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Sex Differences in Predictors of Longitudinal Changes in Carotid Artery Stiffness: The Multi-Ethnic Study of Atherosclerosis (MESA)

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Abstract

Objective—To identify sex differences in predictors of longitudinal changes in carotid arterial stiffness in a multi-ethnic cohort.

Approach and Results—Carotid artery distensibility coefficient (DC) and Young's Elastic Modulus (YEM) were measured in 2650 Multi-Ethnic Study of Atherosclerosis participants (45-84 years old and free of cardiovascular disease) at baseline and after a mean of 9.4 years. Predictors of changes in DC and YEM for each sex were evaluated using multivariable linear regression models.

The 1236 men (46.6%) were 60.0 (standard deviation 9.3) years; 40% were White, 22% Black, 16% Chinese, and 22% Hispanic. The 1414 (53.4%) women were 59.8 (9.4) years old with a similar race distribution. Despite similar rates of change in DC and YEM, predictors of changes in distensibility markers differed by sex. In men, Chinese (p=0.002) and Black (p=0.003) race/ethnicity, systolic blood pressure (p=0.012), and diabetes mellitus (p=0.05) were associated with more rapidly decreasing DC (accelerated stiffening). Starting antihypertensive medication was associated with improved DC (p=0.03); stopping anti-hypertensives was associated with more rapid stiffening (increased YEM, p=0.05). In women, higher education was associated with slower stiffening (DC p=0.041; YEM p<0.001) as was use of lipid-lowering medication (p=0.03), whereas baseline use of antihypertensive medications (YEM p=0.01) and systolic blood pressure (DC p=0.02; p=0.04) predicted increasing stiffening in women.

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Conclusions—Longitudinal changes in carotid artery stiffness are associated with systolic blood pressure and antihypertensive therapy in both sexes; however, race/ethnicity (in men) and level of education (in women) may have different contributions between the sexes.

Keywords

Arterial stiffness; Cardiovascular disease; Carotid arteries; Sex differences; Women; Young's elastic modulus

Introduction

Arterial stiffening is associated with development of hypertension, a risk factor for renal disease, heart failure, coronary artery disease, and stroke, particularly among the elderly.[1-6] With aging, arterial stiffening leads to increased pulse wave velocity and pulse pressure, thereby predisposing individuals to hypertension, increased left ventricular afterload, and impaired coronary perfusion.[2] Pathophysiological changes induced by hypertension include increased total peripheral resistance and decreased arterial compliance, ultimately limiting arterial distensibility.[2] An analysis from the Multi-Ethnic Study of Atherosclerosis (MESA) showed significant cross-sectional differences between the sexes in carotid distensibility;[7] however, longitudinal sex-related differences in age-related arterial stiffening and its predictors have not been described previously.

The MESA, a large, well-characterized, longitudinal and multi-ethnic cohort in which participants were free of clinical cardiovascular disease (CVD) at baseline, is ideal for evaluating and characterizing longitudinal associations of sex differences in carotid distensibility and elasticity. We describe sex-related differences in ultrasound measures of carotid arterial stiffness and distensibility in the MESA after nearly one decade of follow-up.

Materials and Methods

Materials and Methods are available in the online-only Data Supplement.

Results

Participant Characteristics at Examination 1

At exam 1, men and women were similar in regard to age and race/ethnicity (Table 1). At exam 1, 441 (31.2%) women were current users of hormone replacement therapy with a duration of 9.9 (8.4) years. At exam 5, only 107 (7.6%) were hormone replacement therapy users. Overall, baseline DC did not differ significantly by sex, but expected sex-related differences were seen in artery sizes, thicknesses, and in certain CVD risk factors. YEM was higher in men, indicating stiffer arteries; men also had thicker carotid walls and artery sizes. As in a previous report from our group, males and females had similar rates of changes in DC and YEM (Table 1).[8] At exam 1, African-American men and women had the lowest baseline DC (indicating more stiff arteries); whereas, Chinese men and women had the highest baseline YEM (also indicating more stiff arteries). Caucasian men and women had the best distensibility measures. African-American men and women had significantly higher mean systolic and diastolic blood pressure, body-mass index, proportions with hypertension

and using antihypertensive treatment, and carotid wall thickness (Data Supplement IV, Supplementary Tables IV-A and IV-B).

