ORIGINAL ARTICLE

Association of sleep characteristics with atrial fibrillation: the Multi-Ethnic Study of Atherosclerosis

Younghoon Kwon,[1] Sina A Gharib,[2] Mary L Biggs,[3] David R JacobsJr,[4] Alvaro Alonso,[4] Daniel Duprez,[1,4] Joao Lima,[5] Gen-Min Lin,[6,7] Elsayed Z Soliman,[8] Reena Mehra,[9] Susan Redline,[10] Susan R Heckbert[11]

▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2014-206655).

For numbered affiliations see end of article.

Correspondence to
Dr Younghoon Kwon, Department of Medicine, University of Minnesota, Mayo Mail Code 508, 420 Delaware St SE, Minneapolis, MN 55455, USA; kwonx208@umn.edu

YK and SAG contributed equally.

Received 9 December 2014
Revised 13 April 2015
Accepted 22 April 2015
Published Online First 18 May 2015

ABSTRACT

Background Population-based studies have linked measures of sleep disordered breathing to nocturnally occurring atrial fibrillation (AF) episodes. Whether measures of sleep disordered breathing and sleep quality are associated with prevalent AF has not been studied in an unselected population. We investigated the cross-sectional association with prevalent AF of objectively collected prespecified measures of overnight sleep breathing disturbances, sleep stage distributions, arousal and sleep duration.

Methods AF prevalence, defined by diagnosis codes, study electrocardiography and sleep study were examined among Multi-Ethnic Study of Atherosclerosis (MESA) participants who underwent polysomnography in the MESA Sleep Study (n=2048).

Measurements and main results Higher apnoea hypopnoea index (AHI) was associated with increased odds of AF, although the significance was attenuated after full adjustment for covariates including prevalent cardiovascular disease (OR: 1.22 (0.99 to 1.49) per SD (17/h), p=0.06). Analyses of sleep architecture measures and AF revealed significantly lower odds of AF associated with longer duration of slow wave sleep (OR: 0.66 (0.5 to 0.89) per SD (34 min), p=0.01) which persisted after additionally adjusting for AHI (OR: 0.68 (0.51 to 0.92), p=0.01). Higher sleep efficiency was significantly associated with lower likelihood of AF but the significance was lost when adjusted for AHI. No significant association was present between sleep duration and AF. In a model including AHI and arousal index, the association between AHI and AF was strengthened (AHI: OR 1.49 (1.15 to 1.91) per SD, p=0.002) and a significant inverse association between arousal index and AF was observed (OR 0.65 (0.50 to 0.86) per SD (12/h), p=0.005).

Conclusions In a study of a large multiethnic population, AF was associated with AHI severity, and was more common in individuals with poor sleep quality as measured by reduced slow wave sleep time, a finding that was independent of AHI.

Linked

▶ http://dx.doi.org/10.1136/thoraxjnl-2015-206970
▶ http://dx.doi.org/10.1136/thoraxjnl-2015-207247
▶ http://dx.doi.org/10.1136/thoraxjnl-2015-206871

CrossMark

To cite: Kwon Y, Gharib SA, Biggs ML, *et al*. *Thorax* 2015;**70**:873–879.

Key messages

What is the key question?
Are measures of sleep disordered breathing (SDB) and sleep architecture associated with prevalent atrial fibrillation (AF)?

What is the bottom line?
AF was associated with severity of SDB as indicated by the apnoea hypopnoea index and the oxygen desaturation index, and with measures of sleep quality including slow wave sleep.

Why read on?
This study highlights the association of SDB metrics with AF and reveals a previously unrecognised role for measures of sleep quality in influencing this common arrhythmia.

INTRODUCTION

Accumulating evidence highlights the importance of sleep in cardiovascular health. Sleep disordered breathing (SDB), insomnia and shortened sleep duration have each been associated with increased risk of cardiovascular diseases (CVDs) including hypertension, metabolic syndrome, coronary heart disease, heart failure and stroke, and CVD related mortality.[1–9] In recent years, there has been growing interest in understanding the link between sleep disorders and atrial fibrillation (AF), the most common chronic arrhythmic condition with considerable impact on quality of life, cardiovascular morbidity and mortality.[10] An association between SDB and AF has been suggested by population-based cross-sectional studies that demonstrated a higher occurrence of sleep study-detected nocturnal AF in subjects with SDB compared with those without SDB.[11 12] In one single-centre retrospective study, nocturnal hypoxaemia, an important pathophysiological consequence of SDB, was predictive of new-onset AF in middle-aged patients.[13] Despite these findings, the association of SDB with prevalent AF is unclear because previous population-based studies focused only on nocturnal AF as determined during the sleep study[11 12] and the above mentioned clinic-based study failed to show any significant association between AF and apnoea hypopnoea index (AHI), the most commonly used metric for SDB. Furthermore, other metrics of sleep quantity and quality that have been implicated in cardiovascular end points[14] have not been objectively studied in association with prevalent AF. Therefore, our primary aim was to examine the cross-sectional association of SDB metrics and sleep quality with AF.

METHODS

Full details are available in the online supplementary material.

Study population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a multisite cohort study of community-dwelling men and women aged 45–84 years without current AF and without known CVD (history of coronary heart disease, heart failure or stroke) at enrolment in 2000–2002.[15] A subset of participants who participated in the MESA Sleep ancillary study shortly following MESA exam 5 (October 2010 through February 2013) were included in the analysis (n=2048).

ECG

Standard 12-lead ECGs obtained in MESA exam 5 were read centrally. Software detected ECG abnormalities, including AF/atrial flutter, were confirmed visually by the ECG reading centre staff.

Sleep data

An overnight inhome polysomnography (PSG) (Compumedics, Abbostville, Australia) was conducted. Actiwatch Spectrum wrist actigraphy (Philips Respironics, Murrysville, Pennsylvania, USA) was performed for 7 days to derive average sleep duration. All the recordings were centrally scored. The primary metric of SDB was AHI defined as the sum of all apnoeas plus hypopnoeas with a ≥4% O_2 desaturation and analysed as a continuous measure. Common clinical cut-offs (AHI<5, 5≤AHI<15/h, 15≤AHI<30, AHI≥30/h) were used to classify SDB severity. Nocturnal hypoxaemia was measured by O_2 desaturation index (ODI) defined as the average number of desaturation episodes of at least a 4% decrease in O_2 saturation (SpO_2) from the pre-event baseline SpO_2 per hour of sleep and by time spent with SpO_2 less than 90%. Sleep stages (N1, N2, N3 or slow wave (SWS), and rapid eye movement sleep) were expressed as absolute times in each stage and proportion of the sleep period (%) in each stage. The arousal index was defined as the number of arousals per hour.[16] Sleep efficiency based on the PSG (sleep efficiency-PSG) was calculated by dividing the PSG-based total sleep time by the total time between sleep onset and lights on. An alternative definition of sleep efficiency based on actigraphy (sleep efficiency-actigraphy) was calculated by taking the sum of all sleep time divided by the sum of all in bed time during main sleep intervals across the recording.

