871)	0.029
Percentage of TST with SpO2 < 90%			
1.0%<	51.0% (352 of 690)	42.5% (370 of 871)	<0.0001
1.0% to < 3.5%	21.3% (147 of 690)	28.9% (252 of 871)	
3.5% to < 10%	17.0% (117 of 690)	13.8% (120 of 871)	
>=10%	10.7% (74 of 690)	14.8% (129 of 871)	
Other			
Neck size (cm)	38.0 ± 2.6	38.9 ± 2.6	<0.0001
ESS	7.0 ± 4.2	6.2 ± 3.6	<0.0001
EDS (ESS > 9) %(n)	25.9% (178 of 688)	13.0% (113 of 871)	<0.0001
Diabetic medications % (n)	11.6% (80 of 690)	8.3% (72 of 871)	0.028
Hypertension %(n)	72.5% (498 of 687)	73.1% (636 of 871)	0.787
History of Stroke %(n)	4.1% (28 of 690)	6.7% (58 of 871)	0.067
History of CHD %(n)	23.6% (163 of 690)	45.1% (391 of 866)	<0.0001
Current Smoking %(n)	4.1% (28 of 687)	0.6% (5 of 871)	<0.0001

AF, Atrial Fibrillation/Flutter; BMI, Body Mass Index; CHD, Coronary Heart Disease; CSA, Central Sleep Apnea.
CSB, Cheyne-Stokes Breathing; ESS, Epworth Sleepiness Scale; EDS, excessive daytime sleepiness.
HAASSA, Honolulu-Asia Aging Study of Sleep Apnea; Mr.OS, Osteoporotic Fracture in Men; N/A, not applicable.
OSA, Obstructive sleep apnea; PSG, Polysomnography; TST, total sleep time.
For continuous variables, P value derived from *t*-test.
For categorical variables, P value derived from chi-square test, or Fisher exact test if any expected cell frequencies are < 5.

Table 2
Characteristics between AF and non-AF groups; the Kuakini HAASSA (1999–2000) and Mr.OS Sleep Study (2003–2005).

	Japanese-American Kuakini HAASSA (n = 690)			White-American Mr.OS Sleep Study (n = 871)		
Variables, (n)	AF, (39)	Non-AF, (6 5 1)	P-value	AF, (78)	Non-AF, (7 9 3)	P-value
Age, year	84.1 ± 2.9	82.8 ± 2.7	0.004	83.3 ± 3.4	82.9 ± 3.1	0.236
BMI, kg/m^2	23.1 ± 2.3	23.3 ± 3.1	0.616	27.0 ± 4.2	26.4 ± 3.4	0.184
Neck size, cm)	37.8 ± 2.4	38.0 ± 2.7	0.680	39.1 ± 3.1	38.8 ± 2.6	0.481
History of						
CHD	33,3% (13 of 39)	23.0% (150 of 651)	0.142	64.5% (49 of 76)	43.3% (342 of 790)	0.0004
Stroke	7.7% (3 of 39)	4.3% (28 of 651)	0.411	9.0% (7 of 78)	6.4% (51 of 793)	0.390
Hypertension	79.5% (31 of 39)	72.1% (467 of 648)	0.314	84.6% (66 of 78)	72.0% (570 of 792)	0.016
Current smoke	0% (0 of 39)	4.3% (28 of 648)	0.396	1.3% (1 of 78)	0.5% (4 of 793)	0.386
Diabetic medications	7.7% (3 of 39)	11.8% (77 of 651)	0.608	10.3% (8 of 78)	8.1% (64 of 793)	0.504
ESS	8.9 ± 4.5	6.9 ± 4.2	0.004	6.0 ± 3.4	6.3 ± 3.6	0.558
EDS (ESS > 9)	41.0% (16 of 39)	25.0% (162 of 649)	0.026	12.8% (10 of 78)	13.0% (103 of 793)	0.966
PSG						
Severe OSA (OAHI > 30)	23.1% (9 of 39)	20.6% (134 of 651)	0.709	19.2% (15 of 78)	11.1% (88 of 793)	0.034
CSA (CAI>=5)	21.6% (8 of 37)	5.7% (35 of 620)	0.002	21.8% (17 of 78)	10.5% (83 of 793)	0.0027
CSB	13.5% (5 of 37)	2.7% (17 of 620)	0.006	21.8% (17 of 78)	4.2% (33 of 793)	<0.0001
Percentage of TST with SpO2 < 90%						
1%<	61.5% (24 of 39)	50.4% (328 of 651)	0.417	33.3% (26 of 78)	43.4% (344 of 793)	0.354
1.0% to < 3.5%	15.4% (6 of 39)	21.7% (141 of 651)		32.1% (25 of 78)	28.6% (227 of 793)	
3.5% to < 10%	10.3% (4 of 39)	17.4% (113 of 651)		18.0% (14 of 78)	13.4% (106 of 793)	
>= 10%	12.8% (5 of 39)	10.6% (69 of 651)		16.7% (13 of 78)	14.6% (116 of 793)	