Sex Differences in Predictors of Changes in Distensibility Coefficient and Young's Elastic Modulus

In models adjusted for baseline stiffness, men and women had different predictors of the rate of change in distensibility markers (Tables 2 and 3). Multivariate regression model goodness of fit measures were higher for changes in DC (Model 1: Men adjusted R^2=0.35, women adjusted R^2=0.34) compared to changes in YEM, (Model 1: Men R^2=0.13, women adjusted R^2=0.18). Age was a significant independent predictor of changes in DC and YEM in both men (DC β=-0.014, p<0.01; YEM β=14.2, p<0.01) and women (β=-0.027, p<0.01; YEM β=21.0, p<0.01) after adjusting for traditional CVD risk factors, treatments, ethnicity, and education.

Among men, Chinese (β=-0.267, p<0.01) and Black race/ethnicity (β=-0.210, p<0.01), compared to White race/ethnicity, were associated with decreasing DC, indicating more rapid stiffening. A weaker association was observed for systolic blood pressure (β=-0.004, p=0.01) and treated diabetes mellitus (β=-0.206, p<0.05). Among men, starting antihypertensive medications was associated with improvements in DC (β=0.155, p=0.03) and stopping antihypertensive therapy was weakly associated with increasing YEM (β=362.8, p<0.05), indicating more rapid arterial stiffening. These associations were similar in unadjusted models (Data Supplement IV).

Among women, higher education level was associated with increasing DC (β=0.170, p=0.04) and decreasing YEM (β=-400.6, p<0.01), indicating a protective effect in regard to arterial stiffening over time (Tables 2 and 3). Baseline use of lipid-lowering medications also was associated with decreasing YEM (β=-209.3, p=0.03). As with DC in men, higher systolic blood pressure at exam 1 was associated with increasing stiffness (DC β=-0.003, p=0.02; YEM β=3.6, p=0.04). Use of antihypertensive therapy at baseline also was associated with increasing YEM in women (β=195.4, p=0.01). When the models in Tables 2 and 3 were re-run after excluding education, no major changes were observed.

When formally tested for interactions with sex, the following variables demonstrated differences between the sexes. For DC, age (p=0.003) and total cholesterol (p=0.04). For YEM, education category (p=0.05) and use of lipid-lowering medication (p=0.05).

At baseline, a higher percentage of females compared to males were hypertensive (42.6% and 39.8%, respectively, p=0.15) and used antihypertensive medication (33.4% and 31.7%, respectively, p=0.36), but these differences were not statistically significant. A similar trend was observed after one decade, including a non-significantly higher proportion of hypertensive females than males (61.2% and 58.8%, respectively, p=0.203) and greater antihypertensive medication use among women (53.0% and 51.9%, respectively, p=0.57). Menopausal status did not have a significant impact on the rate of change in DC (β=-0.113, p=0.15) or YEM (β=-12.3, p=0.90). When formally tested for interactions with menopausal status, neither antihypertensive medication use in model 1 nor antihypertensive medication

category in model 2 were significant for either change in DC (p=0.25 in model 1 and p=0.68 in model 2) or change in YEM (p=0.88 in Model 1 and p=0.98 in Model 2).

