Obstructive Sleep Apnea and Structural/Functional Properties of the Thoracic Ascending Aorta: The Multi-Ethnic Study of Atherosclerosis (MESA)

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Keywords

Aorta · Arterial stiffness · Sleep apnea

Abstract

Background: Structural and functional properties of the proximal thoracic aorta have important implications in clinical and subclinical cardiovascular disease (CVD). We examined whether obstructive sleep apnea (OSA) is associated with proximal aortic size and aortic stiffness in a multi-ethnic community-based cohort. **Methods:** The sample included the Multi-Ethnic Study of Atherosclerosis (MESA) Sleep Ancillary study participants without known CVD who underwent cardiac magnetic resonance imaging. The main exposure variable was OSA severity based on the polysomnography-derived apnea hypopnea index (AHI; normal, AHI <5/h; mild, 5 ≤ AHI <15/h; moderate to severe, AHI ≥15/h). The study outcomes were ascending aortic diameter (AoD, cm),

aortic pulse wave velocity (AoPWV, m/s), and ascending aortic distensibility (AAD, %/mm Hg). Analyses were performed in the overall sample and in sex-specific strata, adjusted for multiple potential confounders. **Results:** The 708 participants were 55.9% female and on average 68 years old (54–93 years). There was a significant trend ($p < 0.0001$) of greater mean (SD) AoD across the three OSA groups: normal ($n = 87$), 3.13 cm (0.35); mild ($n = 215$), 3.25 (0.34); moderate to severe ($n = 406$), 3.37 (0.36). In adjusted analysis, participants with moderate to severe OSA had a greater mean AoD compared with the normal group: adjusted mean difference (95% CI), 0.12 cm (0.05, 0.20), $p = 0.002$. This AoD gradient was observed in women but not in men (p for interaction = 0.02). No differences were found in AoPWV or AAD among the OSA groups. **Conclusion:** In a diverse community-based cohort, moderate to severe OSA (vs. no OSA) was associated with a larger ascending AoD in women.

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Background

Thoracic aortic disease such as thoracic aneurysm and dissection are often undetected but represent serious vascular diseases with potentially life-threatening consequences. Recognized risk factors are those associated with atherosclerosis, hypertension, as well as other congenital conditions such as bicuspid aortic valve and Marfan syndrome [1]. Obstructive sleep apnea (OSA) is associated with both atherosclerosis and uncontrolled hypertension [2, 3] and was recently reported to be associated with thoracic aortic dissection [4]. OSA has also been linked to a greater thoracic aortic size [5]. However, the association of OSA with structural properties of the thoracic aorta has not been assessed in a general population.

Moreover, there is a paucity of data examining the association of OSA with the functional property of the thoracic aorta. Aortic stiffness is increasingly recognized as an important contributor to the development of cardiovascular disease (CVD) and an independent predictor of cardiovascular morbidity and mortality [6]. Long-term exposure to untreated OSA may adversely impact on the thoracic aorta through mechanical stresses associated with wide intrathoracic pressure changes that occur with obstructed breathing, sympathetic activation, and intermittent hypoxemia [7]. Although a number of studies have suggested increased aortic stiffness in patients with OSA, the majority of these studies involved a small number of clinic-based patients and thus may be prone to selection bias [8]. In addition, these studies mainly used applanation tonometry-based pulse wave velocity (PWV) as a measure of central aortic stiffness. This method does not fully account for the contributions of the proximal thoracic aorta, which is the most significant contributor to global arterial stiffness and vascular buffering [9].

To address this gap, we analyzed data from the Multi-Ethnic Study of Atherosclerosis (MESA) to test the hypothesis that OSA is adversely associated with structural and functional properties of the proximal thoracic aorta in a community sample. Given evidence that endothelial dysfunction is more strongly associated with OSA in women than men, we also explored potential sex differences in the associations [10].

Methods

Study Population

The MESA is a multi-site cohort study of community-dwelling men and women aged 45–84 years without known CVD (history of coronary heart disease, heart failure, or stroke) at enrollment in

2000–2002 (MESA visit 1) [11]. We included MESA visit 5 (April 2010 through February 2012) participants who underwent cardiac magnetic resonance imaging (MRI) and polysomnography as part of the MESA Sleep ancillary study (October 2010 through February 2013). Participants with a history of adjudicated CVD up to visit 5 and who were being treated for OSA with continuous positive airway pressure were excluded.

