SUPPLEMENTAL MATERIAL

Associations between sleep apnea and subclinical carotid atherosclerosis: The Multi-Ethnic Study of Atherosclerosis

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Methods

Study Population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective study designed to investigate risk factors for incident CVD and progression of subclinical CVD in an ethnically diverse population. Details of the study design have been published previously.[1] Between July 2000 and August 2002, 6,814 men and women aged 45 to 85 and free of clinically apparent CVD were recruited from six U.S. Centers: Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; New York, New York; and St. Paul, Minnesota. At MESA Exam 5 (2010 to 2013), all active MESA participants not reporting regular use of oral appliances, nocturnal oxygen, or nightly positive airway pressure therapy were invited to participate in the MESA Sleep Study, which consisted of sleep questionnaire data, polysomnography and actigraphy. Of the 4,077 participants approached, 147 (6.5%) were ineligible (95 due to a history of positive airway pressure device use; 4 due to the use of an oral appliance; and 4 due to oxygen use) and 141 participants lived too far away to participate. Of the remaining 3,789 participants, 2,261 participated in the sleep exam (59.7%). Comparison of characteristics between sleep study participants and those who did not participate in the sleep examination showed that nonparticipants were slightly more likely to be White, older, current/ex-smokers, and to have hypertension and chronic obstructive pulmonary disease. However, there was no statistically significant difference in the prevalence of self-reported doctor-diagnosed sleep apnea. In total, 2,060 participants had successful polysomnography data. The present cohort consists of 1,615 participants with successful polysomnography and carotid ultrasound data at Exam 5.

Polysomnography

Details of MESA polysomnography methodology have been published.[2] Briefly, in-home 15-channel polysomnography was conducted using the Somte device (Compumedics Ltd., Abbotsville, AU). The recording montage included electroencephalography, electrooculograms, chin electromyogram, bipolar electrocardiogram, thoracic and abdominal respiratory inductance plethysmography, airflow (by nasal-oral thermocouple and nasal pressure cannula), finger pulse oximetry, and limb movements. Sleep stages and arousals were scored by the Brigham and Women's Hospital Sleep Reading Center according to published guidelines[3] adapted from the Sleep Heart Health Study.[4,5] The arousal index was the number of cortical arousals per sleep hour and sleep was staged according to published guidelines and expressed as percentage time in each stage.[6] The intraclass correlation coefficients for AHI exceeded 0.95 and for arousal index exceeded 0.90.

Carotid Ultrasonography

B-mode ultrasound images of the right and left common, bifurcation, and internal carotid artery (ICA) segments were recorded with a Logiq 700 ultrasound system using the M12L transducer (General Electric Medical Systems, 13 MHz transducer).[7] The intraclass correlation coefficients for inter- and intrareader reproducibility for CIMT was > 0.95; for carotid plaque presence Kappa scores were 0.83 and 0.89, respectively.[7]

Other Measures

Diabetes was defined as a fasting serum glucose level ≥ 126 mg/ml or diabetes medication use (oral antihyperglycemics or insulin) or hemoglobin A1C ≥6.5%. Hypertension was defined as an average seated systolic blood pressure ≥140 mmHg (average of 3 sets) or average seated diastolic blood pressure ≥90 mmHg or use of antihypertensive medication.

Self-reported snoring was obtained by sleep questionnaires. Participants were asked: (a) "Have you ever snored?" and, if yes, (b) "How often do you snore?" Habitual snoring was considered if participants reported snoring sometimes (3-5 nights/week) or always/almost always (6-7 nights/week).

Measured weight and height were used to calculate body mass index (BMI; weight in kilograms divided by height in meters squared), and categorized as <25 (referent), 25-29.9, and ≥30 kg/m^2 to represent normal, overweight, and obese individuals, respectively.[8]

References

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Table I: Baseline Characteristics by the Presence or Absence of Carotid Plaque