Trends in Distensibility Coefficient and Young's Elastic Modulus by Sex and Decade

Among those aged 45-54 years at baseline, women had significantly higher (less stiff) DC (p=0.003) than men. Beyond 55 years of age, DC was similar among the sexes (Table 4). Similarly, women in the youngest age category (45-54 years) had a lower YEM than men of similar age. However, in the oldest age group (ages 75-84 years) women had a significantly higher YEM compared to men. Comparisons by decade showed no significant differences in baseline DC and YEM by sex between ages 55-64 and 65-74 years of age. Further analyses by decade revealed that men and women had similar rates of change of YEM, though not DC in the youngest age decade (Table 5). The greatest changes in age-related stiffening for both men and women occurred in the oldest decades (ages 75-84 years) for DC and YEM. These findings are consistent with our prior analysis of carotid distensibility changes in MESA.[7]

Discussion

Despite similar rates of change in DC and YEM between men and women, this analysis highlights different predictors of change in carotid arterial stiffness parameters between the sexes over nearly a decade of follow-up. Sex-specific analyses revealed very consistent results. In men, Chinese and Black race/ethnicity compared to White ethnicity and baseline systolic blood pressure were associated with more rapid stiffening (decreasing DC) whereas starting antihypertensive medication was associated with improved DC. Stopping antihypertensive medications was associated with increased stiffening (higher YEM). In women, higher education level was associated with slower rates of stiffening. Baseline use of lipid-lowering medication also predicted slower stiffening; however, baseline use of antihypertensive therapy and higher systolic blood pressure also predicted increasing YEM in women. Despite age-related differences in stiffness between men and women, these observations seem to be unrelated to menopausal status.

A previous report from MESA found that the rate of change in distensibility markers did not differ significantly by ethnicity.[8] However, our data showed that stratified by gender, Chinese and Black race/ethnicity were strongly associated with worsening DC in men. Our findings of YEM progression in men are consistent with results from The Northern Manhattan Study, which found greater arterial stiffening with older age among Hispanics compared to Blacks or Caucasians.[9] Sex-stratified models were also consistent with higher baseline (cross-sectional) stiffness in Hispanics and Blacks compared to Whites in that study. Our previous report from MESA described longitudinal improvements in DC among participants who started antihypertensive therapy.[8] This subsequent analysis only identified strong effects of starting or stopping antihypertensive medications on the progression rates of distensibility markers in men. This may be due to metabolic differences between men and women,[10-13] because differing effects of antihypertensive therapy in women, because women start antihypertensive therapy with more advanced arterial stiffness, so the effects of

antihypertensive therapy may be blunted,[14,15] or may reflect delays to the diagnosis and under-treatment of hypertension in women.[16,17]

In women, baseline carotid stiffness measures were significantly worse after age 75 years, suggesting that older women bear a greater cardiac afterload than men and may be more predisposed to heart failure.[7] Sex-related differences in the effects of antihypertensive therapy on distensibility progression may reflect lower control rates in older hypertensive women than men despite greater awareness and higher treatment rates among women.[18,19] Though some studies reported non-significant differences in control rates by sex,[20] our data shows that among treated hypertensives at baseline, men had better hypertension control. Similar findings were observed among treated hypertensives at examination 5; however, the sex differences were not statistically significant. Age-related increases in CVD morbidity and mortality may reflect hormonal changes following the menopausal transition leading to a higher incidence of systolic hypertension and rapid arterial stiffening in women, though we were not able to identify an effect of menopause in our analyses.[21,22] Sex differences in preventive treatments also have been described among older women with prior history of myocardial infarction, who were less likely to receive lipid-lowering medication following an event and were less frequently treated with aspirin, beta-blockers or thrombolytic therapy during an acute event coronary syndrome.[23,24]

Given these imbalances, our data suggest that healthcare providers should address hypertension promptly and aggressively to help women optimize blood pressure control before arterial stiffness is evident or too far advanced, especially among women of low educational status. Early and effective blood pressure management may help limit progressive increases in YEM in women. Additional studies are needed to determine the degree to which hormonal imbalances and estrogen receptor activity contribute to arterial aging, and how the interaction of antihypertensive treatment with hormone replacement therapies affects distensibility progression.