Sleep Study

Detailed methods of the MESA Sleep ancillary study have been previously described [12]. An overnight in-home polysomnography study (Compumedics Ltd., Abbotsville, Australia) was conducted. All recordings were centrally scored blinded to other data by trained research polysomnologists as described before [13]. Apneas were scored when the thermocouple signal flattened or nearly flattened for greater than 10 s. Hypopneas were scored when the amplitude of the nasal pressure flow signal decreased by 30% or more for greater than or equal to 10 s. The apnea-hypopnea index (AHI) was calculated based on the average number of all apneas plus hypopneas associated with a 3% desaturation or arousal per hour of sleep, consistent with the current recommendation of the American Academy of Sleep Medicine [14]. OSA severity was classified by the following cutoffs: AHI <5/h (reference or “normal”), $5 \leq \text{AHI} < 15/\text{h}$ (mild), $\text{AHI} \geq 15/\text{h}$ (moderate to severe OSA). Inter- and intrascorer reliability for the AHI measurements were high, with intraclass correlation coefficients ranging from 0.95 to 0.99.

Aortic Measurements from Cardiac MRI

Cardiac MRI was performed using 1.5-T whole-body MRI scanners as described elsewhere [15]. Phase-contrast cine gradient echo sequence with electrocardiography gating was used to evaluate the proximal aortic size and stiffness. We used the ascending luminal aortic diameter (AoD) as an index of the structural properties of the ascending aorta. Aortic maximum and minimum cross-sectional areas of the ascending and descending aortas were first measured with automated software (ARTFUN, INSERM LIM) [16]. The measurements were thereafter verified by 4 readers. The maximum and minimum AoDs were then determined from the maximum and minimum cross-sectional areas of the ascending aorta at the pulmonary artery bifurcation level. Intra- and interobserver reproducibility was excellent for aortic areas as described by Noda et al. [17]. The mean of the maximum and minimum AoDs were used for the analysis. The functional property of the ascending aorta was assessed using measures of aortic PWV (AoPWV) and ascending aortic distensibility (AAD). AoPWV has been the most commonly used measure of arterial stiffness and is a well-established predictor of cardiovascular risk [18]. MRI-based PWV has the advantage of providing a more accurate distance than tonometer-based PWV. AAD represents a direct measure of the mechanical property of aortic stiffness. It is a less studied arterial stiffness index than PWV but has been shown to predict CVD and all-cause mortality in MESA [19]. AoPWV (m/s) was determined by dividing the distance (m) between the ascending and descending aorta (m/s) by the transit time. By using ARTFUN software (INSERM U678), the flow wave transit time between the ascending and descending aorta was calculated as the average time difference among all data points on the systolic upslope of the ascending and descending aortic flow curves after peak flow normalization [16]. The distance between the ascending and descending aorta

Fig. 1. Cohort construction: the MESA (visit 5: 2010–2013).

was precisely measured at locations where velocities were measured using the oblique sagittal image (perpendicular to the aortic lumen) at the level of the right pulmonary artery during breath holds. AAD (%/mm Hg) was calculated using the following formula: [(maximum ascending aortic area – minimum ascending aortic area)/minimum ascending aortic area]/(systolic blood pressure [BP] – diastolic BP).

Covariate Assessment

Covariates were based on information obtained from the MESA visit 5 examinations and included demographic data, smoking habits, and anthropometric measures. Body weight and height were directly measured. Body surface area (BSA) was calculated as $0.20247 \times \text{height (m)}^{0.725} \times \text{weight (kg)}^{0.425}$. BP was measured immediately preceding cardiac MRI. Fasting blood samples were assayed for glucose level, low-density lipoprotein, and high-density lipoprotein cholesterol. Diabetes (American Diabetes Association Fasting Criteria 2003) and hypertension (Joint National Committee VI 1997) were determined by the fasting glucose level and BP measured at MESA clinic visit 5.