Ascertainment of AF

AF ascertainment for the period from MESA study entry up to and including the sleep study was based on (1) ICD-9 (International Classification of Diseases, Ninth Revision) discharge diagnosis codes from hospitalisations ascertained during regular MESA events follow-up, (2) ICD-9 inpatient discharge diagnosis codes or outpatient ICD-9 codes from Medicare claims data, (3) 12-lead ECGs obtained at the baseline MESA exam and about 10 years later with a reading of AF or atrial flutter, or (4) a nocturnal episode of physician-verified AF or atrial flutter detected in a single lead ECG during the sleep study at exam 5. A second more restrictive definition of AF excluding the outpatient ICD-9 codes from Medicare claims data was also used in a sensitivity analysis. We were not able to determine whether AF was paroxysmal, persistent or permanent as of the time of the sleep study.

Covariates

Demographic characteristics, health habits, medication use, body habitus (body mass index and height[17]), alcohol intake and blood pressure were based on information from the exam 5 visit. Blood samples were collected and assayed for fasting glucose level, low density lipoprotein and high density lipoprotein cholesterol. We used diabetes and hypertension, as well as prevalent coronary heart disease, stroke and heart failure as covariates.

Statistical analysis

Logistic models were used to assess the association between sleep measures and AF prevalence adjusting for demographic factors (Model 1), body habitus (Model 2), CVD risk factors (Model 3) and prevalent CVD (Model 4). An additional model adjusting for the full model plus alcohol consumption and physical activity yielded similar results as Model 4 and therefore results are not reported.

We performed secondary analyses by fitting models that included multiple sleep measures that were significantly associated with AF in the primary models. Sensitivity analyses using the more restrictive definition of AF and using an alternative AHI definition were performed to check for consistency of the results. All statistical analyses were performed using Stata V.13 (StataCorp, 2013, College Station, Texas, USA)

RESULTS

Participant characteristics

The distribution of baseline characteristics of the exam 5 MESA sleep study participants by AHI categories is shown in table 1.

Characteristics of participants by SWS quartile, a measure of deep sleep, are also shown (see online supplementary table S1). Participants with longer duration of SWS were characterised by younger age and higher high density lipoprotein levels; a larger proportion were white, and a smaller proportion were men or had hypertension or diabetes. Distributions of sleep indices overall and by the presence of AF are shown in table 2.

Compared with the No AF group, the AF group was characterised by more severe SDB as shown by a higher AHI and more nocturnal hypoxaemia, and had poorer sleep quality as shown by lower sleep efficiency and reduced SWS.

Correlations among the sleep measures are shown in the online supplementary table S2. AHI was positively associated with ODI (r=0.98) and arousal index (r=0.58), and inversely associated with SWS time/% SWS time (r=−0.18/−0.17) and sleep efficiency-PSG (r=−0.22).

Atrial fibrillation

Based on the primary definition of AF used for this study, AF was present in 100 participants (4.9%). The majority of AF cases were ascertained via MESA events surveillance, or from inpatient or outpatient Medicare Claims data. Twenty-four participants manifested AF during the sleep study, but only eight of these were identified by the sleep study alone (see online supplemental table S3). Participants with AF tended to have a higher prevalence of hypertension and treatment for hypertension (see online supplementary table S4). The prevalence of AF was higher among white participants compared with other races, particularly African-Americans.

Association of AHI and hypoxaemic indices with AF

In the unadjusted analysis, AF prevalence increased across AHI severity categories: 4.0% in participants without SDB (n=707, AHI<5/h); 4.0% with mild SDB (n=650, 5≤ AHI<15/h); 6.0% with moderate SDB (n=384, 15≤ AHI<30/h); and 7.5% in subjects with severe SDB (n=307, AHI ≥30/h) (linear trend: p=0.04). This linear trend, however, was no longer present in adjusted models (figure 1). In adjusted models, each SD increase

Table 1 Characteristics of MESA Sleep study participants by sleep disordered breathing (SDB) severity (apnoea hypopnoea index)

	Overall n=2048	<5 n=707	5–14 n=650	15–29 n=384	≥30 n=307
Age (years)	68.4±9.2	67.2±9.1	69.3±9.2	69.2±9.0	68.8±9.1
Male (%)	46.4	32.7	44.3	57.3	68.7
Race/ethnicity (%)					
White	36.2	38.6	37.5	34.4	30.3
Chinese-American	12.2	12.2	10.3	13.8	14.0
African-American	27.7	29.3	27.4	25.8	27.4
Hispanic	23.9	19.9	24.8	26.0	28.3
Attained education (%)					
High school or less	31.3	29.7	32.8	29.2	34.5
At least some college or technical school	48.5	47.3	48.5	50.8	48.5
Graduate or professional school	20.2	22.9	18.7	20.1	16.9
Cigarette smoking status (%)					
Never	47.0	50.2	45.8	47.1	41.7
Former	45.9	41.9	46.9	47.9	50.8
Current	7.1	7.9	7.2	4.9	7.5
Alcoholic drinks/week (%)					
None	67.5	67.1	68.1	69.8	64.5
≤7	21.1	23.5	22.1	18.1	16.9
>7	11.4	9.4	9.9	12.1	18.6
Physical activity (met-min/wk)	5433±6425	5776±6849	5204±5960	5823±7466	4649±4682
Height (cm)	165.4±10.1	164.3±9.8	164.9±10.1	166.8±10.2	167.4±10.1
Body mass index (kg/m^2)	28.7±5.6	26.7±5.0	28.8±5.1	29.7±5.6	31.5±6.1
Seated systolic blood pressure (mm Hg)	122.8±20.2	121.0±21.5	123.6±19.7	122.6±18.9	125.8±19.7
Seated diastolic blood pressure (mm Hg)	68.3±9.9	67.2±9.9	68.2±9.8	68.9±9.9	70.1±10.0
Total cholesterol (mg/dL)	184.0±36.9	188.8±36.7	185.0±35.8	179.4±37.6	176.6±36.8
HDL (mg/dL)	55.6±16.3	59.9±17.8	55.5±15.6	51.7±14.4	50.6±13.6
Fasting glucose (mg/dL)	102.0±28.4	98.3±23.9	101.1±27.2	104.1±28.4	109.8±37.2
Hypertension (%)*	56.7	51.2	58.2	59.4	62.9
Hypertension medication (%)	53.4	47.5	55.1	55.2	60.9
Lipid-lowering medication (%)	37.3	32.5	37.8	41.4	41.7
Diabetes (%)	19.9	14.3	19.4	24.2	28.3
Prevalent coronary heart disease (%)	1.6	1.0	1.5	2.3	2.0
Prevalent stroke (%)	1.0	1.3	0.9	0.5	1.0
Prevalent heart failure (%)	1.3	0.4	0.9	2.6	2.6

All data are expressed as the mean±SD or frequency as percentage.
*by Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (1997) criteria.
HDL, high density lipoprotein; MESA, Multi-Ethnic Study of Atherosclerosis.