Another important observation was that higher education status among women was strongly associated with slowing the progression of YEM and limiting the decline of DC. CVD risk factors are related inversely to educational status, a reliable marker of socioeconomic status that is closely associated with CVD risk factors.[25,26] Previous studies also have found that over time, the gap in educational inequalities widened for women but persisted or narrowed for men, suggesting increased susceptibility to CVD for the lowest-educated women.[27] Socioeconomic determinants including education and income likely contributed to CVD risk factor profiles. Educational status among women favored Caucasians and African Americans, particularly beyond high school. Hispanic and Chinese women were most disadvantaged in terms of education and income, and both groups had the highest (worst) baseline YEM.

Men in the youngest age category demonstrated stiffer vessels at baseline with a more rapid progression over the observation time period. Accelerated stiffening in younger men suggests earlier concentric remodeling, which may occur in order to accommodate blood pressure and larger arterial diameter. Adverse arterial remodeling is assessed by YEM, which takes into account wall thickness. Women in the oldest age category had the stiffest

vessels at baseline, but experienced a similar rate in progression as men over the decade. The advanced stiffness in the oldest women at baseline may reflect higher prevalence of systolic hypertension[21,28] or impaired remodeling due to genetic or hormonal differences. Though we did not observe a significant association between menopause and stiffness progression in women, other studies have found that for post-menopausal women, the loss of estrogenic activity in arterial walls contributes to decreased elasticity and rapid stiffening.[21] The rate of decline in DC was most dramatic for both sexes between ages 75-84 years and was significant compared to each other decade within each sex. Among those aged >75 years, the rate of change in DC and YEM may have been blunted by floor and ceiling effects, meaning that there was minimal physiological capacity to stiffen more among the oldest participants with the most advanced degree of stiffening.

Limitations

As previously reported,[8] there was not a significant interaction between sex and changes in DC or YEM, so the data in this report are subset analyses that attempt to describe and understand the differences in predictors of changes in carotid arterial stiffness measures among the sexes. When considering the sexes separately, our power to identify formal interactions was limited, though formal interaction testing did identify consistent differences for the effects of age, total cholesterol level, education category, and use of lipid-lowering medications that were consistent with our separate models for each sex. This report still is the largest assessment of sex-specific effects on progressive arterial stiffening to date. As an observational study, albeit a longitudinal one, this study is subject to certain biases and the possibility of residual confounding. For example, the findings related to educational status and stiffness in women may be explained by a factor correlated with it, such as nutritional quality, access to health care, air quality, or unmeasured factors. Also, these data are from a subset of MESA participants with valid distensibility measurements at baseline and exam 5. Those who survived to or who participated in exam 5 are healthier than those who did not, though this would be expected to create a null bias and limit identification of significant but weaker associations with the outcome measures. Because we only had stiffness measures at Exams 1 and 5, intermediate changes, the shape of the arterial stiffness progression curve, and our ability to discern cause and effect are limited. In this report, we used brachial artery blood pressures. Carotid artery blood pressures may vary because of pulse pressure amplification, which likely changed with aging and differs by height and sex; however, measurement of carotid blood pressures or waveforms in a large cohort was not feasible at the inception of this study.[2,22] This technique used in this report has been adequate to find expected associations with risk factors for DC and YEM and aortic calcification in MESA in multiple previous publications.[7,8,29,30] Finally, as a longitudinal observational study, we cannot exclude the possibility that some of our findings may be affected by unconsidered confounding. For example, the effect of educational status on longitudinal changes in DC and YEM likely is mediated by a physiological factor not captured in our models. To investigate this, we re-ran the full models in Tables 2 and 3 after excluding educational status; however no major changes were detected.

Conclusions

Changes in carotid artery stiffness parameters over a decade are associated with blood pressure and antihypertensive therapy in both men and women. However, in men, race/ethnicity, and in women, educational level, may have differential contributions. These observations have implications for the pathophysiology and clinical management of age-related arterial stiffening. There is acceleration in arterial stiffening after age 75 years for both men and women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

CVD	cardiovascular disease
DC	distensibility coefficient
HDL	high-density lipoprotein
MESA	Multi-Ethnic Study of Atherosclerosis
YEM	Young's Elastic modulus

Significance

These findings emphasize the importance of identifying and treating hypertension to prevent its arterial complications in both sexes. Extra attention should be focused on Black and Chinese men as well as women with low education status as these subgroups had more rapid stiffening. These findings have implications for the pathophysiology of arterial stiffening and hypertension.