Statistical Analysis

The baseline characteristics of participants were summarized by OSA severity classification. The main outcomes included AoD, AoPWV, and AAD. Continuous values were expressed by the mean (SD) unless specified otherwise. Point estimates and error bars represent the means and 95% CIs, respectively. Multiple linear regression was used to compare the three outcomes across the three AHI-based severity groups, adjusting for age, sex, race, BSA, systolic BP, antihypertensive medication status, diabetes, smoking, and cholesterol levels. We ran an additional model in which height was substituted for BSA [20]. Effect modification by age, sex, and

race/ethnicity were tested by including each cross-product terms in the models. Linearity was checked by visual inspection of the distribution and homoscedasticity of residuals. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). All reported tests were two-tailed and a threshold of 0.05 was used to define statistical significance.

Results

A total of 708 participants were eligible for the analysis (Fig. 1); they were 55.9% female and on average were 68 years old (54–93 years). When comparing the analytic sample to MESA visit 5 participants excluded from this analysis, there were no significant differences in regards to demographics, body habitus, or cardiovascular risk factors (data not shown). Of the 708 participants, 57.3% had moderate to severe OSA (AHI ≥ 15 /h), 30.4% had mild OSA ($5 \leq \text{AHI} < 15$ /h), and 12.3% were normal (AHI < 5 /h). Table 1 shows participant characteristics overall, and according to OSA status and sex. Participants with moderate to severe OSA tended to be male and have more adverse cardiovascular risk profiles compared to those without OSA. When stratified by sex, men had a higher prevalence of current smoking, hypertension, and of being on antihypertensive medications. Table 2 provides participant characteristics cross-classified by sex and OSA severity. In unadjusted analyses, there was a significant trend ($p < 0.001$) of greater mean (SD) AoD across the three OSA groups: normal (AHI < 5 /h; $n = 87$), 3.13 cm (0.35); mild ($5 \leq \text{AHI} < 15$ /h; $n = 215$), 3.25 cm (0.34); moderate to severe (AHI ≥ 15 /h; $n = 406$), 3.37 cm (0.36; Table 3). AoPWV also showed a significant trend ($p = 0.005$) of greater mean (SD) across the three OSA groups: normal (AHI < 5 /h), 8.07 m/s (3.50); mild ($5 \leq \text{AHI} < 15$ /h), 8.27 m/s (3.52); moderate to severe (AHI ≥ 15 /h), 9.11 m/s (4.44). No such trend was found for AAD across OSA severity groups (Fig. 2).

In adjusted analysis, participants with moderate to severe OSA had a greater mean AoD compared with the normal group: adjusted mean difference (95% CI), 0.12 cm (0.05, 0.20), $p = 0.002$ (Table 4). A significant interaction ($p_{\text{interaction}} = 0.02$) by sex was observed; the results were significant only in women but not in men. Women with mild OSA and moderate to severe OSA had about 4.5 and 7% larger diameters, respectively, compared with those without OSA (Fig. 3). No significant differences were found with AoPWV or AAD across the OSA groups: AoPWV: 0.48 (–0.46, 1.41), $p = 0.32$ (moderate to severe vs. normal group), –0.06 (–1.01, 0.9), $p = 0.91$ (mild

Table 1. Baseline characteristics by sleep-disordered breathing ($n = 708$): the MESA (2010–2013)

