Journal of the American Heart Association

ORIGINAL RESEARCH

Sex Differences in Longitudinal Determinants of Carotid Intima Medial Thickening With Aging in a Community-Dwelling Population: The Baltimore Longitudinal Study on Aging

Ajoy C. Karikkineth, MD*; Majd AlGhatrif, MD, MA*; Matt T. Oberdier, PhD; Chris Morrell, PhD; Elango Palchamy, PhD; James B. Strait, MD; Luigi Ferrucci, MD; Edward G. Lakatta, MD*

BACKGROUND: Common carotid intima medial thickness (IMT) increases with aging. However, the longitudinal association between IMT and other age-associated hemodynamic alterations in men and in women are not fully explored.

METHODS AND RESULTS: We analyzed repeated measures of IMT, blood pressure, and carotid-femoral pulse wave velocity over a 20-year period in 1067 men and women of the Baltimore Longitudinal Study on Aging; participants were ages 20 to 92 years at entry and free of overt cardiovascular disease. Linear mixed-effects models were used to calculate the individual rates of change ($_{Change}$) of IMT, pulse pressure, mean arterial pressure, and pulse wave velocity, among other covariates. Multivariate regression analysis was used to examine the association of IMT_{Change} with baseline and rates of change of hemodynamic parameters and cardiovascular risk factors. IMT increased at accelerating rates from 0.02 mm/decade at age 50 years to 0.05 mm/decade at age 80 years greater rates in men than in women. IMT_{Change} was positively associated with baseline low-density lipoprotein, low-density $lipoprotein_{Change}$, and baseline systolic blood pressure and $systolic\ blood\ pressure_{Change}$, but inversely with baseline diastolic blood pressure and $diastolic\ blood\ pressure_{Change}$. When blood pressure was expressed as pulse pressure and MAP, IMT_{Change} was positively associated with baseline pulse pressure and $pulse\ pressure_{Change}$ and inversely with baseline mean arterial pressure and $mean\ arterial\ pressure_{Change}$. In sex-specific analysis, these associations were observed in women, but not in men.

CONCLUSIONS: In summary, our analyses showed that IMT increases at accelerating rates with aging. Age-associated changes in IMT were modulated by concurrent changes of low-density lipoprotein in both sexes, and of pulsatile and mean blood pressure in women but not men.

Key Words: aging ■ hypertension ■ intima-medial thickness ■ longitudinal

Common carotid artery intima medial thickness (IMT) is a surrogate measure of intimal smooth muscle cell migration, proliferation, and inflammation and is considered a marker of arterial aging.[1] IMT has also been found to be independently associated with incident cardiovascular events, including myocardial infarction and stroke,[2–4] and hence used as a marker for atherosclerosis and an end point in clinical trials aimed at atherosclerosis prevention and treatment.[5]

Correspondence to: Majd AlGhatrif, MD, MA, Laboratory of Cardiovascular Science, National Institute on Aging, NIH, Biomedical Research Center, 251 Bayview Blvd, Suite 100, Baltimore, MD 21224-6825. E-mail: majd.alghatrif@nih.gov

Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.015396

*Dr Karikkineth, Dr AlGhatrif, and Dr Lakatta contributed equally to this work.

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Intima medial thickness progression in this community-dwelling population increased with aging, with men and those of Black race having greater increase compared with women, and nonblack race, respectively.
- Age-associated intima medial thickness progression is exaggerated with higher low-density lipoprotein, increased pressure pulsatility, and reduced mean blood pressure, with women being more prone to the adverse outcomes of pulsatile pressure on intima medial thickness progression.

What Are the Clinical Implications?

- Additional studies are needed to explore mechanistic pathways linking pulse pressure to intima medial thickness progression and the role of interventions that reduce pulse pressure, beyond traditional blood pressure control, to halt intimal medial thickening with aging.

Nonstandard Abbreviations and Acronyms

BLSA	Baltimore Longitudinal Study of Aging
DBP	diastolic blood pressure
DBP_{Change}	rate of change of DBP
IMT	intima medial thickness
IMT_{Change}	rate of change of IMT
LDL_{Change}	rate of change of LDL
PP	pulse pressure
PP_{Change}	rate of change of PP
PWV	pulse wave velocity
PWV_{Change}	rate of change of PWV
SBP	systolic blood pressure
SBP_{Change}	rate of change of SBP

Cross-sectional[6] and longitudinal studies,[7,8] however, have shown that the association between IMT and traditional atherogenic risk factors such as blood pressure and dyslipidemia were dwarfed by its dominant association with age. In addition to this, other manifestations of arterial aging (ie, systolic and pulse pressure and arterial stiffness parameters) demonstrate the strongest correlations with IMT in cross-sectional studies.[9,10]

While these findings suggest a primary role of arterial aging and its associated blood pressure changes in IMT progression, to our knowledge, no studies have explored the patterns of longitudinal change in IMT with aging over a broad age range, nor its association with other age-associated hemodynamic changes; namely, rising blood pressure pulsatility and central arterial stiffness are not fully explored. In addition, such longitudinal data on IMT change would also provide an integrative parameter that captures the cumulative burden of the various cardiovascular risk factors.