	Total Sample N=1615	**Carotid Plaque N=1073**	**No Carotid Plaque N=542**	**P value**
Age (years)				
Mean ± SD	68.7 ± 9.1	70.3 ± 9.1	65.4 ± 8.1	<0.0001
Median [IQR]	68.0 [61, 76]	70.0 [63, 77]	64.0 [59, 71]	
Male, n (%)	741 (45.9)	506 (47.2)	235 (43.4)	0.1479
Race, n (%)				
White	573 (35.5)	414 (38.6)	159 (29.3)	0.0028
Chinese	207 (12.8)	128 (11.9)	79 (14.6)	
Black	447 (27.7)	280 (26.1)	167 (30.8)	
Hispanic	388 (24.0)	251 (23.4)	137 (25.3)	
BMI, kg/m^2	28.6 (5.5)	28.6 ± 5.4	28.7 ± 5.6	0.9830
Smoking status, n (%)				
Never	759 (47.2)	473 (44.3)	286 (52.9)	0.0045
Former	740 (46.0)	516 (48.3)	224 (41.4)	
Current	110 (6.8)	79 (7.4)	31 (5.7)	
Pack years smoked	0 (0, 12.4)	0 (0, 14)	0 (0, 8.1)	0.0001
Current alcohol use, n (%)	690 (42.9)	457 (42.8)	233 (43.1)	0.9152
Lipid lowering medication use, n (%)	612 (37.9)	464 (43.2)	148 (27.3)	<0.0001
HMG-CoA Reductase (statin) use, n (%)	581 (36.0)	443 (41.3)	138 (25.5)	<0.0001
Antihypertensive use, n (%)	873 (54.1)	639 (59.6)	234 (43.2)	<0.0001
Presence of hypertension, n (%)	973 (60.3)	709 (66.1)	264 (48.7)	<0.0001
Presence of diabetes, n (%)	352 (22.1)	263 (24.9)	89 (16.6)	0.0002
Serum total cholesterol, mg/dL	183.9 ± 36.2	183.1 ± 36.1	185.6 ± 36.4	0.1735
Serum low-density lipoprotein, mg/dL	106.4 ± 32.0	105.4 ± 32.1	108.4 ± 31.8	0.0819
Serum high-density lipoprotein, mg/dL	55.8 ± 16.4	55.5 ± 16.6	56.4 ± 16.1	0.1633
Serum triglyceride, mg/dL	110.0 ± 61.8	112.4 ± 64.1	105.2 ± 56.7	0.0206
Self-reported snoring, n (%)				
None habitual snorer (1-2 nights/week)	449 (28.0)	288 (27.1)	161 (29.7)	0.2587
Habitual snorer (3-7 nights/week)	644 (40.1)	422 (39.7)	222 (41.0)	
Unknown	512 (31.9)	353 (33.2)	159 (29.3)	
Carotid ultrasound measures				
Mean common carotid intima-				

media thickness, mm Mean ± SD Median [IQR]	0.86 (0.20) 0.82 [0.73, 0.96]	0.89 ± 0.2 0.86 [0.75, 0.99]	0.80 ± 0.2 0.77 [0.69, 0.88]	<0.0001
Polysomnography sleep measures				
Total sleep duration, min	360.8 ± 81.8	358.7 ± 84.3	365.1 ± 76.4	0.1337
Sleep maintenance efficiency, %	79.7 ± 12.6	78.9 ± 12.9	81.3 ± 11.9	<0.0001
Apnea-hypopnea index, events/h Mean ± SD Median [IQR]	14.5 ± 16.4 9.0 [3.3, 19.2]	15.0 ± 16.4 9.4 [3.5, 19.6]	13.6 ± 16.1 7.8 [2.6, 18.0]	0.0178
Apnea-hypopnea index ≥15, n (%)	531 (32.9)	373 (34.8)	158 (29.2)	0.023
Arousal index, events/h	22.0 ± 11.9	22.6 ± 12.0	20.8 ± 11.7	0.0008
Sleep time in stage 1 sleep, %	14.2 ± 8.9	14.9 ± 9.1	12.9 ± 8.2	<0.0001
Sleep time in stage 2 sleep, %	57.6 ± 10.1	57.4 ± 10.1	57.8 ± 10.0	0.5799
Sleep time in stage 3 and 4 sleep, %	10.2 ± 9.0	10.1 ± 8.9	10.4 ± 9.0	0.4014
Sleep time in REM sleep, %	18.1 ± 6.7	17.6 ± 6.7	19.0 ± 6.7	0.0003
Sleep time with SpO_2 <90%, %	0.64 [0.1, 3.1]	0.73 [0.1, 3.3]	0.5 [0.0, 2.7]	0.0068
Average SpO_2 in sleep, %	94.3 ± 1.7	94.3 ± 1.8	94.5 ± 1.6	0.0079

Data are presented as number (%), mean ± SD, or median [IQR].
P values for continuous data are from Wilcoxon rank sum test. P values for categorical data are from a chi-square test.
AHI indicates apnea hypopnea index; BMI, body mass index; IQR, interquartile range; REM, rapid eye movement sleep; SD, standard deviation; and SpO_2, oxygen saturation.