	Overall	OSA status			p value	Sex		
		normal (AHI <5/h)	mild (5 ≤ AHI <15)	significant (AHI ≥15)		male	female	p value
n	708 (100)	87 (12.3)	215 (30.4)	406 (57.3)	–	312 (44.1)	396 (55.9)	–
Age, years	67.7±8.9	65.5±8.6	67.1±8.8	68.5±8.9	0.006	67.5 (9.2)	67.9 (8.6)	0.629
Sex					<0.0001			
Male	312 (44.1)	22 (25.3)	73 (34.0)	217 (53.5)		–	–	–
Female	396 (55.9)	65 (74.7)	142 (66.1)	189 (46.6)		–	–	–
Race					0.14			0.811
White	256 (36.2)	26 (29.9)	88 (40.9)	142 (34.9)		107 (41.8)	149 (58.2)	
Chinese	139 (19.6)	19 (21.8)	41 (19.1)	79 (19.5)		62 (44.6)	77 (55.4)	
Black	193 (27.3)	29 (33.3)	60 (27.9)	104 (25.6)		87 (45.1)	106 (54.9)	
Hispanic	120 (17.0)	13 (14.9)	26 (12.1)	81 (19.9)		56 (46.7)	64 (53.3)	
BSA, m ²	1.8±0.2	1.7±0.2	1.8±0.2	1.9±0.2	<0.0001	2.0 (0.2)	1.73 (0.2)	<0.0001
Current smoking, yes	268 (37.9)	33 (37.9)	75 (34.9)	160 (39.4)	0.54	140 (44.9)	128 (32.3)	0.001
Hypertension, yes	388 (54.8)	42 (48.3)	113 (52.6)	233 (57.4)	0.22	156 (50.0)	232 (58.6)	0.023
Diabetes					<0.0001			0.017
Normal	458 (64.69)	68 (78.16)	159 (73.95)	231 (56.90)		185 (59.29)	273 (68.94)	
Impaired fasting glucose	138 (19.49)	12 (13.79)	31 (14.42)	95 (23.40)		74 (23.72)	64 (16.16)	
Diabetes	112 (15.82)	7 (8.05)	25 (11.63)	80 (19.70)		53 (16.99)	59 (14.90)	
Antihypertensive medications, yes	361 (51.0)	42 (48.3)	110 (51.2)	209 (51.5)	0.86	143 (45.8)	218 (55.1)	0.015
Total cholesterol, mg/dL	187±35	193±31	189±35	185±36	0.18	176±34	196±34	<0.0001
HDL, mg/dL	56±16	64±19	58±16	53±15	<0.0001	49±13	61±17	<0.0001
LDL, mg/dL	110±31	110±28	110±30	109±32	0.95	105±31	113±31	0.002
Statin use, yes	239 (33.8)	24 (27.59)	74 (34.42)	141 (34.73)	0.43	112 (35.9)	127 (32.1)	0.285
SBP, mm Hg	127±17	121±18	126±17	129±17	0.0017	128±18	127±17	0.393
Fasting glucose, mg/dL	100±28	95±22	97±25	103±30	0.012	102±25	99±30	0.146
LVEF, %	62.7±7.0	63.1±6.4	63.1±6.9	62.4±7.2	0.47	60.4±7.2	64.5±6.3	<0.0001

Data are presented as the mean ± SD or n (%). p values represent the overall group difference from ANOVA for continuous variables and χ^2 statistic for categorical variables. The significant obstructive sleep apnea (OSA) group refers to moderate-severe OSA. BSA, body surface area; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; LVEF, left ventricular ejection fraction.

vs. normal group); AAD: 0.17 (–0.11, 0.44), $p = 0.23$ (moderate to severe vs. normal group), –0.04 (–0.32, 0.24), $p = 0.78$ (mild vs. normal group). Substituting height for BSA yielded similar results (data not shown). No interactions by sex, age, or race/ethnicity were found for results pertaining to AoPWV or AAD.

Discussion

In a multi-ethnic community cohort, OSA was associated with a larger ascending aortic size. After adjusting for potential confounders, AoD was significantly larger in those with moderate to severe OSA compared to those without OSA. Notably, this finding was only detected in women. In women, moderate to severe OSA was associated with an approximately 7% larger AoD compared with individuals without OSA. Given that the risk of a catastrophic event, such as aortic dis-

section, increases with the diameter of the aorta, our results may have clinical implications especially in patients with already enlarged ascending aortas. In contrast to AoD, no association was found with the measures of aortic stiffness. Although AoPWV increased (i.e., higher stiffness) with higher OSA severity, no differences by OSA severity were found after adjusting for potential confounders. Similarly, no meaningful association was found with AAD. To our knowledge, this represents the first large-scale community-based study to examine OSA's independent association with structural and functional properties of the proximal thoracic aorta.

