

## ORIGINAL ARTICLE

# Carotid Artery Stiffening With Aging: Structural Versus Load-Dependent Mechanisms in MESA (the Multi-Ethnic Study of Atherosclerosis)

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**ABSTRACT:** Elastic arteries stiffen via 2 main mechanisms: (1) load-dependent stiffening from higher blood pressure and (2) structural stiffening due to changes in the vessel wall. Differentiating these closely coupled mechanisms is important to understanding vascular aging. MESA (Multi-Ethnic Study of Atherosclerosis) participants with B-mode carotid ultrasound and brachial blood pressure at exam 1 and exam 5 (year 10) were included in this study (n=2604). Peterson and Young elastic moduli were calculated to represent total stiffness. Structural stiffness was calculated by adjusting Peterson and Young elastic moduli to a standard blood pressure of 120/80 mmHg with participant-specific models. Load-dependent stiffness was the difference between total and structural stiffness. Changes in carotid artery stiffness mechanisms over 10 years were compared by age groups with ANCOVA models adjusted for baseline cardiovascular disease risk factors. The 75- to 84-year age group had the greatest change in total, structural, and load-dependent stiffening compared with younger groups ( $P < 0.05$ ). Only age and cessation of antihypertensive medication were predictive of structural stiffening, whereas age, race/ethnicity, education, blood pressure, cholesterol, and antihypertensive medication were predictive of increased load-dependent stiffening. On average, structural stiffening accounted for the vast majority of total stiffening, but 37% of participants had more load-dependent than structural stiffening. Rates of structural and load-dependent carotid artery stiffening increased with age. Structural stiffening was consistently observed, and load-dependent stiffening was highly variable. Heterogeneity in arterial stiffening mechanisms with aging may influence cardiovascular disease development. (*Hypertension*. 2022;79:00–00. DOI: 10.1161/HYPERTENSIONAHA.121.18444.) • [Supplemental Material](#)

**Key Words:** aging ■ blood pressure ■ cholesterol ■ humans ■ vascular stiffness

Arterial stiffness is associated with increased risk for incident hypertension, cardiovascular disease (CVD), stroke, and damage to end organs with low-resistance capillary beds such as the brain and kidneys.<sup>1–6</sup> Large elastic arteries stiffen via 2 main mechanisms<sup>7</sup>: (1) load-dependent stiffening due to elevated blood pressure (BP) increasing collagen fiber loading without an intrinsic change to the artery wall composition and (2) structural stiffening due to growth (eg, intima-media thickening), remodeling (eg, elastin fragmentation, collagen accumulation), or both. Prior studies have shown that age is a major determinant of arterial stiffness both in cross-sectional and longitudinal analyses.<sup>7–10</sup> It is unclear whether increased arterial stiffness with aging is due to structural changes in the artery wall with aging, a load-dependent response

to age-associated increased systolic BP (SBP), or a combination of both mechanisms. As highlighted by the 2015 American Heart Association scientific statement on arterial stiffness,<sup>11</sup> understanding whether the age-associated increase in arterial stiffness is driven by structural or load-dependent mechanisms is an important unanswered question that could yield valuable insights into the physiology of arterial aging. The aim of this study was to evaluate the longitudinal changes in structural and load-dependent carotid artery stiffness in a diverse cohort without baseline CVD.

## METHODS

The data are available to other researchers through the National Institutes of Health, National Heart, Lung, and Blood

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## Novelty and Significance

### What Is New?

- This study is the first to quantify the age-associated longitudinal changes in structural and load-dependent carotid artery stiffness in a large, multiethnic cohort study with a decade of observation.
- On average, the vast majority of the age-associated increases in carotid artery stiffness were due to structural stiffening intrinsic to the arterial wall rather than being a concomitant effect of increased systolic BP with aging.
- There was high individual variability; 37% of participants had more load-dependent than structural stiffening.

### What Is Relevant?

- The longitudinal rates of structural and load-dependent carotid artery stiffening increased with age.
- Results suggest that load-dependent stiffness could be a more modifiable component of arterial stiffness compared with the structural stiffness component.
- Load-dependent stiffness could be novel target for hypertension management and antihypertensive therapy.

### Summary

Over a decade of aging, structural carotid artery stiffening was consistently observed, and load-dependent carotid artery stiffening was highly variable.