Table 2 Distribution of sleep characteristics of the cohort, overall and by the presence of atrial fibrillation (AF)

	Overall (n=2048)				No AF (n=1948)		AF (n=100)		
	N	Mean	SD	Median	Mean	SD	Mean	SD	p Value
AHI (events/h)	2048	14.8	16.7	9.1	14.6	16.5	20	20.6	0.01
CAI (events/h)	2026	0.4	1.7	0	0.4	1.8	0.5	1.3	0.02
ODI (events/h)	2018	14.2	16.2	8.2	13.9	15.9	19.7	20.3	0.004
% time SpO_2 <90%	2048	3.8	9	0.6	3.7	8.8	6.4	12.8	0.003
SWS time (min)	2026	36.9	34.2	29	37.6	34.4	23.9	26.5	<0.001
% SWS time	2026	10	9	8.1	10.2	9	7.3	8	<0.001
REM time (min)	2026	66.4	29.9	66	66.7	30	60.5	28.7	0.05
% REM time	2026	18	6.7	18.3	18	17.7	17.6	6.4	0.6
Arousal index (events/h)	2026	22.3	12	19.8	22.3	12	22.1	12.3	0.7
Sleep efficiency-PSG (%)	2018	79.6	12.7	82.2	79.9	12.6	73.4	13.3	<0.001
Sleep efficiency-actigraphy (%)	1938	89.8	3.8	90.4	89.8	3.6	89.2	5.7	0.08
Sleep duration-actigraphy (h)	1938	6.5	1.4	6.6	6.5	1.3	6.4	1.6	0.8

Sleep characteristics between AF versus No AF group were compared using unpaired student's t test.
AHI: apnoea hypopnoea index based on all obstructive and central apnoeas and hypopnoeas with ≥4% desaturation/sleep hour; CAI, central apnoea index; all central apnoeas with 4% desaturation or arousal/sleep hour; ODI, oxygen desaturation index; SpO_2, oxygen saturation; SWS, slow wave sleep; REM, rapid eye movement; PSG, polysomnography.

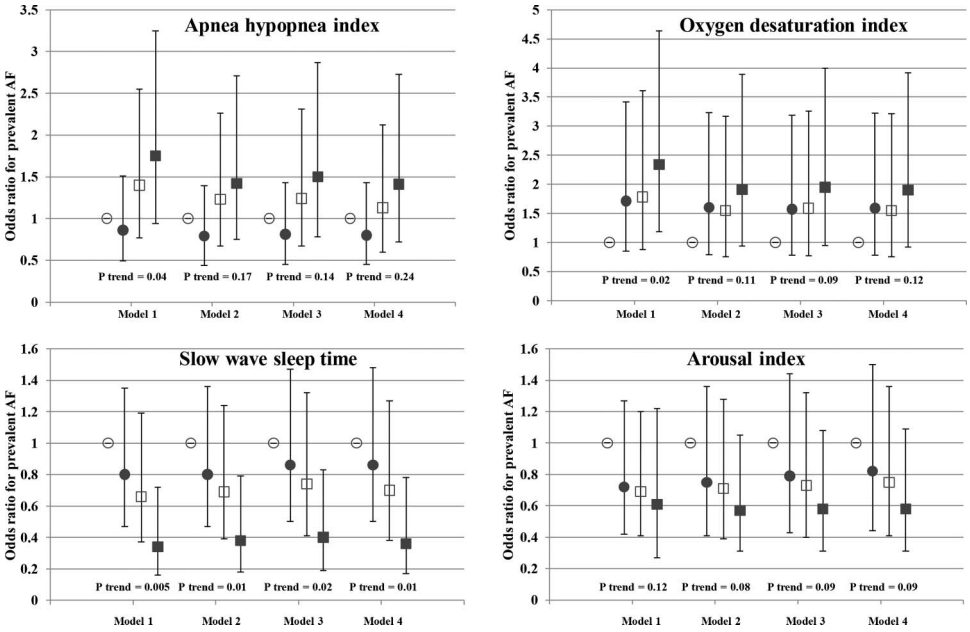

Figure 1 Adjusted OR (point estimate and 95% CI) of atrial fibrillation (AF) (per 1 SD) for: (A) common clinical cut-off points of AHI (apnoea hypopnoea index; No sleep disordered breathing: AHI <5; Mild: 5≤AHI <15; Moderate: 15≤AHI<30; Severe: AHI≥30/h) and for quartiles of (B) ODI (oxygen desaturation index), (C) SWS (slow wave sleep) time and (D) arousal index. No sleep disordered breathing group and first quartile are references. Point estimates for first through fourth quartiles are indicated by open circle (○), filled circle (●), open square (□) and filled square (■), respectively.

(16.7/h) in AHI was associated with a modest increase in the odds of prevalent AF in all models, although statistical significance was attenuated to borderline in a model accounting for prevalent CVD (table 3).

The mean central apnoea index was low among the study population and was not associated with AF. Sensitivity analyses using an alternative definition of AHI that included an arousal-based definition of hypopnoea resulted in loss of association with AF in all models (see online supplementary table S5). Higher ODI, a measure of intermittent hypoxaemia, was also associated with significantly higher odds of prevalent AF in unadjusted and all adjusted models. However, no significant linear trend was observed in quartile based analysis (figure 1). No significant association with AF was observed for % time with SpO_2<90%, a measure of cumulative burden of low haemoglobin SpO_2.