OSA is a highly prevalent sleep disorder that is increasingly recognized as a risk factor for cardiovascular morbidity such as hypertension, stroke, and heart failure, as well as overall mortality [21–24]. A number of previous studies have suggested, albeit inconsistently, the association of OSA with thoracic aortic size. One of

Table 2. Baseline characteristics by sleep-disordered breathing in men and women: the MESA (2010–2013)

	Men (<i>n</i> = 312)				Women (<i>n</i> = 312)			
	OSA status			<i>p</i> value*	OSA status			<i>p</i> value*
	normal (AHI <5/h)	mild (5 ≤ AHI <15)	significant (AHI ≥15)		normal (AHI <5/h)	mild (5 ≤ AHI <15)	significant (AHI ≥15)	
<i>n</i>	22 (7.1)	73 (23.4)	217 (69.6)	–	65 (16.4)	142 (35.9)	189 (47.7)	–
Age, years	65.4±8.4	65.9±7.9	68.3±9.6	0.07	65.6±8.7	67.7±9.2	68.8±7.9	0.03
Race				0.12				0.23
White	5 (22.7)	27 (37.0)	75 (34.6)		21 (32.3)	61 (43.0)	67 (35.4)	
Chinese	3 (13.6)	11 (15.1)	48 (22.1)		16 (24.6)	30 (21.1)	31 (16.4)	
Black	10 (45.5)	26 (35.6)	51 (23.5)		19 (29.2)	34 (23.9)	53 (28.0)	
Hispanic	4 (18.2)	9 (12.3)	43 (19.8)		9 (13.8)	17 (12.0)	38 (20.1)	
BSA, U	1.9±0.2	1.9±0.2	2.0±0.2	0.19	1.7±0.2	1.7±0.2	1.8±0.2	<0.0001
Current smoking, yes	13 (59.1)	35 (47.9)	92 (42.4)	0.27	20 (30.8)	40 (28.2)	68 (36.0)	0.31
Hypertension, yes	12 (54.5)	30 (41.1)	114 (52.5)	0.22	30 (46.2)	83 (58.5)	119 (63.0)	0.06
Diabetes				0.11				0.004
Normal	16 (72.7)	51 (69.9)	118 (54.4)		52 (80.0)	108 (76.1)	113 (59.8)	
Impaired fasting glucose	3 (13.6)	14 (19.2)	57 (26.3)		9 (13.8)	17 (12.0)	38 (20.1)	
Diabetes	3 (13.6)	8 (11.0)	42 (19.4)		4 (6.2)	17 (12.0)	38 (20.1)	
Antihypertensive medications, yes	11 (50.0)	31 (42.5)	101 (46.5)	0.77	31 (47.7)	79 (55.6)	108 (57.1)	0.41
Total cholesterol, mg/dL	176±29	173±36	177±34	0.70	198±29	197±32	195±37	0.75
HDL, mg/dL	55±15	50±14	48±12	0.05	67±20	62±16	58±16	0.001
LDL, mg/dL	104±28	104±33	106±31	0.91	111±29	113±29	113±33	0.92
Statin use, yes	6 (27.3)	26 (35.6)	80 (36.9)	0.67	18 (27.7)	48 (33.8)	61 (32.3)	0.68
SBP, mm Hg	124±21	126±15	129±18	0.36	120±16	127±18	128±16	0.003
Fasting glucose, mg/dL	102±30	101±29	102±24	0.93	93±19	95±22	104±36	0.01
LVEF, %	61.0±6.2	60.4±6.4	60.3±7.5	0.91	63.8±6.4	64.5±6.8	64.8±6.0	0.53

Data are presented as the mean ± SD or *n* (%). *p* values represent the overall group difference from ANOVA for continuous variables and χ^2 statistic for categorical variables. The significant obstructive sleep apnea (OSA) group refers to moderate-severe OSA. BSA, body surface area; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; LVEF, left ventricular ejection fraction.