Table 1

Participant Characteristics

	Men (N=1236)	Women (N=1414)	*P*-value
Age, years	60.0 (9.3)	59.8 (9.4)	0.72
Race/Ethnicity, %			**0.01**
White	498 (40.3)	541 (38.3)	
Black	275 (22.2)	385 (27.2)	
Chinese	195 (15.8)	185 (13.1)	
Hispanic	268 (21.7)	303 (21.4)	
Blood pressure parameters			
Systolic blood pressure, mmHg	123.5 (18.1)	123.2 (21.5)	0.66
Diastolic blood pressure, mmHg	75.1 (9.1)	68.6 (10.0)	**<0.001**
Hypertension, %	492 (39.8)	602 (42.6)	0.15
Use of antihypertensive medications, %	392 (31.7)	472 (33.4)	0.62
Lipids			
Total cholesterol, mg/dL	187.3 (33.5)	200.0 (35.1)	**<0.001**
High-density lipoprotein cholesterol, mg/dL	44.8 (11.4)	57.4 (15.4)	**<0.001**
Use of lipid-lowering medications, %	205 (16.6)	195 (13.8)	**<0.05**
Body-mass index, kg/m^2	27.4 (4.0)	28.0 (5.7)	**0.001**
Diabetes mellitus status, %			0.08
None	934 (44.3)	1176 (55.7)	
Impaired fasting glucose	184 (14.9)	133 (9.41)	
Untreated	25 (2.0)	17 (1.2)	
Treated	93 (7.5)	88 (6.2)	
Smoking, %			**<0.001**
Former	539 (43.6)	401 (28.4)	
Current	145 (11.7)	152 (10.8)	
Distensibility coefficient, 10^{-3} $mmHg^{-1}$	3.1 (1.2)	3.1 (1.3)	0.43
Change in Distensibility Coefficient, 10^{-3} $mmHg^{-1}$	-0.41 (1.1)	-0.39 (1.1)	0.60
Young's elastic modulus, mmHg	1623 (926)	1543 (926)	0.03
Change in Young's Elastic Modulus, mmHg	160.7 (1241)	174.0 (1281)	0.79
Carotid wall thickness, cm	0.075 (0.016)	0.072 (0.014)	**<0.001**
Carotid artery peak systolic internal diameter, cm	0.654 (0.076)	0.603 (0.007)	**<0.001**
Carotid artery end-diastolic internal diameter, cm	0.608 (0.070)	0.557 (0.061)	**<0.001**

All values are mean (standard deviations)