## Nonstandard Abbreviations and Acronyms

<b>BP</b>	blood pressure
<b>CVD</b>	cardiovascular disease
<b>MESA</b>	Multi-Ethnic Study of Atherosclerosis
<b>PEM</b>	Peterson elastic modulus
<b>SBP</b>	systolic blood pressure
<b>YEM</b>	Young elastic modulus

Institute, Biologic Specimen and Data Repository Information Coordinating Center.<sup>12</sup> Analytic methods may be requested from the author. Researchers with interest in the ultrasound images or other study materials are invited to contact MESA (Multi-Ethnic Study of Atherosclerosis) via the study authors about access to images, which are held internally at MESA because of the size of the archive and to protect participant privacy in accordance with participant consent.

## Study Participants and Design

The MESA is a large prospective cohort study investigating the prevalence, causes, and progression of subclinical CVD. MESA has a population-based sample of 6814 men and women aged 45 to 84 years, free of known CVD at baseline, recruited from 6 US communities. The study objectives and design have been published previously.<sup>13</sup> All participants gave informed consent for the study protocol, which was approved by the institutional review boards of the ultrasound reading center and all MESA field centers.

The present analyses include a subset of MESA participants with valid carotid distensibility measurements at the first (baseline) and fifth examinations who were not missing key covariates ( $n=2604$ ; Figure S1: flowchart). Demographic, medical history, and laboratory data for the present study were obtained from the first (July 2000 to August 2002) and fifth (April 2010 to February 2012) examinations of the cohort. Hypertension was defined as SBP  $\geq 140$  mmHg, diastolic BP  $\geq 90$  mmHg, or use of antihypertensive medications. Diabetes was defined

as fasting blood glucose  $\geq 126$  mg/dL or use of antidiabetic medications. Impaired fasting glucose was defined as blood glucose of 100 to 125 mg/dL. Total and high-density lipoprotein cholesterol levels were measured after a 12-hour fast. Low-density lipoprotein cholesterol was calculated.

## B-Mode Ultrasound and Brachial BP Measurements

At examination 1, B-mode ultrasound video-loop recordings of a longitudinal section of the distal right common carotid artery were recorded on S-VHS videotapes using a Logiq 700 ultrasound system (General Electric Medical Systems; transducer frequency, 13 MHz). Videotaped images were digitized at high resolution and frame rates using a medical digital recording device (PACSGEAR, Pleasanton, CA), which were converted into DICOM-compatible digital records. At examination 5, a similar protocol was performed using the same ultrasound and digitizing equipment; however, the video output was directly digitized using the same medical digital recording settings without the use of videotape. Certified and trained sonographers from all 6 MESA sites used selected reference images from examination 1 to match the scanning conditions of the initial study, including common carotid artery display depth, angle of approach, surrounding tissues and internal landmarks, degree of jugular venous distension, and ultrasound system settings. After 10 minutes of rest in the supine position and immediately before ultrasound image acquisition, repeated measures of brachial BP were obtained using a standardized protocol with an automated upper arm sphygmomanometer (DINAMAP; GE Medical Systems, Milwaukee, WI). Ultrasound images were reviewed and interpreted by the MESA Carotid Ultrasound Reading Center (the University of Wisconsin Atherosclerosis Imaging Research Program, Madison, WI). Systolic and diastolic diameters were determined as the largest and smallest diameters during the cardiac cycle. All measurements were made manually tracing a 1-cm-long segment and performed in triplicate from 2 to 3 consecutive cardiac cycles. Internal and external artery diameters were measured using Access Point Web, version 3.0 (Freeland Systems LLC, Carmel, IN).

## Carotid Artery Stiffness

Peterson elastic modulus (PEM) was calculated<sup>14</sup>:

$$PEM = \frac{V_p D d^2}{(D_s^2 - D_d^2)} \quad (1)$$

where  $D_s$  represents the internal arterial diameter at peak systole,  $D_d$  represents the internal arterial diameter at end diastole, and  $\Delta p$  represents the brachial BP difference between the systolic and diastolic measurements (pulse pressure). Young elastic modulus (YEM) was calculated<sup>14</sup>:

$$YEM = PEM \left( \frac{D_d}{h} \right) \quad (2)$$

where  $h$  is the carotid artery wall thickness at end diastole.

To differentiate the structural and load-dependent components of carotid artery stiffness, a participant-specific exponential model was used to describe arterial mechanics<sup>15</sup> using a nonlinear stiffness parameter at the common reference pressure of 120/80 mm Hg.