Table II: Sex-Specific Association between Sleep Apnea, Arousal Index, and the Presence of Carotid Plaque

	Model 1		Model 2		Model 3	
	OR [95% CI]	*P*-int	OR [95% CI]	*P*-int	OR [95% CI]	*P*-int
SA (AHI ≥15 events/h)						
Male	1.37 [0.99,1.91]	0.467	1.34 [0.96,1.88]	0.377	1.29 [0.92,1.83]	0.356
Female	1.15 [0.81,1.62]		1.08 [0.75,1.55]		1.03 [0.71,1.48]	
Arousal index (events/h)						
Male	1.01 [1.00,1.02]	0.999	1.01 [0.99,1.02]	0.946	1.01 [1.00,1.02]	0.638
Female	1.01 0.99,1.02]		1.01 [0.99,1.02]		1.01 [0.99,1.02]	

†Model 1: adjusted for demographics (continuous age, sex, and race/ethnicity) and interaction term between sex and sleep parameter.
Model 2: additionally adjusted for pack-years smoked and body mass index
Model 3: additionally adjusted for alcohol use, presence of hypertension and diabetes mellitus, serum total cholesterol, serum triglyceride level, HMG-CoA reductase (statin) use.
AHI indicates apnea hypopnea index; OR, odds ratio; SA, sleep apnea; and SpO_2, oxygen saturation.

Table III: Race/Ethnicity-Specific Association between Sleep Apnea, Arousal Index, and the Presence of Carotid Plaque

	Model 1		Model 2		Model 3	
	OR [95% CI]	*P*-int	OR [95% CI]	*P*-int	OR [95% CI]	*P*-int
SA (AHI ≥15 events/h)						
White	1.65 [1.06,2.56]	0.195	1.55 [0.99,2.45]	0.238	1.50 0.94, 2.38]	0.278
Chinese	1.09 [0.60,2.00]		1.07 [0.58,1.97]		1.09 [0.59, 2.01]	
Black	1.47 [0.94,2.31]		1.43 [0.91,2.26]		1.32 [0.82, 2.11]	
Hispanic	0.87 [0.56,1.37]		0.85 [0.54,1.35]		0.82 [0.51, 1.30]	
Arousal index (events/h)						
White	1.01 [0.99,1.03]	0.681	1.01 [0.99,1.03]	0.771	1.01 [0.99,1.03]	0.588
Chinese	1.00 [0.97,1.03]		1.00 [0.97,1.02]		0.99 [0.97,1.02]	
Black	1.02 [1.00,1.03]		1.01 [1.00,1.03]		1.02 [1.00,1.04]	
Hispanic	1.00 [0.99,1.02]		1.00 [0.99,1.02]		1.01 [0.99,1.02]	

†Model 1: adjusted for demographics (continuous age, sex, race/ethnicity) and interaction term between race/ethnicity and sleep parameter.
Model 2: additionally adjusted for pack-years smoked and body mass index
Model 3: additionally adjusted for alcohol use, presence of hypertension and diabetes mellitus, serum total cholesterol, serum triglyceride level, HMG-CoA reductase (statin) use.
AHI indicates apnea hypopnea index; OR, odds ratio; SA, sleep apnea; and SpO_2, oxygen saturation.

Table IV: Sex-Specific Association between Sleep Apnea, Arousal Index, and Carotid Intima-Media Thickness

	Model 1		Model 2		Model 3	
	β ± SE	*P*-int	β ± SE	*P*-int	β ± SE	*P*-int
SA (AHI ≥15 events/h)						
Male	0.0035 ± 0.0132	0.411	-0.0076 ± 0.0133	0.551	-0.0115 ± 0.0133	0.437
Female	0.0194 ± 0.0142		0.0039 ± 0.0146		0.0036 ± 0.0146	
Arousal index (events/h)						
Male	-0.0001 ± 0.0005	0.200	-0.0003 ± 0.0005	0.225	-0.0003 ± 0.0005	0.341
Female	0.0009 ± 0.0006		0.0006 ± 0.0006		0.0005 ± 0.0006	

†Model 1: adjusted for demographics (continuous age, sex, race/ethnicity) and interaction term between sex and sleep parameter.
Model 2: additionally adjusted for pack-years smoked and body mass index
Model 3: additionally adjusted for alcohol use, presence of hypertension and diabetes mellitus, serum total cholesterol, serum triglyceride level, HMG-CoA reductase (statin) use.
AHI indicates apnea hypopnea index; SA, sleep apnea; and SpO_2, oxygen saturation.