Table 2

Predictors of Changes in Distensibility Coefficient

Predictors	Men		Women	
	Beta, 95% Confidence Intervals (10^{-3} mmHg^{-1})	P-value	Beta, 95% Confidence Intervals (10^{-3} mmHg^{-1})	*P*-value
Model 1				
Age	-0.014 [-0.206, -0.008]	**<0.001***	-0.027 [-0.034, -0.020]	**<0.001***
Baseline Distensibility Coefficient (10^{-3} mmHg^{-1})	-599.60 [-646.89, -552.30]	**<0.001***	-609.11 [-655.36, -562.85]	**<0.001***
Chinese race/ethnicity	-0.267 [-0.431, -0.103]	**0.002***	-0.068 [-0.242, 0.107]	0.45
Black race/ethnicity	-0.210 [-0.348, -0.072]	**0.003***	-0.103 [-0.236, 0.029]	0.13
Hispanic race/ethnicity	-0.121 [-0.273, -0.030]	0.12*	0.003 [-0.147, 0.152]	0.97
Body-mass index (kg/m^2)	0.003 [-0.012, 0.017]	0.72	-0.009 [-0.019, 0.002]	0.10*
Impaired fasting glucose	0.025 [-0.123, 0.172]	0.74	0.020 [-0.158, 0.198]	0.82
Diabetes without treatment	-0.014 [-0.378, 0.350]	0.94	-0.323 [-0.773, 0.126]	0.16
Diabetes with treatment	-0.206 [-0.409, -0.002]	**<0.05**	-0.142 [-0.364, 0.081]	0.21
Total cholesterol (mg/dL)	0.002 [5.470×10^{-5}, 0.003]	**0.05***	-3.250 ×10^{-5} [-0.002, 0.001]	0.97
High-density lipoprotein cholesterol (mg/dL)	0.003 [-0.002, 0.008]	0.19	8.735 ×10^{-4} [-0.003, 0.004]	0.62
Former smoking	-0.0051 [-0.114, 0.103]	0.93	0.052 [-0.066, 0.171]	0.39
Current smoking	0.025 [-0.144, 0.194]	0.78	0.020 [-0.152, 0.192]	0.82
Baseline systolic blood pressure	-0.004 [-0.007, 9.035×10^{-4}]	**0.01***	-0.003 [-0.006, 4.357 ×10^{-4}]	**0.02***
Baseline use of lipid-lowering medication	-0.012 [-0.156, 0.132]	0.87	0.133 [-0.018, 0.284]	0.08
Baseline use of antihypertensive medication	-0.059 [-0.180, 0.062]	0.34	-0.033 [-0.150, 0.083]	0.57
High school graduate	0.048 [-0.160, 0.255]	0.65*	0.174 [-0.004, 0.352]	**0.05***
Greater than high school education	0.165 [-0.011, 0.342]	0.07*	0.170 [0.007, 0.334]	**0.04***
Menopause	-	-	-0.113 [-0.267, 0.041]	0.15
Model 2*				
Starting antihypertensive medication	0.155 [0.017, 0.292]	**0.03***	0.081 [-0.060, 0.222]	0.26
Stopping antihypertensive medication	0.077 [-0.198, 0.352]	0.58*	-0.251 [-0.577, 0.074]	0.13

Predictors	Men		Women	
	Beta, 95% Confidence Intervals (10^{-3} $mmHg^{-1}$)	P-value	Beta, 95% Confidence Intervals (10^{-3} $mmHg^{-1}$)	*P*-value
Antihypertensive medication use baseline and exam 5	0.002 [-0.140, 0.145]	0.97*	-0.029 [-0.108, 0.167]	0.67

Models were adjusted for baseline distensibility coefficient, age, ethnicity, education, diabetes mellitus, smoking, total and high-density lipoprotein cholesterol, body-mass index, systolic blood pressure, antihypertensive treatment, and menopausal status (in models restricted to females).

Model 2 used same covariates as Model 1 except replaced baseline use of antihypertensive medication in Model 1 with 4 categories: starting, stopping or continuing anti-hypertensive medications (compared to not taking anti-hypertensive medications throughout the observational period. Only those coefficients and standard deviations are provided since the others were very similar.

*Variables with significance at $p<0.10$ in a parsimonious backwards regression model.