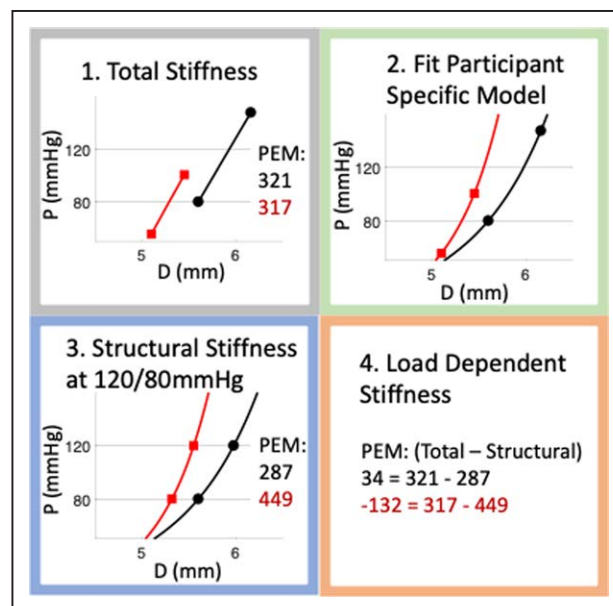
PEM and YEM were calculated at this reference pressure to represent the structural arterial stiffness. All participants were compared at the same reference pressure. The mathematical equations are included as [Supplemental Material](#). The load-dependent arterial stiffness was calculated as the difference between total PEM and YEM calculated at the individuals' measured BP and the structural arterial stiffness (Figure 1). An individual's load-dependent stiffness will be positive if their BP is greater than the 120/80 reference pressure and negative if their BP is less than the 120/80 reference pressure.

## Statistical Analysis

Results are reported as mean and SD for continuous variables. Categorical variables are reported as percentages.

Baseline age was classified into 4 categories by decade: 45 to 54, 55 to 65, 65 to 74, and 75 to 84. Differences in carotid artery stiffness parameters from baseline to examination 5 between age categories were assessed using ANCOVA models. ANCOVA models were adjusted for baseline covariates: sex, race/ethnicity, study site, education level, income, traditional CVD risk factors (body mass index, diabetes status, SBP, smoking status, lipids), baseline use of lipid-lowering medications, and use of antihypertensive medications ([1] never treated with antihypertensive medication, [2] continuous treatment with antihypertensive medication, [3] started treatment with antihypertensive medication, and [4] stopped treatment with antihypertensive medication). ANCOVA model results used a Bonferroni correction to account for multiple comparisons, and results are presented as estimated means and 95% CIs. To identify the impact that the reference pressure of 120/80 mm Hg had on our calculations, a sensitivity analysis was performed by repeating ANCOVA analyses with reference pressures of 105/70, 135/90, and 160/90 mm Hg. A second set of ANCOVA models was also created that included all covariates in the primary models and added the change in intima-media thickness, diastolic diameter, SBP, and pulse pressure as covariates from exams 1 to 5.

Exploratory analyses were also performed after grouping participants into those with greater load-dependent stiffening versus those with greater structural stiffening. Since this was not prespecified, differences in continuous variables between the groups were assessed by calculating the effect size (Hedge  $g$ ).



**Figure 1.** Graphical representation of methods used to differentiate structural and load-dependent stiffness.

Representative results are shown for 2 participants (one in red, one in black) who had similar total Peterson elastic modulus (PEM; 321 vs 317 mm Hg) but via different mechanisms. One participant (red lines and text) had higher structural PEM (449 vs 287 mm Hg) while the other participant (black lines and font) had higher load-dependent PEM (34 vs -132 mm Hg). For graphs, the y axis label P is pressure (mmHg) and the x axis label D is diameter (mm).

## RESULTS

### Participant Characteristics

Participant characteristics are presented in Table 1. Participants were  $59.9 \pm 9.4$  years old at baseline (45–54: 35% [n=907], 55–64: 31% [n=798], 65–74: 27% [n=712], 75–84: 7% [n=184]), and 54% were female. Participants were identified as 39% White, 25% Black, 14% Chinese, and 21% Hispanic. The average time from baseline to follow-up at examination 5 was  $9.5 \pm 0.6$  years. SBP, pulse pressure, carotid artery wall thickness, and carotid artery diameter all increased over the duration from baseline to examination 5.