AF, Atrial Fibrillation/Flutter; BMI, Body Mass Index; CAI, Central Apnea Index; CHD, Coronary Heart Disease; CSA, Central Sleep Apnea; CSB, Cheyne-Stokes Breathing; EDS, Excessive Daytime Sleepiness; ESS, Epworth Sleepiness Scale; HAASSA, Honolulu-Asia Aging Study of Sleep Apnea; Mr.OS, Osteoporotic Fracture in Men; OAHI, Obstructive Apnea–Hypopnea Index OSA, Obstructive sleep apnea; PSG, Polysomnography; TST, total sleep time.
For continuous variables, P value derived from *t*-test.
For categorical variables, P value derived from chi-square test, or Fisher exact test if any expected cell frequencies are < 5.

3.2. Characteristics between AF and non-AF groups

Table 2 indicates that CSA and CSB were significantly associated with prevalence of AF in the Japanese-Americans as well as White-Americans. On the other hand, crude (unadjusted) severe OSA was only significantly associated with prevalence of AF in the White-Americans (Table 2).

3.3. Adjusted associations between sleep apnea and prevalence of AF in two different ethnic groups

Fig. 2**a-b (**Supplemental Tables 1 and 2**)** also showed that CSA and CSB were significantly associated with prevalence of AF in the elderly Japanese-Americans as well as in the elderly White-Americans. However, the severity of OSA was not significantly associated with prevalence of AF in either group **(**Fig. 2**c and Supplemental Table 3)**. This association persisted after multivariable adjustment for age, BMI, hypertension and other confounding variables in the Japanese-Americans as well as White-Americans. In multivariable-adjusted logistic regression models, CSA was associated with higher odds of AF, and the association was stronger in the Japanese-Americans [Odds Ratio (OR) = 4.77, 95% confidence interval (CI): 1.95–11.67] than in the White-Americans (OR = 2.09, 95% CI: 1.09–4.01) **(**Fig. 2**d and Supplemental Table 4)**. CSB was also associated with higher odds of AF after multivariable adjustment. However, the odds ratios were similar between the Japanese-Americans (OR = 5.75, 95% CI: 1.85–17.84) and the White-Americans (OR = 5.84, 95% CI: 2.85–11.95) **(**Fig. 2**e and Supplemental Table 4)**. On the other hand, OSA was not significantly associated with the prevalence of AF in either group **(**Fig. 2**f and Supplemental Table 4)**.

4. Discussion

Despite observed ethnic differences in the prevalence of CSA, CSB, severe OSA and AF, CSA and CSB were significantly associated with the prevalence of AF in both the older Japanese-American and White-American men. In contrast, severe OSA was not significantly associated with AF in either ethnicity after multivariable adjustments. This study is innovative because this was the first study to compare the association between AF and CSA/CSB among different ethnic groups in general populations.

4.1. CSA prevalence

Bixler et al. showed that the prevalence of CSA (defined as CAI $\geq$ 10) in a general population of 741 men was an average of 0.4% for all ages but 1.1% for individuals over the age of 65[14]. Similarly, Donovan et al. reported the prevalence of CSA in men aged 65 years and older was 2.7% (95% CI: 1.9–3.6%) [15]. The prevalence of CSA in our study (Japanese-Americans, 6.5% and White-Americans, 11.5%) was much higher than the previous general population studies [14,15]. It might be because the age of our study participants was older than participants in the previous studies since the prevalence of CSA increases with aging.

In our study, the prevalence of CSA in the White-Americans was higher than in the Japanese-Americans.

The increased prevalence of CSA may also reflect the higher frequency of comorbid conditions, such as AF, stroke, and CHD [16]. In fact, the prevalence of several comorbid conditions (AF, stroke, and CHD) in the White-Americans was higher than in the Japanese-Americans in our study (Supplemental Table 1).