Table 3

Predictors of Changes in Young's Elastic Modulus

Predictors	Men		Women	
	Beta, 95% Confidence Intervals (mmHg)	P-value	Beta, 95% Confidence Intervals (mmHg)	*P*-value
Model 1				
Age	14.2 [6.4, 22.1]	**<0.001***	21.0 [12.0, 30.0]	**<0.001***
Baseline Young's Elastic Modulus (mmHg)	-0.5 [-0.5, -0.4]	**<0.001***	-0.6 [-0.6, -0.5]	**<0.001***
Chinese race/ethnicity	152.0 [-60.3, 364.4]	0.16	108.2 [-115.9, 332.4]	0.34*
Black race/ethnicity	65.9 [-112.4, 244.2]	0.47	101.1 [-68.3, 270.5]	0.24*
Hispanic race/ethnicity	6.9 [-189.2, 203.1]	0.94	-144.2 [-335.8, 47.4]	0.14*
Body-mass index (kg/m^2)	0.07 [-18.9, 19.0]	0.99	-1.6 [-15.1, 11.8]	0.81
Impaired fasting glucose	-63.0 [-254.6, 128.6]	0.52	-61.1 [-289.4, 167.2]	0.60
Diabetes without treatment	-82.8 [-554.9, 389.3]	0.73	486.1 [-90.3, 1062.5]	0.10
Diabetes with treatment	134.0 [-130.2, 398.2]	0.32	176.6 [-108.7, 461.8]	0.22
Total cholesterol (mgdL)	-1.6 [-3.6, 0.5]	0.14*	-0.7 [-2.6, 1.2]	0.47
High-density lipoprotein cholesterol (mgdL)	-2.7 [-8.9, 3.4]	0.38	2.1 [-2.4, 6.6]	0.37
Former smoking	-90.0 [-230.9, 50.8]	0.21	-121.7 [-273.6, 30.2]	0.12
Current smoking	-56.3 [-275.2, 162.6]	0.61	-43.6 [-263.7, 176.6]	0.70
Baseline systolic blood pressure	0.2 [-3.9, 4.2]	0.93	3.6 [0.1, 7.0]	**0.04***
Baseline use of lipid-lowering medication	77.7 [-109.0, 264.3]	0.41	-209.3 [-402.7, -15.8]	**0.03***
Baseline use of antihypertensive medication	133.8 [-23.8, 291.5]	0.10*	195.4 [45.5, 345.3]	**0.01***
High school graduate	29.9 [-239.5, 299.3]	0.82	-447.4 [-675.3, -219.5]	**<0.001***
Greater than high school education	-92.7 [-321.7, 136.3]	0.43	-400.6 [-610.9, -190.3]	**<0.001***
Menopause	-	-	-12.3 [-209.6, 184.9]	0.90
Model 2*				
Starting antihypertensive medication	-123.6 [-301.8, 54.5]	0.17*	-83.6 [-264.6, 97.4]	0.37*
Stopping antihypertensive medication	362.8 [5.9, 719.7]	**<0.05***	259.4 [-158.4, 677.2]	0.22*
Antihypertensive medication use at Baseline and exam 5	32.6 [-152.0, 217.2]	0.73*	146.2 [-30.6, 323.1]	0.10*

Models were adjusted for baseline Young's Elastic Modulus and as in Table 2.

Table 4

Decade Trends in Adjusted* Mean Baseline Stiffness Measures

Baseline Age Decade (years)	Distensibility Coefficient at Exam 1 (10^{-3} mmHg $^{-1}$)			Young's Elastic Modulus at Exam 1 (mmHg)		
	Men	Women	P-value	Men	Women	P-value*
45-54	3.36	3.59	**0.002**	1631.5	1451.6	**0.003**
55-64	3.00	2.95	0.54	1714.1	1597.3	0.07
65-74	2.66	2.63	0.71	1740.0	1726.9	0.84
75-84	2.46	2.33	0.41	1741.3	2013.7	**0.04**

*Adjusted for ethnicity, education, diabetes mellitus, smoking, total and high-density lipoprotein cholesterol, body-mass index, systolic blood pressure, lipid-lowering medication, and antihypertensive treatment

Table 5

Decade Trends in Adjusted* Mean Progression of Stiffness Measures

Baseline Age Decade (years)	Change in Distensibility Coefficient (10^{-3} mmHg $^{-1}$)			Change in Young's Elastic Modulus (mmHg)		
	Men	Women	P-value	Men	Women	P-value
45-54	-0.36	-0.18	**0.004**	188.7	87.8	0.21
55-64	-0.44	-0.50	0.39	235.1	245.7	0.90
65-74	-0.61	-0.67	0.47	338.8	289.4	0.59
75-84	-0.84†	-0.87†	0.80	755.6†	850.6†	0.58

*Adjusted for baseline distensibility coefficient or Young's Elastic Modulus and as in Table 4.

†p<0.05 compared to each other decade within each sex