### Change in PEM

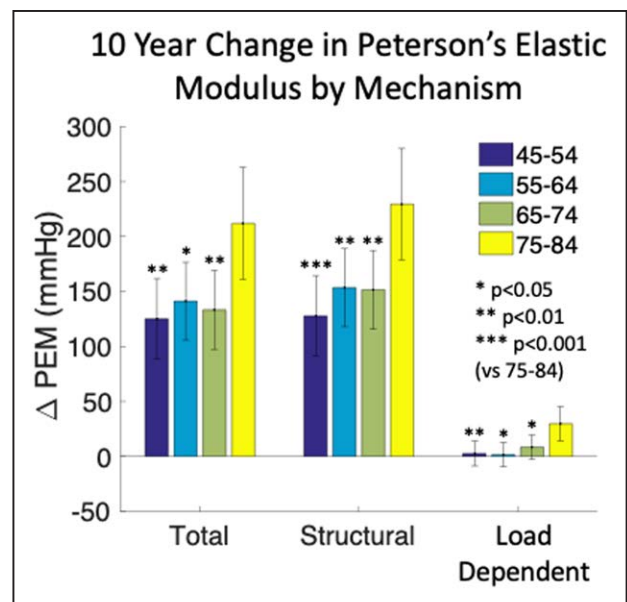
The mean total PEM increased during the study period (Table 1). Total PEM increased the most in 75- to 84-year-old (at baseline) participants compared with younger participants ( $\Delta 212 \pm 26$  versus  $\Delta 122 \pm 18$  mm Hg;  $P < 0.05$ ; Figure 2). In addition to age category, self-identification with Black race and stopping antihypertensive medication before exam 5 assessment were associated with a greater increase in total PEM. Conversely, having more than high school education and greater baseline SBP were associated with less increase in total PEM (Table 2). Structural PEM similarly increased during the study period (Table 1), and the change was also greatest

**Table 1. Participant Characteristics at Baseline and Exam 5**

n=2604	Baseline	Examination 5
Age, y	59.9±9.4	69.3±9.3
Women, n (%)	1392 (53.5%)	
Race/ethnicity, n (%)		
White	1020 (39.2%)	
Black	656 (25.2%)	
Chinese	373 (14.3%)	
Hispanic	555 (21.3%)	
BP parameters, mmHg		
SBP	123.2±19.9	129.4±18.7
DBP	71.7±10.1	69.4±9.7
Pulse pressure	51.6±15.5	60.1±15.1
Hypertension, n (%)	1074 (41.2%)	1597 (61.3)
Hypertension medication, n (%)	740 (28.4%)	1363 (52.3%)
Diabetes status, n (%)		
Impaired fasting glucose	313 (12.0%)	549 (21.1%)
Untreated	39 (1.5%)	38 (1.5%)
Treated	177 (6.8%)	411 (15.8%)
Lipids, mg/dL		
Total cholesterol	193.6±33.8	183.3±36.6
Low-density lipoprotein cholesterol	117.4±30.5	105.6±32.0
High-density lipoprotein cholesterol	51.8±15.0	56.7±17.0
Triglycerides	122.3±62.7	105.2±51.9
Lipid-lowering medication, n (%)	383 (14.7%)	978 (37.6%)
Body mass index, kg/m <sup>2</sup>	27.7±5.0	27.9±5.3
Smoking, n (%)		
Current	288 (11.1%)	188 (7.2%)
Former	924 (35.5%)	1185 (45.5%)
Carotid artery dimensions		
Wall thickness, mm	0.74±0.15	0.82±0.16
PSI diameter, mm	6.26±0.74	6.43±0.80
EDI diameter, mm	5.80±0.70	5.99±0.76
Stiffness parameters, mmHg		
Total PEM	353±200	460±312
Structural PEM	374±189	482±295
Load-dependent PEM	-21±68	-23±88
Total YEM	2865±1700	3481±2555
Structural YEM	3140±1660	3760±2448
Load-dependent YEM	-275±669	-279±761

All values are mean and SD. BP indicates blood pressure; DBP, diastolic blood pressure; EDI, end diastolic internal; PEM, Peterson elastic modulus; PSI, peak systolic internal; SBP, systolic blood pressure; and YEM, Young elastic modulus.

in 75- to 84-year-old participants compared with younger age groups ( $\Delta 229 \pm 26$  versus  $\Delta 144 \pm 18$  mmHg;  $P < 0.01$ ; Figure 2). Stopping antihypertensive medication was associated with greater increase in structural PEM (Table 2). For the 78 participants who stopped using antihypertensive medications, the estimated increase in structural PEM ( $\Delta 210 \pm 33$  mmHg) was greater than for participants who were continuously treated ( $\Delta 141 \pm 17$



**Figure 2. Estimated means and 95% CIs for total, structural, and load-dependent changes in carotid artery Peterson elastic modulus (PEM) over 10 y of aging by age groups.**

Older individuals (75-84, yellow bars) had greater rates of total, structural, and load-dependent stiffening. ANCOVA model covariates were sex, race/ethnicity, education level, income, smoking status, diabetes status, systolic blood pressure, total cholesterol, HDL (high-density lipoprotein) cholesterol, body mass index, antihypertensive medication, and lipid-lowering medication.

mmHg) or were never treated ( $\Delta 139 \pm 18$  mmHg). On average, load-dependent PEM did not increase during the study period (Table 1) although the 75- to 84-year-old participants had an increase that was not observed in younger participants ( $\Delta 30 \pm 8$  versus  $\Delta 4 \pm 6$  mmHg;  $P < 0.05$ ; Figure 2). Self-identification with Black race was associated with greater increase in load-dependent PEM (Table 2). Self-identification with Chinese ethnicity, more than high school education, starting antihypertensive medication, greater baseline SBP, and greater baseline HDL cholesterol were associated with less increase in load-dependent PEM (Table 2).