Association of sleep architecture and sleep duration with AF

The associations of SWS, rapid eye movement sleep, arousal index, sleep efficiency and sleep duration with prevalent AF are summarised in table 3. Greater SWS time was significantly associated with lower odds of AF in all models (OR: 0.66 (0.50 to 0.89) per 1 SD increase in model 4). In category-based analyses of SWS time, there was a significant linear trend of lower

Table 3 Adjusted ORs of atrial fibrillation prevalence by sleep measures (per 1 SD* increment)

		Model 1			Model 2			Model 3			Model 4		
	N	OR	95% CI	p Value	OR	95% CI	p Value	OR	95% CI	p Value	OR	95% CI	p Value
AHI (events/h)	2048	1.3	1.08 to 1.56	0.006	1.22	1.00 to 1.49	0.04	1.23	1.01 to 1.50	0.04	1.22	0.99 to 1.49	0.06
CAI (events/h)	2026	0.97	0.79 to 1.19	0.8	0.98	0.81 to 1.20	0.9	0.99	0.81 to 1.20	0.9	0.97	0.79 to 1.19	0.8
ODI (events/h)	2018	1.33	1.11 to 1.60	0.002	1.25	1.03 to 1.52	0.02	1.26	1.03 to 1.54	0.02	1.24	1.01 to 1.52	0.04
% time SpO_2 <90%	2048	1.16	1.00 to 1.34	0.05	1.11	0.95 to 1.29	0.2	1.1	0.94 to 1.29	0.2	1.06	0.90 to 1.25	0.5
SWS time (min)	2026	0.65	0.49 to 0.86	0.003	0.67	0.51 to 0.90	0.007	0.69	0.52 to 0.92	0.01	0.66	0.50 to 0.89	0.006
% SWS time	2026	0.74	0.58 to 0.96	0.02	0.77	0.60 to 0.99	0.04	0.79	0.61 to 1.02	0.07	0.77	0.59 to 1.00	0.05
REM time (min)	2026	0.99	0.79 to 1.24	0.9	1.01	0.81 to 1.27	0.9	1.02	0.81 to 1.29	0.9	1.01	0.80 to 1.28	0.9
% REM time	2026	1.12	0.90 to 1.39	0.3	1.13	0.91 to 1.41	0.3	1.14	0.91 to 1.41	0.3	1.13	0.91 to 1.41	0.3
Arousal index (events/h)	2026	0.87	0.69 to 1.09	0.2	0.84	0.67 to 1.05	0.1	0.83	0.67 to 1.05	0.1	0.84	0.66 to 1.05	0.1
Sleep efficiency-PSG (%)	2026	0.80	0.66 to 0.97	0.02	0.81	0.67 to 0.98	0.03	0.82	0.68 to 1.00	0.05	0.81	0.66 to 0.99	0.04
Sleep efficiency-Actigraphy (%)	1938	0.83	0.68 to 1.00	0.06	0.84	0.70 to 1.02	0.08	0.83	0.68 to 1.01	0.06	0.82	0.67 to 1.00	0.05
Sleep duration-Actigraphy (h)	1938	0.91	0.74 to 1.11	0.4	0.92	0.75 to 1.13	0.4	0.91	0.75 to 1.12	0.4	0.92	0.75 to 1.14	0.4

*SD for each variable is found in table 2. Model 1 adjusted for age, age squared, field centre, race/ethnicity, sex; model 2 adjusted for model 1 covariates plus BMI and height; model 3 adjusted for model 2 covariates plus smoking status, diabetes, systolic blood pressure, hypertension medication; model 4 adjusted for model 3 covariates plus prevalent coronary heart disease, prevalent stroke, prevalent heart failure.
AHI: apnoea hypopnoea index based on all obstructive and central apnoeas and hypopnoeas with ≥4% desaturation/sleep hour; BMI, body mass index; CAI, central apnoea index, all central apnoeas with 4% desaturation or arousal/sleep hour; ODI, oxygen desaturation index; SpO_2, oxygen saturation; SWS, slow wave sleep; REM, rapid eye movement; PSG, polysomnography.

likelihood of AF with higher quartile of SWS time (figure 1). Per cent SWS time showed a similar, albeit slightly weaker, association with AF. Higher sleep efficiency was significantly associated with lower likelihood of AF. Surprisingly, a higher arousal index was associated with lower likelihood of AF, though it did not reach statistical significance. To explore the potential mechanism of such an inverse association, we tested if negative correlation existed between arousal index and apnoea duration and % time with SpO_2<90%. No significant inverse correlation was present for either of the two. No association between average daily sleep duration estimated by actigraphy and AF was found.

Joint modelling of SDB metrics and measures of sleep quality

To further explore whether the primary measures of SDB, namely AHI and ODI, were independent of, or confounded by, sleep fragmentation, sleep architecture or sleep duration, we first modelled AHI with arousal index, and with sleep efficiency together. Given similar findings in models 1–4, only results based on the more comprehensive model 4 are presented. When AHI and arousal index were jointly modelled, we observed a stronger positive association between AHI and AF (model 4: OR: 1.49 (1.15 to 1.91) per 1 SD increase, p=0.002) and a significant negative association between arousal index and AF (model 4: OR: 0.68 (0.52 to 0.89) per 1 SD increase, p=0.005) in all models. When AHI and sleep efficiency-PSG were jointly modelled, the association between AHI and AF was non-significant in all models except in model 1 (model 4: OR: 1.18 (0.96 to 1.46) per 1 SD increase, p=0.12). The association between sleep efficiency-PSG and AF was also non-significant in all models (model 4: OR: 0.84 (0.68 to 1.03) per 1 SD increase, p=0.09). The results were similar for the association of sleep efficiency-actigraphy with AF (data not shown).

Alternatively, when SWS was added to the model, the significance of the association between AHI and AF was lost except in model 1 (see online supplementary table S6). In contrast, the results were largely unchanged when sleep duration was added to the model (data not shown). Similarly, we explored whether SWS, the sleep index most significantly associated with AF, was independent of AHI, arousal index or sleep duration. The significant association between SWS time and AF persisted after adding AHI to the model (model 4 OR (CI) 0.68 (0.51 to 0.92), p=0.01) or adding arousal index or sleep duration to the model (see online supplementary table S7). Similar findings were observed with ODI when the additional sleep terms were jointly considered (data not shown). No significant interactions were found between sleep indices and age, sex or race/ethnicity.

DISCUSSION

We identified three key findings in our analyses of prevalent AF in a large, ethnically diverse community-based cohort using rigorously scored and standardised PSG and actigraphy. First, severity of SDB as measured by AHI and ODI was modestly associated with prevalence of AF. Second, we identified a novel association between time in SWS and AF prevalence. Third, we found a negative association between arousal frequency and AF prevalence. Furthermore, the arousal index partly confounded the association between AHI and AF such that once arousal index was accounted for, a more significant association between AHI and AF was observed. These findings highlight the importance of SDB metrics on the likelihood of AF while also revealing a previously unrecognised role for measures of sleep quality in influencing AF.