4.2. CSB prevalence

In our study, the prevalence of CSB in the Kuakini HAASSA and Mr.OS sleep study were 3.3% and 5.7% respectively. The result was consistent with a previous SHHS study, which indicated that about half of the CSA patients had associated CSB [15]. Moreover, the SHHS study indicated the prevalence of CSB was 1.4% (95% CI: 0.8–2.0%), which was lower than our study. The reason might also be explained by the difference of participants' age distribution.

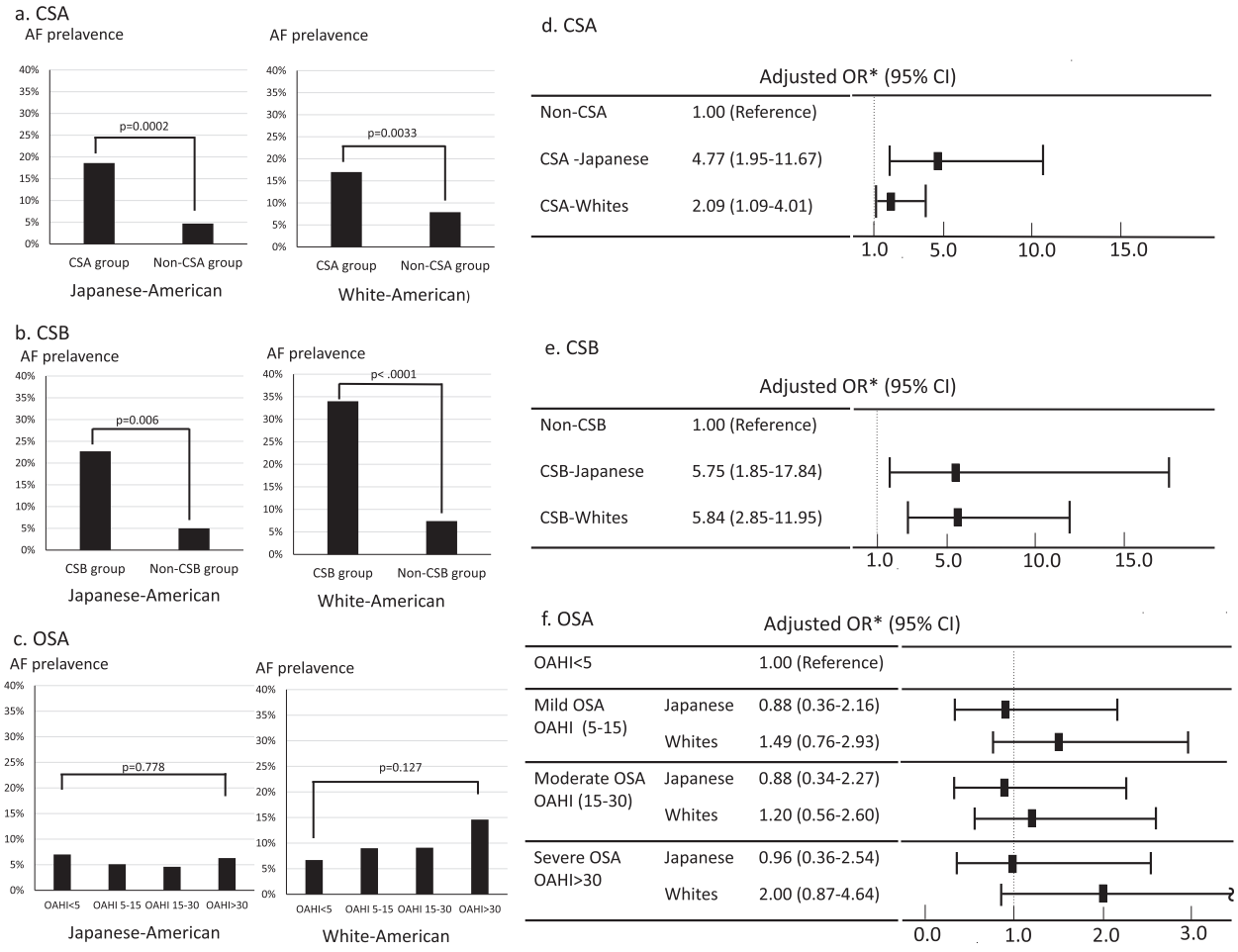

Fig. 2. AF prevalence between sleep apnea and no-sleep apnea in two different ethnic groups and adjusted associations (Odds Ratios and 95% Confidence Interval) between sleep apnea and prevalence of AF estimated by multiple logistic regression models; the Kuakini HAASSA (1999–2000) and Mr.OS sleep study (2003–2005). AF, Atrial Fibrillation/Flutter; CI, Confidence Interval; CSA, Central Sleep Apnea; CSB, Cheyne-Stokes Breathing; HAASSA, Honolulu-Asia Aging Study of Sleep Apnea; Mr. OS, Osteoporotic Fracture in Men; OAHI, Obstructive Apnea–Hypopnea Index; OR, Odds Ratio; OSA, Obstructive sleep apnea; P value derived from chi-square test, or Fisher exact test if any expected cell frequencies are < 5. *Adjusted Model: Age, Body Mass Index, Hypertension, Type2-diabetes medication use, and History of stroke and Coronary Heart Disease.

4.3. OSA prevalence

Somers et al. (2008) reported that 1 in 5 adults in the US have at least mild OSA (AHI $\geq$ 5) and 1 in 15 have moderate or severe OSA (AHI $\geq$ 15) [17]. A cross-ethnicity sleep study among middle-aged White-Americans and Japanese indicated that the ethnic difference in OSA was explained by a difference in BMI distribution [18]. The authors reported the biological gradient between the prevalence of OSA and BMI in White-Americans as well as Japanese.

In our study, the mean BMI of the Japanese-Americans was lower than that of the White-Americans (BMI 23.2 vs 26.4). The prevalence of severe OSA in the Japanese-Americans (20.7%) was approximately twice that of the White-Americans (11.8%).

Ong et al. and Li et al. demonstrated that Asians were less obese but had an equivalent or greater prevalence of severe OSA [19,20]. This is consistent with our study.

However, in our study, there was a biological gradient between the prevalence of OSA and BMI only in the White-Americans, but not in the Japanese-Americans (**Supplemental Table 3**). Therefore, the mechanism of OSA in late-age Japanese men may differ from that of middle-age Japanese men and older-age White-Americans. Li et al. reported that it might be explained by differences in the craniofacial profile [19,21]. Unfortunately, in this study, the craniofacial profile of the participants was not available. Moreover, the ethnic difference of association between severity of OSA and BMI in this study seems to be difficult to explain only on the basis of the craniofacial profile. Therefore, there might be other unknown subclinical differences between the Kuakini HAASSA and Mr.OS Sleep Study participants. More investigation is needed in the future.