Table 3. Unadjusted AoD, AoPWV, and AAD overall and by OSA status: the MESA (visit 5: 2010–2013)

	Overall	OSA status			<i>p</i> value
		normal (AHI<5/h)	mild (5 ≤ AHI <15)	significant (AHI ≥15)	
<i>n</i>	708 (100)	87 (12.3)	215 (30.4)	406 (57.3)	–
AoD, cm	3.30±0.36	3.13±0.35	3.25±0.34	3.37±0.36	<0.0001
AoPWV, m/s	8.72±4.09	8.07±3.50	8.27±3.52	9.11±4.43	0.014
AAD, %/mm Hg	1.65±1.20	1.73±1.27	1.54±1.02	1.68±1.27	0.27

Data are presented as the mean ± SD. *p* values represent the overall group difference from ANOVA. The significant obstructive sleep apnea (OSA) group refers to moderate-severe OSA. AoD, ascending aortic diameter; AoPWV, aortic pulse wave velocity; AAD, ascending aortic distensibility.

the first clinic-based studies by Tanriverdi et al. [25] showed no difference in aortic root diameter. In another study predominantly consisting of middle-aged men, AoD as measured by thoracic computerized tomography was higher among patients with OSA compared with those without [5]. In the Systeme Nerveux

Autonome Physiologie Sommei (SYNAPSE) ancillary study, investigators found a correlation between selected measures of OSA, including oxygen desaturation index and mean nocturnal oxygen saturation with aortic root diameter. However, this association was no longer significant in multivariable-adjusted analyses [26].

Fig. 2. Unadjusted ascending AoD (a), AoPWV (b), and aortic distensibility (c) by OSA severity (the MESA visit 5: 2010–2013; $n = 708$: no OSA = 87; mild OSA = 215; significant OSA = 406). p values for linear trend: <0.0001 (a); 0.005 (b); 0.7 (c).

Table 4. Adjusted mean ascending AoD compared to the no OSA group in all subjects and by sex: the MESA (visit 5: 2010–2013)

	Mean, cm	95% CI	p value
All ($n = 708$)			
No OSA (ref.)	3.20	3.12, 3.27	–
Mild	3.27	3.22, 3.32	0.08
Moderate to severe	3.32	3.29, 3.36	0.002
Men ($n = 312$)			
No OSA (ref.)	3.52	3.44, 3.60	–
Mild	3.41	3.37, 3.46	0.21
Moderate to severe	3.46	3.43, 3.48	0.44
Women ($n = 396$)			
No OSA (ref.)	2.98	2.94, 3.02	–
Mild	3.12	3.09, 3.15	0.002
Moderate to severe	3.20	3.17, 3.22	<0.0001

Adjusted for age, sex, race, body surface area, systolic blood pressure, antihypertensive medication status, diabetes, smoking, and cholesterol levels. p values are based on comparison to the reference group. OSA, obstructive sleep apnea.

Similarly, hypertension, but not OSA, was found to be a determinant of AoD among patients presenting with acute myocardial infarction [27]. Such conflicting results can be partly explained by the different patient characteristics included in each study. The cohort in our study represents a much older and racially/ethnically diverse population as compared to the prior studies. More importantly, one should note that our study population was not selected due to symptoms of OSA or OSA-related morbidities, and thus findings from the present analysis may be more generalizable than those from clinic-based populations.

There are several proposed mechanisms through which OSA may exert its adverse impact on thoracic aortic structural and functional properties. Intermittent hypoxemia/hypercapnia and arousal cause a sympathetic surge, and subsequently a BP surge [28]. The heightened sympathetic tone carries over to daytime as well in patients with OSA [28]. Not surprisingly, OSA is associated with both nocturnal and daytime hypertension [29]. Also, the large negative intrathoracic pressure change that occurs with obstructive breathing may impose shear stress against the wall. Furthermore, increases in AoD during obstructive breathing have been described in animals [30]. These mechanisms are feasible but there has been a lack of studies on this topic, particularly from unselected (i.e., non-clinical) population-based samples.

A notable finding was that the association between OSA thoracic aortic size was specific to women. The biological underpinnings of this differential association by sex are unclear. OSA has a greater impact on endothelial dysfunction in women as compared to men [10]. It is possible that the aortic shear stress in response to the intrathoracic pressure swing caused by OSA may be more exaggerated in women than men, although this is speculative. Regardless, this finding is consistent with emerging literature that older women, who presumably experience OSA-related stressors for years after menopause (when OSA is typically exacerbated), may be more susceptible to the adverse cardiovascular sequelae than men, with mechanisms including propensity for subclinical ischemia and cardiac remodeling [31]. The current finding adds to the literature on sex differences, supporting the likelihood that older women are more susceptible to CVD due to OSA.