Sleep disordered breathing and atrial fibrillation

Our results indicate that the odds of having AF increases in proportion to the severity of SDB as indicated by AHI and ODI (odds increase of approximately 20–30% with a 1 SD increase in AHI or ODI). The similar association of ODI and AHI with AF supports a role for chronic intermittent hypoxaemia as a mechanistic contributor to arrhythmogenesis. Repetitive obstructive breathing and the associated intermittent hypoxaemia can lead to sympathetic activation,[18] inflammation[19] and atrial remodeling,[20 21] providing plausible explanations for the observed relationship between SDB and AF.

Our finding is consistent with results from prior epidemiological studies. In the Sleep Heart Health Study, Mehra *et al*[11] reported a higher frequency of sleep study-detected nocturnal AF episodes among those with severe SDB compared with those without SDB. This observation was expanded in the subsequent Osteoporotic Fractures in Men Sleep study in which a dose response association was found between the severity of SDB (as measured by respiratory disturbance index)and the odds of sleep study-detected nocturnal AF.[12] In contrast to these works, our study sought to quantify the association of SDB with prevalent AF defined as a chronic arrhythmic condition (either paroxysmal or persistent) rather than a solely sleep study-detected nocturnal event. Accordingly our analysis involved AF ascertained from multiple sources of information including ICD-9 codes, study ECG and sleep study. The association of SDB with a clinical diagnosis of AF has been previously suggested by a clinic-based retrospective cohort study.[13] However, in that study only the average magnitude of nocturnal O_2 desaturation was associated with increased risk of incident AF in multivariate analysis.[13] In contrast we found that severity of intermittent hypoxaemia, as measured by AHI or ODI, was linearly associated with AF, but not persistent hypoxaemia, as indicated by % SpO_2 time spent below 90%. Finally, it is also important to note that unlike prior studies, we were able to meticulously control for key sleep metrics related to SDB. For example, in our study, the association between AHI (or ODI) and AF was not confounded by sleep duration, which has been associated with AF in a recent study,[22] but was confounded by arousal frequency as discussed below. A somewhat higher prevalence of SDB in our study (AHI ≥15 (events/hour) was 34%) compared with other cohorts with a similar age distribution might be partly related to the multiethnic composition of MESA. We observed a higher prevalence of moderate to severe SDB among Asians and Hispanics than among whites, and those two groups comprised about a third of the entire cohort. However, the overall distribution of AHI (as shown in table 2) appears to be comparable to other similar cohorts such as the Sleep Heart Health Study and the Osteoporotic Fractures in Men study.[23 24]

SWS, sleep efficiency and AF

Among all sleep variables, SWS time was most strongly associated with reduced AF prevalence. Importantly, this association persisted after adjusting for AHI, indicating that this measure of sleep quality may modulate AF risk independent of any association with SDB. Furthermore, the strong association of SWS time with AF highlights the importance of the absolute 'quantity' of time in SWS as a relevant measure of sleep health. SWS is the sleep state with the highest parasympathetic activity[25] and thus may be cardioprotective. SWS decreases with age, is lower in older men than women,[26] and its reduction is associated with incident hypertension.[27] Indeed, emerging evidence points to the importance of SWS in regulation of metabolic and

physiological homoeostasis beyond its role in 'restorative' function of the brain.[28 29] More formal quantitative analysis employing EEG power spectral analysis of slow wave activity would be valuable in confirming our findings.

Sleep efficiency is another commonly measured index for assessing overall sleep quality in the clinical setting and several reports have linked low sleep efficiency to hypertension.[30–32] In our study, the significant inverse association found between sleep efficiency and AF was no longer present after adjustment for AHI, suggesting that the association is in part explained by SDB.

Arousal index and AF

Surprisingly, we found that a higher arousal index, although associated with more severe SDB and reduced sleep efficiency, was associated with a lower prevalence of AF when adjusted for AHI. Furthermore, adjustment for arousal index strengthened the association between AHI and AF. Similarly, a sensitivity analysis based on an AHI definition that included hypopnoeas scored if associated with either a desaturation or an arousal showed weaker associations with AF than the AHI based on the desaturation criteria alone. The arousal index is a commonly derived index from PSG used to quantify sleep fragmentation, with each arousal considered to reflect sudden, brief change in sleep state, likely due to bursts of sympathetic activity. Although more frequent arousals are associated with risk of hypertension and can adversely affect the cardiovascular system,[33 34] arousals may also serve as a protective mechanism to terminate apnoeic episodes.[35] In fact, a low arousal index has been linked to increased risk for brainstem white matter disease and incident stroke.[8 36] Thus, two distinct pathophysiological scenarios are plausible—that is, while frequent arousals may indicate excessive sympathetic activation, low arousal responses may reflect abnormalities in autonomic control, respiratory reflexes, or result from chronic sleep fragmentation. Further research is needed to determine whether the inverse association between arousal index and AF is generalisable, and if so, if it reflects an inherent susceptibility to AF (such as that due to abnormal autonomic function) or is a respiratory-specific phenomenon. Interpretation of our finding is limited by lack of differentiation of arousal mechanisms (ie, spontaneous vs respiratory related vs periodic limb movement related) in this study. Nevertheless, our findings imply that arousals represent an important and distinct feature of sleep, and scoring hypopnoeas using an associated arousal provides different information than hypopnoeas identified only by an associated desaturation.

Sleep duration and AF

Lastly, sleep duration, objectively measured with actigraphy, was not found to be associated with AF or to confound any of our observed associations. Prior literature has indicated that self-reported sleep duration often is associated with a U-shaped relationship with CVD or CVD risk factors.[1] Specifically, self-reported long sleep duration was linked to increased risk of AF in the Physician's Health Study.[22] In our study neither linear nor U-shaped association was found when using an objective measure of sleep duration. The basis for differences between these studies is unclear; however, self-reported and objectively measured sleep duration are only weakly associated.[37] Subjective long sleep duration may reflect poor sleep quality,[14] or reflect unmeasured confounders such as depression, which is associated with cardiovascular risk.[38] Our analyses focused on objectively measured sleep parameters. Future work can further interrogate the influences of self-reported behaviours on risk of AF, as well as whether symptoms of insomnia, which may interact with short sleep duration to increase risk of CVD,[39] may modify the associations with objective measurements observed in the current study.

Our study has several strengths including objective measurements of sleep characteristics using PSG and actigraphy and its large community-based multiethnic population design. However, because our analysis was cross-sectional, the temporal relationship between sleep abnormalities and the development of AF cannot be established, particularly since both conditions may be present for considerable periods before they are clinically recognised. Thus, a causal association of sleep abnormalities with AF cannot be inferred. Moreover, asymptomatic and paroxysmal cases of AF may have been missed by our case ascertainment, suggesting that the true prevalence of AF in this population is likely higher than reported. Finally, some of our significant findings could have resulted from multiple testing and as such, replication using independent cohorts is needed in the future.