In a second set of ANCOVA models that incorporated the change in IMT, diastolic diameter, SBP, and pulse pressure as covariates (Supplemental Material); race/ethnicity and educational attainment were no longer significantly associated with changes in total and load-dependent PEM. Cessation of antihypertensive medication was still associated with increased total PEM ( $\beta = 74$  mmHg;  $P = 0.02$ ) and structural PEM ( $\beta = 71$  mmHg;  $P = 0.02$ ). Starting antihypertensive medication was no longer associated with the change in load-dependent PEM. The change in IMT, diastolic diameter, SBP, and pulse pressure were all significantly associated with changes in total, structural, and load-dependent PEM (Supplemental Material). Changes in SBP and pulse pressure had opposite associations with the different stiffness mechanisms. Increased change in SBP



**Table 2. Multivariate ANCOVA Model for Change in PEM\***

	$\beta$	P value
Change in total PEM		
Age category (vs 75–84)		
45–54	–129	<0.001
55–64	–104	<0.001
65–74	–99	<0.001
Black (vs mean)	26	0.02
More than HS education (vs did not graduate HS)	–41	0.046
HTN medication cessation (vs untreated)	105	0.002
SBP (per 10 mmHg)	–19	<0.001
Change in structural PEM		
Age category (vs 75–84)		
45–54	–102	<0.001
55–64	–76	0.001
65–74	–78	0.001
HTN medication cessation (vs untreated)	89	0.007
Change in load-dependent PEM		
Age category (vs 75–84)		
45–54	–27	<0.001
55–64	–28	<0.001
65–74	–21	0.002
Black (vs mean)	9	<0.001
Chinese (vs mean)	–20	0.002
More than HS education (vs did not graduate HS)	–12	0.05
Starting HTN medication (vs untreated)	–11	0.02
SBP (per 10 mmHg)	–17	<0.001
HDL cholesterol (per 10 mg/dL)	–6	<0.001

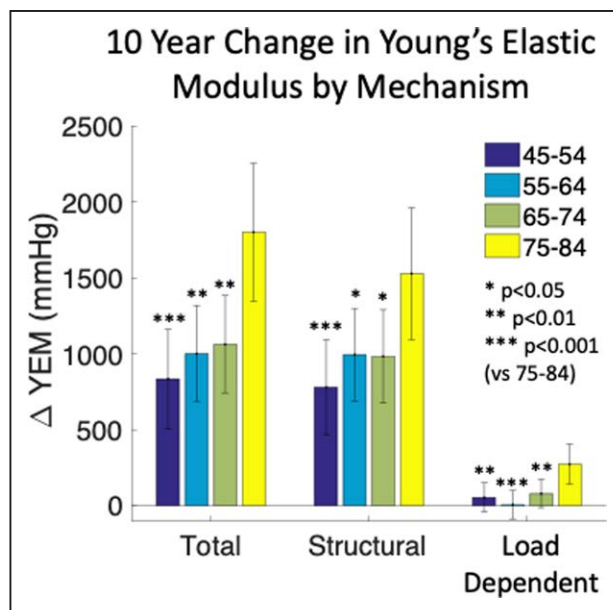
HDL indicates high-density lipoprotein; HS, high school; HTN, hypertension; PEM, Peterson elastic modulus; and SBP, systolic blood pressure.

\*Only significant predictors are included in the table.

increased total PEM ( $\beta=27$  mmHg per 10 mmHg;  $P<0.001$ ), decreased structural PEM ( $\beta=-39$  mmHg per 10 mmHg;  $P<0.001$ ), and increased load-dependent PEM ( $\beta=69$  mmHg per 10 mmHg;  $P<0.001$ ). Increased change in pulse pressure increased total PEM ( $\beta=40$  mmHg per 10 mmHg;  $P<0.001$ ), increased structural PEM ( $\beta=81$  mmHg per 10 mmHg;  $P<0.001$ ), and decreased load-dependent PEM ( $\beta=-41$  mmHg per 10 mmHg;  $P<0.001$ ).