4.3.1. OSA and AF

Even though previous studies have indicated an association between OSA and AF [2], in our study, severe OSA was only significantly associated with prevalence of AF in the White-Americans (Table 2).

We also found that the severity of OSA was not significantly associated with prevalence of AF in either group before and after multivariable adjustment (Fig. 2c and f).

Since we observed the biological gradient between the severity of OSA and AF in the White-Americans, the result might be explained by the lack of an adequate sample size (statistical power) for the White-Americans. However, in the Japanese-Americans, the results might not be explained by inadequate sample size since a biological gradient between the severity of OSA and AF was not demonstrated. There might be undetected bias such as survival bias as the target population was very old.

4.4. AF and CSA/CSB among different ethnicities

Tung et al. indicated that CSA was associated with incident AF and that CSA was a predictor of incident AF after multiple adjustments (OR 3.0; 95% CI, 1.4–6.4) in SHHS (Aged 62.8 ± 11.2, 88% White-Americans) [6]. May et al. also reported CSB was associated with AF incidence (OR 2.3; 95% CI, 1.1–4.6) in another Mr.OS sleep study (aged 65 years and older, 91% White-Americans). However, previous studies did not mention ethnic differences [3].

4.5. Biological mechanism for CSA in AF

A previously published review provides several potential mechanisms to explain the observed association between CSA and AF, such as congestive heart failure, sympathovagal imbalance and cardiac remodelling [5].

(1) Subclinical congestive heart failure (CHF) and stroke

Subclinical CHF might be a residual confounder. CSA was observed in 25–40% of patients with CHF in previous clinical studies [22,23]. Oldenburg et al. reported that CSA patients had increased AF incidence and reduced systolic left ventricular (LV) function when compared to OSA patients [24]. Unfortunately, CHF data were not available in the Kuakini HAASSA. However, in the MrOS Sleep study, there were two questions about CHF: "Has a doctor or other health care provider ever told you that you had congestive heart failure or enlarged heart?" and "Are you currently being treated for congestive heart failure or enlarged heart by a doctor?". A total 7.6% of Mr.OS Sleep Study participants (66 out of 871) reported that they had a history of CHF. CSA was associated with higher odds of AF, and the association was stronger in the CHF group (OR = 6.39, 95% CI: 1.33–30.59) than in the non-CHF group (OR = 2.03, 95% CI: 1.04–3.98). The history of CHF modified the association between CSA and AF. A current study indicated that the prevalence of CHF in the US was 9.5% [25], which was higher than our result (7.6%). Therefore, it is possible that we may have underestimated the prevalence of CHF in our study. Hence subclinical CHF might be a residual confounder in this study.