In conclusion, we found a modest relationship between severity of AHI or ODI and likelihood of AF while also identifying a novel association between SWS duration and AF, highlighting the potential importance of sleep stage distribution in modulating the risk of arrhythmogenesis. We also observed a previously unrecognised link between low arousal index and increased AF prevalence, implying the need for a more nuanced interpretation of cortical arousals to better understand the association between sleep characteristics and AF.

Author affiliations
[1]Department of Medicine, University of Minnesota, Minneapolis, Minnesota, USA
[2]Department of Medicine, University of Washington, Seattle, Washington, USA
[3]Department of Biostatistics, University of Washington, Seattle, Washington, USA
[4]Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, Minnesota, USA
[5]Department of Medicine, Johns Hopkins University, Baltimore, Maryland, USA
[6]Department of Preventive Medicine, Northwestern University, Chicago, Illinois, USA
[7]Department of Medicine, Hualien-Armed Forces General Hospital, Hualien, Taiwan
[8]Department of Medicine, Wake Forest University, Winston-Salem, North Carolina, USA
[9]Department of Medicine, Cleveland Clinic, Cleveland, Ohio, USA
[10]Departments of Medicine, Brigham and Women's Hospital and Beth Israel Deaconess Medical Center; Harvard Medical School, Boston, Massachusetts, USA
[11]Department of Epidemiology, University of Washington, Seattle, Washington, USA

Contributors Conception, design, analysis and interpretation of data and drafting of the manuscript: YK, SAG, MLB, SR, SRH. Conception, interpretation of data and revision of the manuscript for important intellectual content: DRJ, AA, DD, JL, G-ML, EZS, RM. Final approval of the manuscript: YK, SAG, MLB, SR, SRH, DRJ, AA, DD, JL, G-ML, EZS, RM.

Funding This research was supported by contracts N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168 and N01-HC-95169 from the NHBLI, by grants UL1-TR-000040, UL1-RR-025005 from NCRR, R01HL098433 (MESA Sleep, R21HL121348) and T32-HL069764.

Competing interests None declared.

Patient consent Obtained.

Ethics approval IRB.

Provenance and peer review Not commissioned; externally peer reviewed.

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Online Data Supplement for "Association of sleep characteristics and atrial fibrillation: the MESA study"

Younghoon Kwon, Sina A. Gharib, Mary L.Biggs, David R. Jacobs Jr., Alvaro Alonso, Daniel Duprez, Joao Lima, Gen-Min Lin, Elsayed Z. Soliman, Reena Mehra, Susan Redline, Susan R. Heckbert

Methods.

Study population

The Multi-Ethnic Study of Atherosclerosis (MESA) participants were recruited from 6 U.S. communities (Forsyth County, NC; Northern Manhattan and the Bronx, NY; Baltimore County, MD; St. Paul, MN; Chicago, IL; and Los Angeles County, CA) and self-identified as White, Chinese, African American or Hispanic.(1)

For this cross-sectional study, we analyzed data from a subset of participants who participated in the MESA Sleep ancillary study that occurred during exam 5 (April 2010- December 2011) (n=2,211). Among them, those with satisfactory quality of the polysomnography (PSG or 'sleep study' hereafter) data (n =2,057) and with available covariate data were included in the analysis (n =2048). For analyses using actigraphy data, participants with both PSG and actigraphy were used (n = 1996).

ECG

Standard 12-lead electrocardiograms (ECGs) were recorded in all participants using standardized procedures in both visit 1 and visit 5. However since atrial fibrillation (AF) or atrial flutter was one of the exclusion criteria for MESA visit 1, only ECG at exam 5 was used.

Identical electrocardiographs (GE MAC 1200 model; GE, Milwaukee, WI) were used in all MESA field centers to digitally record ECGs at a 10 mm/mV calibration and speed of 25 mm/s. The digital ECG data

stored in the electrocardiographs were transmitted regularly over analog telephone lines for central reading at the Epidemiological Cardiology Research Center (EPICARE), Wake Forest School of Medicine, Winston-Salem, NC. Initially, all ECGs were visually inspected for technical errors and inadequate quality, then automatically processed with the 2001 version of the GE Marquette 12-SL program (GE, Milwaukee, WI). ECG abnormalities, including atrial fibrillation (AF)/flutter, were classified using the Minnesota ECG Classification (Minnesota Code). Software detected ECG abnormalities, including AF/atrial flutter, were confirmed visually by the ECG reading center staff. Mean (SD) time between MESA exam 5 and sleep study was 341 (199) days.

Sleep data

An overnight in-home PSG was conducted using the Compumedics Somte System (Compumedics Ltd., Abbostville, Australia). Sleep sensor and recording montage included standard airflow measurement (nasal-oral thermocouple and nasal pressure channels), thoracic and abdominal respiratory inductance plethysmography, cortical electroencephalograms (EEG), bilateral electrooculograms and chin electromyogram, lead II ECG; leg movements, and finger pulse oximetry (Nonin Medical Inc., Plymouth, MN, USA). Nocturnal recordings downloaded at 6 field centers were transmitted to a centralized reading center (Brigham and Women's Hospital, Harvard Medical School, Boston, MA) where the sleep studies were manually scored by trained technicians.(2)

Definitions of Key Sleep Measurements

Apnea hypopnea index and hypoxemia:

The apnea hypopnea index (AHI) was defined as the number of apnea and hypopnea events per hour (hr) of sleep. Apnea was defined on the basis of a reduction in airflow by more than 90% of the pre-event baseline for longer than 10 seconds using a thermocouple signal, and further classified as obstructive or central apneas on the basis of the presence of respiratory effort. Hypopneas were scored when the amplitude of the nasal pressure flow signal decreased by more than 30% of the pre-event baseline for

longer than 10 seconds accompanied. In this analysis, the primary metric of SDB was the AHI, defined as the sum of all apneas plus hypopneas with a ≥ 4% O_2 desaturation and analyzed as a continuous measure as well as according to common clinical cutoffs (AHI< 5, 5≤AHI<15/hr, 15≤AHI<30, AHI≥ 30/ hr). CAI (central apnea index) was defined as all central apneas with a ≥4% O_2 desaturation or arousal/hr sleep. In sensitivity analyses, alternative desaturation and arousal criteria were applied to AHI definitions (Hypopnea determined by either≥4% O_2 desaturation or arousal). O_2 desaturation index (ODI) was defined as the average number of desaturation episodes of at least a 4% decrease in O2 saturation (SpO_2) from the pre-event baseline SpO_2 per hour of sleep. Nocturnal hypoxemia was also evaluated as time spent with SpO_2 less than 90% (% time SpO_2< 90%). Inter- and intra-scorer intraclass correlation coefficients for the AHI ranged from 0.95 to 0.99.