### Change in YEM

The mean total YEM increased during the study period (Table 1). Total YEM increased the most in 75- to 84-year-old participants compared with younger participants ( $\Delta 1801 \pm 231$  versus  $\Delta 966 \pm 164$  mmHg;  $P<0.01$ ; Figure 3). In addition to age category, stopping antihypertensive medication was associated with greater increase in total YEM while high school education and greater baseline SBP were associated with less increase in total YEM (Table 3). Structural YEM similarly increased during



**Figure 3. Estimated means and 95% CIs for total, structural, and load-dependent changes in carotid artery Young elastic modulus (YEM) over 10 y of aging.**

Older individuals (75-84) had greater rates of total, structural, and load-dependent stiffening. ANCOVA model covariates were sex, race/ethnicity, education level, income, smoking status, diabetes status, systolic blood pressure, total cholesterol, HDL (high-density lipoprotein) cholesterol, body mass index, antihypertensive medication, and lipid-lowering medication.

the study period (Table 1), and the change was also the greatest in 75- to 84-year-old participants compared with younger participants ( $\Delta 1529 \pm 221$  versus  $\Delta 920 \pm 157$  mmHg;  $P<0.01$ ; Figure 3). In addition to age category, stopping antihypertensive medication was associated with greater increase in structural YEM (Table 3). The average load-dependent YEM did not increase during the study period (Table 1) although 75- to 84-year-old participants had an increase that was not observed in younger participants ( $\Delta 273 \pm 67$  versus  $\Delta 47 \pm 48$  mmHg;  $P<0.01$ ; Figure 3). In addition to age category, self-identification with Black race and stopping antihypertensive medication were associated with greater increase in load-dependent YEM (Table 3). Self-identification with Chinese ethnicity, starting antihypertensive medication, greater baseline SBP, and greater baseline HDL cholesterol were associated with less increase in load-dependent YEM (Table 3).

In a second set of ANCOVA models that incorporated the change from exams 1 to 5 in IMT, diastolic diameter, SBP, and pulse pressure as covariates (Supplemental Material), race/ethnicity and educational attainment were no longer significantly associated with changes in YEM. Cessation of antihypertensive medication was still associated with increased total YEM ( $\beta=657$  mmHg;  $P=0.01$ ) and structural YEM ( $\beta=596$  mmHg;  $P=0.02$ ). Antihypertensive medication usage was no longer associated with the change in load-dependent

**Table 3. Multivariate ANCOVA Model for Change in YEM\***

	$\beta$	P value
Change in total YEM		
Age category (vs 75–84)		
45–54	−966	<0.001
55–64	−800	<0.001
65–74	−738	<0.001
HS education (vs did not graduate HS)	−380	0.04
HTN medication cessation (vs untreated)	1010	0.001
SBP (per 10 mmHg)	−140	<0.001
Change in structural YEM		
Age category (vs 75–84)		
45–54	−747	<0.001
55–64	−533	0.008
65–74	−544	0.006
HTN medication cessation (vs untreated)	840	0.003
Change in load-dependent YEM		
Age category (vs 75–84)		
45–54	−219	<0.001
55–64	−267	<0.001
65–74	−194	0.001
Black (vs mean)	58	<0.001
Chinese (vs mean)	−193	<0.001
HTN medication cessation (vs untreated)	170	0.05
Starting HTN medication (vs untreated)	−115	0.003
SBP (per 10 mmHg)	−167	<0.001
HDL cholesterol (per 10 mg/dL)	−44	<0.001

HDL indicates high-density lipoprotein; HS, high school; HTN, hypertension; SBP, systolic blood pressure; and YEM, Young elastic modulus.

\*Only significant predictors are included in the table.

YEM. Changes in SBP and pulse pressure had opposite associations with the different stiffness mechanisms. Increased change in SBP increased total YEM ( $\beta=193$  mmHg per 10 mmHg;  $P<0.001$ ), decreased structural YEM ( $\beta=-419$  mmHg per 10 mmHg;  $P<0.001$ ), and increased load-dependent YEM ( $\beta=612$  mmHg per 10 mmHg;  $P<0.001$ ). Increased change in pulse pressure increased total YEM ( $\beta=299$  mmHg per 10 mmHg;  $P<0.001$ ), increased structural YEM ( $\beta=737$  mmHg per 10 mmHg;  $P<0.001$ ), and decreased load-dependent YEM ( $\beta=-438$  mmHg per 10 mmHg;  $P<0.001$ ).