Fig. 3. Adjusted mean sex-specific ascending AoD (women, $n = 396$; men, $n = 312$): the MESA (visit 5: 2010–2013). p values for linear trend: <0.0001 (a); 0.95 (b). * $p < 0.05$ when compared to the reference group (no OSA). Adjusted for age, race, BSA, systolic BP, antihypertensive medication status, diabetes, smoking, and cholesterol levels.

In contrast to proximal aortic structure, we did not identify a meaningful association of OSA with functional properties of the proximal aorta. A number of previous clinic-based studies have linked OSA with aortic stiffness. The null findings in this study may possibly reflect that we studied a relatively healthy sample with overall well-controlled levels of BP and lipids. Our sample was also older (mean age 68 years); risk factor associations are generally attenuated in older compared to younger individuals [32]. Moreover, our results may also differ from prior studies due to technical differences between the current approach (i.e., cardiac MRI-based AoPWV) and the approach typically used in prior studies (i.e., applanation tonometry-based carotid-femoral PWV used in prior studies) [25, 27]. Absence of a significant association with AAD is not surprising as AAD is closely related to AoPWV [9].

While our study highlights the potential impact of OSA on structural remodeling of the proximal thoracic aorta, the clinical relevance of our findings is limited due to the small magnitude of the associations observed between OSA and AoD. Moreover, this study does not allow us to assess OSA's impact on clinically significant thoracic aortopathy, such as aortic aneurysm, primarily because of the few cases with such endpoints in our study. As such, interpretation of this finding should be confined within the relatively normal range of AoD. Because of the need for a much larger sample size and also longer follow-up to examine the association of OSA with clinically meaningful thoracic aortic disease, we speculate that it will remain challenging to study this in the general population. In this regard, a recent case control study utilizing a large national health insurance database of about 50,000 people in Taiwan is of interest. This study, however, found no association between the diagnosis of OSA and future incidence of aortic dissection [33]. However, bias may be present as individuals with undiagnosed OSA would have been misclassified as not having OSA. Approximately 85% of indi-

viduals who meet the diagnostic criteria for OSA are unaware of their status [34]. An interesting and practical study design to test this hypothesis would be to assess the progression of AoD or outcomes among patients with OSA and preexisting aortic aneurysm.

The key strengths of the present analysis include the comprehensive assessment of OSA using polysomnography, the aortic assessment using state-of-the-art MRI techniques, and the ability to assess sex differences. In determining the severity of OSA, we used a respiratory scoring rule that is currently recommended in clinical practice. This rule typically yields higher AHI than the more conservative alternative rule and, as such, the OSA prevalence in our study may have been overestimated compared to studies that used the alternative rule. The cross-sectional nature of this study precludes us from determining causal associations. Moreover, the possibility of residual confounding exists, despite adjusting for key potential confounders.

In conclusion, in a racially/ethnically diverse community cohort, OSA was associated with higher AoD, a potential marker of structural remodeling of thoracic aorta in women. These findings suggest a sex-specific thoracic aortic vulnerability to OSA.

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Statement of Ethics

All participants provided their written informed consent. The study protocol was approved by the research institute's committee on human research. The research protocols were ap-

proved by the Institutional Review Boards at each participating institution (Wake Forest University [IRB00008492 under Federal-Wide Assurance, FWA, 00001435]; Columbia University [IRB00002973 under FWA00002636]; Johns Hopkins University [IRB00001656 under FWA00005752]; University of Minnesota [IRB00000438 under FWA00000312]; Northwestern University [IRB00005003 under FWA00001549]; University of California Los Angeles [IRB number 00000172 under FWA00004642]; University of Washington [IRB00005647 under FWA00006878]).

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Y.K. and P.L. developed the study design. Y.K. and J.L. performed data analysis. All other authors provided data interpretation, critical review, and revision of the manuscript.

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