Sleep architecture:

Sleep stages (N1, N2, N3 or slow wave sleep (SWS), and rapid eye movement (REM) sleep) were expressed both as absolute times in each stage and proportion of the sleep period (%) in each stage. The arousal index was defined as the number of arousals per hour according to standard criteria per AASM guideline.(3) Sleep efficiency was calculated by the PSG-based total sleep time divided by total time between sleep onset and lights on. The inter- and intra-scorer intraclass correlation coefficients were 0.84 to 0.99 for arousal index, 0.78 to 0.99 for % REM sleep and 0.91 to 0.98 for % SWS.

Sleep duration:

Actigraphy was performed using the Actiwatch Spectrum wrist actigraph (Philips Respironics, Murrysville, PA) worn on the participant's wrist for 7 days. Output was transmitted to the Sleep Reading Center where records were scored with reference to a sleep diary. Actigraphic data during 30 second epochs were scored as sleep or wake by Actiware-Sleep® v. 5.59 analysis software (Mini Mitter Co., Inc.). This device uses a validated algorithm in which activity counts recorded during the measured epoch are modified by the level of activity in the surrounding 2-minute time period (i.e. ±2 minute) to yield the

final activity count for each epoch.(4) Actigraphy-derived average sleep time was used for the main analyses of sleep duration.

Ascertainment of AF

PSG-based arrhythmias were manually annotated from the lead II ECG channel, and were verified by a board certified sleep physician. In addition, AF ascertainment for the period from MESA study entry up to and including the sleep study was based on [1] ICD-9 (International Classification of Diseases, Ninth Revision) discharge diagnosis codes from hospitalizations ascertained during regular MESA events follow-up, [2] ICD-9 inpatient discharge diagnosis codes or outpatient ICD-9 codes from Medicare claims data, [3] 12-lead ECGs obtained at both the baseline MESA exam and about 10 years later with a reading of AF or atrial flutter, or [4] a nocturnal episode of physician-verified AF or atrial flutter detected in single lead ECG during the sleep study at exam 5. Codes for both AF (ICD-9 427.31) and atrial flutter (427.32) were included in "prevalent AF," as defined for this analysis.

Covariates

Information on demographic characteristics, health habits, and medication use was obtained by questionnaire at the exam 5 visit. Alcohol use was categorized as 0, ≤7, and >7 drinks per week. Physical activity was defined as moderate and vigorous physical activity assessed using the MESA Typical Week Physical Activity Survey (TWPAS) adapted from the Cross-Cultural Activity Participation Study and expressed as minutes of activity multiplied by metabolic equivalent (MET) level.(5, 6) Body habitus (body mass index [BMI] and height) and blood pressure were measured at the exam 5 visit. Blood samples collected after a 12 hour fast were assayed for fasting glucose level, low (LDL) and high density lipoprotein (HDL) cholesterol. Diabetes was defined as a fasting glucose ≥7.0 mmol/l (126 mg/dl), or use of insulin or oral hypoglycemic medications. Hypertension was defined as seated systolic blood pressure ≥ 140, diastolic blood pressure ≥ 90, or the combination of anti-hypertensive medication use and a

physician diagnosis of hypertension (Sixth report of the Joint National Committee (1997) criteria). CVD events occurring between baseline and exam 5 were determined by MESA events follow up as previously described.(1) For missing data on BMI, height, smoking habit, and diabetes, information from the closest prior visit (exam 4: September 2005 - May 2007) was used.

Statistical analysis

Following logistic models were used to assess the association between sleep measures and AF prevalence. Model 1: adjusted for age, age^2, sex, race/ethnicity and site; Model 2: model 1 variables + BMI and height; Model 3: model 2 variables + smoking status, diabetes, systolic blood pressure and anti-hypertensive medication 3); Model 4: model 3 variables + prevalent CVD events. An additional model adjusting for model 4 variables, alcohol consumption and physical activity yielded similar results as Model 4 and therefore were not reported in the results.

There was no evidence of non-linearity of any of the associations of sleep measures with AF when tested with generalized additive models. Odds ratios (OR) and 95% confidence intervals (CI) for the association of continuous measures with AF were expressed per SD increment of the sleep measure. We performed secondary analyses by fitting models that included multiple sleep measures that were significantly associated with AF in the primary models. Sensitivity analyses using the more restrictive definition of AF and using an alternative AHI definition were performed to check for consistency of the results. Possible effect modification of associations by age, sex and race were tested by including cross-product terms in the models. Multi-colinearity was evaluated by computing the variance inflation factor (Variance Inflation Factor > 10 was used to determine the presence of multi-colinearity). All statistical analyses were performed using Stata 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.)

Table 1. Characteristics based on the quartiles of slow wave sleep (SWS) time.

		SWS (minute)			
	Overall	<=7	>7-29	>29-57	>57
	n=2026	(n=513)	(n=502)	(n=509)	(n=502)
Age (years)	68.4 ± 9.2	69.9 ± 9.3	69.1 ± 9.2	67.9 ± 8.8	66.9 ± 8.9
Male (%)	46.4	67.4	53.6	41.3	22.3
Race / ethnicity (%)					
White	36.2	26.7	35.7	39.3	44.6
Chinese-American	12.2	9.7	10.8	14.1	13.9
African-American	27.7	36.1	28.5	26.5	19.1
Hispanic	23.9	27.5	25.1	20.0	22.3
Attained education (%)					
High school or less	31.3	32.9	31.1	26.9	33.7
At least some college or technical school	48.5	47.8	47.9	50.0	48.4
Graduate or professional school	20.2	19.3	21.0	23.1	17.9
Cigarette smoking status (%)					
Never	47.0	40.5	43.8	48.7	55.2
Former or current	53.0	59.5	56.2	51.3	44.8
Current alcohol use (%)					
No	67.3	65.3	67.0	67.9	69.0
Yes	32.7	34.7	33.0	32.1	31.0
Physical activity (MET-minute/week)	5433 ± 6425	5591 ± 5637	5634 ± 8025	5308 ± 5532	5237 ± 6342
Height (cm)	165.4 ± 10.1	168.5 ± 10.2	166.3 ± 10.3	164.7 ± 9.9	162.1 ± 8.6
Body mass index (kg/m^2)	28.7 ± 5.6	28.9 ± 5.3	28.9 ± 5.6	28.6 ± 5.7	28.1 ± 5.5
Seated systolic blood pressure (mmHg)	122.8 ± 20.2	122.8 ± 19.2	124.6 ± 21.7	121.9 ± 20.1	122.0 ± 9.8
Seated diastolic blood pressure (mmHg)	68.3 ± 9.9	69.2 ± 9.9	68.9 ± 9.7	68.1 ± 10.5	66.8 ± 9.1
Total cholesterol (mg/dl)	184.0 ± 36.9	177.1 ± 35.8	180.6 ± 36.2	187.0 ± 37.8	191.5 ± 6.0
HDL (mg/dl)	55.6 ± 16.3	53.3 ± 14.8	54.6 ± 16.5	56.2 ± 17.0	58.4 ± 16.9
Fasting glucose (mg/dl)	102.0 ± 28.4	103.6 ± 28.4	102.8 ± 27.6	102.3 ± 31.6	99.0 ± 25.3
Hypertension by JNC VI (1997) criteria (%)	56.7	62.2	59.8	53.6	50.2
Any hypertension medication (%)	53.4	59.6	55.2	50.7	46.8
Any lipid-lowering medication (%)	37.3	39.2	39.0	34.6	35.7
Diabetes (%)	19.9	24.4	21.3	18.3	14.7

All data are expressed as the mean ± SD or frequency as percentage.