AF is an important risk factor for stroke. Parra et al. indicated that CSA was often seen after stroke [26]. Therefore, subclinical stroke might also be a residual confounder in this study. We previously reported the prevalence of poor cognition, which could be caused by subclinical stroke, was much higher in the CSA group compared with the non-CSA group (30% vs 13%) [4].

Even though we adjusted for "history of CHD and stroke" in the logistic regression analysis, subclinical CHF and stroke might still be residual confounders.

(2) Sympathetic activation

CSA might enhance vagal activity that causes autonomic dysfunction [27]. AF is triggered by repeated excessive vagal stimulation and shortening the atrial refractory period [28]. Therefore, the excessive vagal activity might be a potential mechanism for a causal association between CSA and AF.

(3) Right ventricular (RV) dysfunction

Pulmonary artery pressure is the major factor of RV systolic function [29]. Javaheri et al. indicated that severe pulmonary hypertension was observed in patients with CSA resulting in RV dysfunction [30]. Since RV dysfunction in acute decompensated systolic failure patients was reported as a risk factor for the incidence of AF [31], RV dysfunction could also be a potential mechanism for a causal association between CSA and AF.

4.6. Strengths and limitations

There are several strengths of this study. First, we used data from organized, large, population-based cross-sectional sleep studies. The participants of the two studies were restricted to men belonging to the same age range. These limitations were placed to reduce confounding factors such as age, disease and sex-related factors.

Second, we obtained full PSG data, which is considered the gold standard to analyze CSA and CSB. The association between CSA/CSB and AF has rarely been reported previously due to the difficulty in carrying out a full PSG in the general population. Our findings make a substantive contribution to furthering the understanding of CSA/CSB prevalence in older general populations.

There are several limitations. First, the Kuakini HAAS and the Mr.OS original cohorts were initiated in different time periods, and differed in location and inclusion criteria. These differences could affect the results of our study. Second, the participants of PSG only represented half of the entire participants in the seventh Kuakini HAAS Exam and the Mr.OS original cohort (Fig. 1). There might be a volunteer bias because volunteer groups would be healthier than non-volunteer groups and volunteer groups could be more interested in their health and sleep problems. Third, it was possible that we underestimated the prevalence of AF since we might not have detected paroxysmal AF in our study. However, the underestimation of AF might be unbiased with regards to apnea, resulting in a nondifferential misclassification which would bias estimates towards the null. Fourth, the definition of CSB were different in the Kuakini HAASSA and the Mr.OS sleep study. CSB was defined as a minimum consecutive **10**-minute period of a crescendo-decrescendo respiratory pattern during CSA in the Mr. OS sleep study, and a **5**-minute period of a crescendo-decrescendo respiratory pattern during CSA in the Kuakini HAASSA. Therefore, we might have overestimated the number of participants with CSB in the Japanese-Americans. Fifth, the small sample sizes of CSA and CSB with AF might affect the ability to detect significant differences. In fact, 95% CIs of ORs in CSA and CSB were wide in both ethnic groups. Sixth, this study did not include data from female participants and young persons. Since this study has limited external validity of gender and age, the findings may not be broadly generalizable. Finally, several potential confounders were missing, such as dyslipidemia, CHF chronic obstructive pulmonary disease, pacemaker placement, alcohol consumption, and physical activity. These variables were adjusted for in previous studies since these variables could increase the risk of AF [3,6].

5. Conclusion

This is the first study to estimate the relationship between AF and sleep apnea, especially CSA and CSB among different ethnic groups. This study indicated that CSA and CSB were significantly associated with prevalence of AF in elderly Japanese-Americans and White Americans. This association persisted after multivariable adjustments for age, BMI, hypertension, and other confounding variables.

In contrast, the severity of OSA was not significantly associated with AF in either ethnicity.

The results of this study could be useful in identifying individuals at risk and potentially prevent AF in older Japanese-American as well as White-American population.

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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.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2021.100834.

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