### Differences in Stiffness Mechanisms Based on Reference Pressure

Complete results from ANCOVA models using reference pressures of 105/70, 135/90, and 160/90 mmHg are presented in [Supplemental Material](#). Increasing the reference pressure from 120/80 to 135/90 or 160/90 increased the change in structural carotid artery stiffness and decreased the change in load-dependent carotid artery stiffness over the study period. Decreasing the

reference pressure to 105/70 had the opposite effect. For structural stiffness, statistical comparisons between age groups were unaffected by changing the reference pressure. For load-dependent stiffness, decreasing the reference pressure did not affect statistical results by age category, but increasing the reference pressure changed several comparisons between the 75- to 84-year age group and younger age groups to be non-significant. Besides age, the other strong predictors of change in load-dependent stiffness (race/ethnicity, starting antihypertensive medication, SBP, HDL cholesterol) were largely still significant predictors after increasing the reference pressure.

### Grouping by Mechanism

On average, structural stiffening accounted for the vast majority of total stiffening, but 27% ( $n=700$ ) and 37% ( $n=954$ ) of participants had more load-dependent than structural stiffening based on PEM and YEM, respectively. At baseline, participants with greater load-dependent stiffening were found to have lower SBP and diastolic BP compared with participants with greater structural stiffening (small-to-moderate effect, Hedges  $g$ ,  $-0.27$  to  $-0.49$ ). The participants with greater load-dependent stiffening were also found to have greater total stiffness (small-to-moderate effect, Hedges  $g$ ,  $0.31$ – $0.56$ ), greater structural stiffness (moderate-to-large effect, Hedges  $g$ ,  $0.50$ – $0.77$ ), lower load-dependent stiffness (small-to-moderate effect, Hedges  $g$ ,  $-0.40$  to  $-0.52$ ), and a thinner carotid artery wall (Hedges  $g$ ,  $-0.19$  to  $-0.36$ ). Demographics, diabetes status, smoking status, and lipid levels were similar among participants with greater load-dependent stiffening compared with participants with greater structural stiffening. Of note, participants with greater load-dependent stiffening were distributed evenly across age groups. Complete results of the exploratory analysis are presented in [Supplemental Material](#).

### DISCUSSION

This study is the first to quantify the age-associated longitudinal changes in structural and load-dependent carotid artery stiffness in a large, multiethnic cohort study with a decade of observation. The major finding of this study was that, on average, the vast majority of the age-associated increases in carotid artery stiffness were due to structural stiffening intrinsic to the arterial wall rather than being a concomitant effect of increased SBP with aging. The rates of both structural and load-dependent carotid artery stiffness increased with age. There was also large individual variability, with up to 37% of participants having greater load-dependent than structural stiffening, which was evenly distributed across age groups. The methods of this study will be

useful to evaluate whether therapies can be targeted to reduce structural arterial stiffness and if the deleterious CVD outcomes associated with greater stiffening can also be reduced.

Increased structural arterial stiffness is largely due to changes in the arterial wall including elastin degradation and collagen accumulation.<sup>7</sup> New elastin is not generated following the perinatal period, and the half-life of elastin is on the order of decades<sup>16</sup>; therefore, the progressive loss of arterial elastin is expected with aging. The combination elastin degradation and collagen accumulation with aging likely contribute to our finding that the rate of structural carotid artery stiffening increased with age. Besides age, the only predictor of increased changes in structural stiffness in primary ANCOVA models was stopping antihypertensive therapy. In secondary models, greater increases in intima-media thickness were also associated with smaller increases in structural stiffness (Supplemental Material). Intima-media thickening occurs at a greater rate in middle-aged individuals compared with older individuals<sup>10</sup> and may help prevent increases in structural arterial stiffness. Antihypertensive therapy use, baseline SBP, and baseline HDL cholesterol levels were all predictive of changes in load-dependent stiffness. This suggests that load-dependent stiffness is more modifiable than structural stiffness via traditional CVD risk factors, particularly as it relates to individual hypertension management. This discrepancy may also underlie why some but not all studies have found improvements in arterial stiffness with treatment of dyslipidemia.<sup>17–19</sup> The methods of this study will be useful in the assessment of therapies and interventions targeted at reducing structural arterial stiffness.

Van der Bruggen et al<sup>20</sup> used similar methods in the CATOD study to quantify changes in structural carotid artery stiffness in hypertensive individuals (58±9 years old) during a 3-year period. The major discrepancies were that the van der Bruggen group found a greater rate of change in structural stiffness and decreases in load-dependent stiffness while we found, on average, no change in load-dependent stiffness. These differences are likely due to the shorter follow-up period and enrollment criteria in CATOD that only included hypertensive individuals with less race/ethnicity and sex diversity than the MESA cohort.