Table 2. Correlation between sleep variables.

	AHI	ODI	SWS time	REM time	Arousal index	Sleep efficiency	Sleep duration
AHI (events/hr)	NA	0.98	-0.18	-0.24	0.58	-0.22	-0.13
ODI (events/hr)	0.98	NA	-0.17	-0.23	0.55	-0.20	-0.15
SWS time	-0.18	-0.17	NA	0.05*	-0.23	0.26	0.14
REM time	-0.24	-0.23	0.05*	NA	-0.38	0.27	0.09
Arousal index (events/hr)	0.58	0.55	-0.23	-0.38	NA	-0.36	-0.05*
Sleep efficiency-PSG (%)	-0.22	-0.20	0.26	0.27	-0.36	NA	0.19
Sleep duration-Actigraphy (hr)	-0.13	-0.15	0.14	0.09	-0.05*	0.19	NA

Values represent Pearson correlation coefficient (r). All correlations were statistically significant. P values are < 0.0001 unless marked * (P < 0.05). AHI: apnea hypopnea index; NA: not applicable; ODI: oxygen desaturation index; SWS: slow wave sleep; REM: rapid eye movement; hr: hour, PSG: polysomnography

Table 3. Sources of atrial fibrillation ascertainment

Sources	n
Diagnosis code* and either PSG or study ECG or both	21
Diagnosis code only	64
PSG only	9
Study ECG only	3
PSG and study ECG	3

* Diagnosis code from either MESA events follow-up or Medicare claims AF: atrial fibrillation. PSG: polysomnography. ECG: electrocardiography.

Table 4. Characteristics of study participants based on the presence of atrial fibrillation

	Overall	No AF	AF
	n=2048	n=1948	n=100
Age (years)	68.4 ± 9.2	68.0 ± 9.1	76.4 ± 7.3
Male (%)	46.4	46.0	54.0
Race / ethnicity (%)			
White	36.2	35.7	46.0
Chinese-American	12.2	12.1	14.0
African-American	27.7	28.2	19.0
Hispanic	23.9	24.0	21.0
Attained education (%)			
High school or less	31.3	31.2	33.0
At least some college or technical school	48.5	48.9	41.0
Graduate or professional school	20.2	19.9	26.0
Cigarette smoking status (%)			
Never	47.0	47.2	42.0
Former or current	53.0	52.8	58.0
Current alcohol use (%)			
No	67.5	67.4	70.4
Yes	32.5	32.6	29.6
Physical activity (MET-minutes/week)	5433 ± 6425	5498 ± 6471	4145 ±5297
Height (cm)	165.4 ± 10.1	165.4 ± 10.0	165.51 ± 11.0
Body mass index (kg/m^2)	28.7 ± 5.6	28.7 ± 5.6	29.0 ± 5.3
Seated systolic blood pressure (mmHg)	122.8 ± 20.2	122.8 ± 20.3	123.7 ± 19.1
Seated diastolic blood pressure (mmHg)	68.3 ± 9.9	68.4 ± 9.8	65.9 ± 10.8
Total cholesterol(mg/dl)	184.0 ± 36.85	184.8 ± 36.5	167.5 ± 40.7
HDL (mg/dl)	55.6 ± 16.3	55.6 ± 16.3	55.2 ± 15.7
Fasting glucose (mg/dl)	102.0 ± 28.4	101.9 ± 28.1	103.7 ± 32.6
Hypertension by JNC VI (1997) criteria (%)	56.7	56.0	71.0
Any hypertension medication (%)	53.4	52.2	77.0
Any lipid-lowering medication (%)	37.3	36.7	49.0
Diabetes (%)	19.9	19.8	22.0

All data are expressed as the mean ± SD or frequency as percentage.

Table 5. Adjusted odds ratios of atrial fibrillation prevalence by alternative AHI definition (per 1 SD increment).

		Model 1			Model 2			Model 3			Model 4		
	N	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
AHI alternative (events/hr)	2026	1.23	1.0,1.50	0.048	1.15	0.92,1.42	0.20	1.16	0.93,1.43	0.20	1.15	0.92,1.43	0.22

AHI: apnea hypopnea index. In the alternative AHI definition, hypopnea was determined by either ≥4% Oxygen desaturation or arousal. 1 SD = 17.7 events/hr. hr: hour.

Table 6. Adjusted odds ratios of atrial fibrillation by AHI (per 1 SD increment) when SWS time was included in the model.

		Model 1			Model 2			Model 3			Model 4		
	N	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
AHI (events/hr)	2026	1.22	1.00, 1.48	0.05	1.16	0.95, 1.42	0.15	1.18	0.96, 1.44	0.12	1.16	0.94, 1.43	0.16

AHI: apnea hypopnea index. SWS: slow wave sleep. 1 SD = 16.7 events/hr. hr: hour.

Table 7. Adjusted odds ratios of atrial fibrillation by SWS time (per 1 SD increment) when AHI, arousal index or sleep duration is separately included in the model.

		Model 1			Model 2			Model 3			Model 4		
	N	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
AHI (events/hr)	2026	0.67	0.51,0.90	0.007	0.69	0.52,0.92	0.01	0.71	0.53,0.94	0.02	0.68	0.51,0.92	0.01
Arousal index (events/hr)	2026	0.63	0.47,0.83	0.001	0.65	0.48,0.85	0.003	0.66	0.49,0.87	0.005	0.64	0.47,0.85	0.003
Sleep duration-Actigraphy (hr)	1916	0.66	0.48,0.87	0.005	0.68	0.50,0.90	0.01	0.69	0.51,0.92	0.01	0.67	0.49,0.89	0.008

SWS: slow wave sleep. 1 SD = 34.2 minutes. AHI: apnea hypopnea index.

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