Table V: Race/Ethnicity-Specific Association between Sleep Apnea, Arousal Index, and Carotid Intima-Media Thickness

	Model 1		Model 2		Model 3	
	β ± SE	*P*-int	β ± SE	*P*-int	β ± SE	*P*-int
SA (AHI ≥15 events/h)						
White	0.0035 ± 0.0164	0.558	-0.0102 ± 0.0166	0.560	-0.0166 ± 0.0167	0.447
Chinese	-0.0042 ± 0.0254		-0.0139 ± 0.0252		-0.0133 ± 0.0252	
Black	0.0330 ± 0.0185		0.0199 ± 0.0186		0.0207 ± 0.0187	
Hispanic	0.0056 ± 0.0186		-0.0092 ± 0.0188		-0.0106 ± 0.0187	
Arousal index (events/h)						
White	-0.0002 ± 0.0006	0.109	-0.0005 ± 0.0006	0.140	-0.0007 ± 0.0006	0.113
Chinese	0.0014 ± 0.0011		0.0011 ± 0.0011		0.0009 ± 0.0011	
Black	0.0016 ± 0.0008		0.0013 ± 0.0008		0.0014 ± 0.0008	
Hispanic	-0.0005 ± 0.0007		-0.0006 ± 0.0007		-0.0006 ± 0.0007	
Sleep maintenance efficiency (%)						
White	-0.0008 ± 0.0007	0.131	-0.0005 ± 0.0006	0.045	-0.0003 ± 0.0007	0.040
Chinese	-0.0003 ± 0.0010		-0.00009 ± 0.0009		0.00006 ± 0.0010	
Black	-0.0011 ± 0.0007		-0.0010 ± 0.0007		-0.0011 ± 0.0006	
Hispanic	0.0010 ± 0.0007		0.0016 ± 0.0007		0.0016 ± 0.0007	
≥0.64% Sleep time with SpO2 <90%, %						
White	0.0106 ± 0.0148	0.027	-0.0058 ± 0.0152	0.036	-0.0086 ± 0.0153	0.033
Chinese	0.0122 ± 0.0247		0.0019 ± 0.0245		0.0002 ± 0.0246	
Black	0.0627 ± 0.0168		0.0497 ± 0.0170		0.0485 ± 0.0170	
Hispanic	-0.0073 ± 0.0181		-0.0137 ± 0.0184		-0.0145 ± 0.0183	

†Model 1: adjusted for demographics (continuous age, sex, and race/ethnicity) and interaction term between race/ethnicity and sleep parameter.
Model 2: additionally adjusted for pack-years smoked and body mass index
Model 3: additionally adjusted for alcohol use, presence of hypertension and diabetes mellitus, serum total cholesterol, serum triglyceride level, HMG-CoA reductase (statin) use.
AHI indicates apnea hypopnea index; SA, sleep apnea; and SpO_2, oxygen saturation.

Table VI: P-interactions between Demographics and Sleep Measures in Predicting Carotid Plaque Presence

	Model 1			Model 2			Model 3		
	Age	Sex	Race/Ethnicity	Age	Sex	Race/Ethnicity	Age	Sex	Race/Ethnicity
SA (AHI ≥15 events/h)	0.064	0.467	0.195	0.105	0.377	0.238	0.078	0.356	0.278
Arousal index (events/h)	0.252	0.999	0.681	0.404	0.946	0.771	0.264	0.638	0.588
≥0.64% Sleep time with SpO2 <90%, %	0.086	0.427	0.770	0.119	0.265	0.875	0.127	0.195	0.880

†Model 1: adjusted for demographics (age, sex, and race/ethnicity) and interaction term between demographic variable and sleep parameter. Age was modelled continuously when sex and race/ethnicity were tested for effect modification.
Model 2: additionally adjusted for pack-years smoked and body mass index
Model 3: additionally adjusted for alcohol use, presence of hypertension and diabetes mellitus, serum total cholesterol, serum triglyceride level, HMG-CoA reductase (statin) use.
AHI indicates apnea hypopnea index; SA, sleep apnea; and SpO_2, oxygen saturation.

Table VII: P-interactions between Demographics and Sleep Measures in Predicting Carotid Intima-Media Thickness

	Model 1			Model 2			Model 3		
	Age	Sex	Race-ethnicity	Age	Sex	Race-ethnicity	Age	Sex	Race-ethnicity
SA (AHI ≥15 events/h)	0.041	0.411	0.558	0.058	0.551	0.560	0.072	0.437	0.447
Arousal index (events/hr)	0.389	0.200	0.109	0.641	0.225	0.140	0.499	0.341	0.113
Sleep maintenance efficiency (%)	0.810	0.672	0.131	0.774	0.565	0.045	0.653	0.639	0.040
≥0.64% Sleep time with SpO2 <90%, %	0.045	0.977	0.027	0.089	0.666	0.036	0.106	0.744	0.033

†Model 1: adjusted for demographics (age, sex, and race/ethnicity) and interaction term between demographic variable and sleep parameter. Age was modelled continuously when sex and race/ethnicity were tested for effect modification.
Model 2: additionally adjusted for pack-years smoked and body mass index
Model 3: additionally adjusted for alcohol use, presence of hypertension and diabetes mellitus, serum total cholesterol, serum triglyceride level, HMG-CoA reductase (statin) use.
AHI indicates apnea hypopnea index; SA, sleep apnea; and SpO_2, oxygen saturation.