Increased arterial stiffness is believed to be both a cause of hypertension and a consequence of hypertension, creating a positive and detrimental feedback loop through increased pulse pressure and both changes and structural stiffening over time.<sup>2</sup> However, clinical studies utilizing simultaneous carotid ultrasound and tonometry have shown that structural stiffness is not increased in hypertensive individuals,<sup>21,22</sup> indicating that increased arterial stiffness in hypertension is primarily due to load-dependent stiffening. The results of our longitudinal analysis support this finding as baseline SBP was a significant

predictor of changes in load-dependent stiffness but not changes in structural stiffness, which was predominantly driven by age. SBP and pulse pressure also had different longitudinal associations as greater increases in SBP increased load-dependent stiffness while greater increases in pulse pressure increased structural stiffness. The associations between changes in BP and arterial stiffness are likely bidirectional.<sup>2</sup> With regard to hypertension treatment, previous analysis in MESA found that starting and stopping antihypertensive medications were associated with decreased and increased carotid artery stiffness, respectively.<sup>10</sup> The results of the present analysis suggest that starting antihypertensive medication predominately decreased load-dependent stiffness while stopping antihypertensive medication had negative effects on both structural and load-dependent stiffness over the 10-year follow-up period. The mechanisms of how starting or stopping antihypertensive therapy may affect arterial stiffness also are likely dependent on the duration of therapy and the degree of BP control.<sup>23</sup>

While structural stiffening, on average, accounted for the vast majority of increases in carotid artery stiffness over a decade of aging, there was large variability with over 1/3 of participants having greater increases in load-dependent YEM than structural YEM. These participants had a unique pattern of baseline CVD risk factors with lower BP and thinner carotid artery walls, but higher total and structural carotid artery stiffness measures. The observed heterogeneity in mechanisms of arterial stiffness may impact the development of hypertension, CVD, or end organ damage. In patients with end stage renal failure, PWV not decreasing following a successful reduction in BP, possibly indicating elevated structural stiffness, was an independent predictor of both cardiovascular and all-cause mortality.<sup>24</sup> The association of arterial stiffness with incident hypertension, CVD events, and end organ outcomes, including kidney disease, should be a focus of future studies.

Previous analysis of arterial stiffness in MESA has identified associations between carotid artery stiffness, race/ethnicity, and socioeconomic status.<sup>8,10</sup> Novel findings of this study were that race/ethnicity and markers of socioeconomic status (indicated by higher education levels) were significantly associated with changes in load-dependent stiffening but not with structural stiffening over the 10-year period. This finding suggests that disparities in carotid artery stiffness are primarily due to BP control, which is clearly linked to socioeconomic status,<sup>25</sup> not due to intrinsic differences in the artery wall material. Limited access to healthcare and substandard insurance coverage have been identified as key factors driving racial/ethnic disparities in BP control.<sup>25</sup> Measuring differences in the mechanisms of arterial stiffness and targeting at-risk racial and ethnic groups could be a novel way to attempt to improve

these inequities in addition to improving health care access and insurance coverage.

## Limitations

The associations reported in this study cannot confirm causation due to the nonrandomized design. The participants in this analysis were only a subset of the MESA study. There may be a survivorship bias where participants who participated in exam 5 were healthier than the original MESA cohort, but we expect that this bias would increase the chances of a null finding. Like most epidemiological studies, brachial artery BPs were used in place of carotid artery BPs when calculating carotid artery stiffness. The difference between peripheral and central BP decreases with age, which would also result in methodological bias toward a null finding. Sensitivity analysis showed that comparisons of load-dependent stiffness between age groups were dependent on the choice of reference pressure. Differentiating structural from load-dependent stiffness inherently requires comparing stiffness at a common reference BP for all participants. We chose a reference pressure of 120/80, in part, based on prior studies suggesting that arterial stiffness measures should be reported at a standardized loading condition that lies in normal physiological ranges<sup>26</sup> and that a pressure of 120/80 mm Hg more or less represents the common perception of normal resting BP.<sup>27</sup> The other reason for choosing 120/80 mm Hg was to facilitate the comparison of quantitative results between studies.<sup>20</sup> Older studies have utilized simultaneous carotid tonometry and carotid ultrasound to calculate structural stiffness at 100<sup>21</sup> or 110 mm Hg.<sup>22</sup> Lastly, this study did not measure carotid-femoral pulse wave velocity, which is considered the gold standard measure of arterial stiffness.<sup>11</sup>

## Perspectives

The major finding of this study was that, on average, the vast majority of the age-associated increases in carotid artery stiffness were due to structural stiffening intrinsic to the arterial wall rather than being a concomitant effect of increased SBP. The longitudinal rates of structural and load-dependent carotid artery stiffening increased with age. There was high individual variability with a large portion of participants having greater load-dependent than structural stiffening. The heterogeneity in arterial stiffening mechanisms with aging may influence CVD development and warrants future investigation.

## ARTICLE INFORMATION

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## Disclosures

None.



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