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

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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.

Reference

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