To this end, we analyzed repeated measures of IMT in a population across a wide age range within the BLSA (Baltimore Longitudinal Study of Aging). We aimed to determine the following: (1) the patterns and rates of the longitudinal change in IMT over time by age and sex, (2) the association of changes over time in the different blood pressure parameters with parallel changes in IMT and the role of sex, and (3) the association of arterial wall stiffening over time with time-dependent IMT progression by age and sex.

METHODS

Study Population

The BLSA is a prospective study of community-dwelling volunteers. Participants, who vary in age at entry, visit the National Institute on Aging in Baltimore approximately every 2 years for nearly 3 days of medical, physiological, and psychological examinations. Repeated carotid IMT measurements and medical and physiological assessments between 1994 and 2016 were performed on a subset of BLSA participants. Participants selected were free of overt cardiovascular disease and cerebrovascular disease: myocardial infarctions, angina, heart failure, strokes, and transient ischemic attacks. The final sample consisted of 1067 participants and a total of 3001 visits. The number of visits ranged from 2 to 9 per person, with a follow-up duration of at most 19.9 years. Written, informed consent was obtained from all study participants. The BLSA has continuing approval from the Institutional Review Board of the National Institutes of Health. In addition, all institutional guidelines and protocols were followed. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Common Carotid IMT

The details of the methodology followed in the BLSA have been published previously.[11] In summary, carotid IMT was measured using high-resolution B-mode ultrasonography of the right common carotid artery via a linear array, 5- to 10-MHz transducer (Ultramark 9 HDI, Advanced Technology Laboratories, Inc). A

region 1.5 cm proximal to the carotid bifurcation was identified, and the IMT of the far arterial wall was evaluated as the distance between the lumen/intimal interface and the medial/adventitial interface. IMT was measured on a frozen-frame image, magnified to achieve higher resolution. The IMT measurement was obtained from 5 contiguous sites at ≈1-mm intervals; the mean of these values was used in statistical analyses.

Areas of plaque were avoided. Interobserver correlation between repeated carotid IMT measurements on 10 BLSA participants was 0.96 ($P<0.001$). Our analysis included data from 2 time periods, pre-2000 and post-2000, during which IMT was measured by the 2 different methodologies. To account for measurement differences by methodology, adjustments were made according to techniques used in the BLSA to account for device changes[12] (Table S1). Additionally, we adjusted for date of visit in our statistical models to account for any other secular changes over time.

Measures of Arterial Pressure

Bilateral resting brachial systolic and diastolic blood pressure values were obtained 3 times with subjects in the seated position after a 5-minute resting period using an automated oscillometric blood pressure cuff machine. Pulse pressure (PP) was calculated as the difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Pulse Wave Velocity

Details of measurement of pulse wave velocity (PWV) in the BLSA have been described previously.[12] Briefly, carotid-femoral PWV was calculated as the distance traveled by the pulse wave divided by the time difference between the feet of carotid and femoral arterial waveforms gated to an ECG. The distance traveled by the pulse wave was measured to the nearest centimeter with an external tape measure over the body surface.

Other Covariates

Covariate data were collected at each BLSA visit. Age (based on self-reported date of birth) was assessed in years. Height and weight were measured on all participants. Waist circumference was measured as the minimal abdominal circumference between the lower edge of the rib cage and the iliac crests. Smoking status was defined as ever versus never having been a smoker. Concentrations of total cholesterol were determined enzymatically (ABA-200 ATC Biochromatic Analyzer; Abbott) after an overnight fast; blood for lipid assay was drawn from an antecubital vein between 7:00 and 8:00 AM. Further details of covariates (LDL [low-density lipoprotein], HDL [high-density lipoprotein], triglycerides, body mass index [BMI], glucose, and antihypertensive and lipid medications) have been published previously.[12,13]

Status of hypertension, diabetes mellitus, and hyperlipidemia (present or absent) was assessed from the medical history questionnaire. If participants had a history of any of these 3 conditions, we also checked if they reported being on medications, and if on medications, whether the medications helped (controlled or not). Disease status as "controlled" was defined as SBP <120 mm Hg and DBP <80 mm Hg for hypertension, fasting blood glucose <100 mg/dL for diabetes mellitus, and total cholesterol <200 mg/dL for hyperlipidemia.

Among women, we also checked for menopausal status as per self-report, and whether the participant had ever been on hormone replacement therapy (estrogen or progesterone). Additionally, if data were missing regarding menopausal status, those older than age 60 years were classified as menopausal. However, there were still some missing data, which were classified accordingly. A subset analysis including menopausal status was conducted separately.

Statistical Analysis

Baseline characteristics, stratified by sex, were reported and compared by Student t test and χ^2 test. Linear mixed-effects models, the best available analytical tools for unbalanced, unequally spaced observations such as those of the BLSA, were utilized to assess average longitudinal trajectories and estimate individual rates of change of indexed parameters.

The rates of change ($_{Change}$) for IMT and covariates for each individual were calculated from separate linear mixed-effects models regressing each of the index variables against Time as a random-effect variable. Beta coefficients of the random effects were used to calculate individual rates of changes for each of the variables analyzed.[14] Individual rates of changes were indicated by the index variable with rates of change as a subscript; refer to Data S1 for further details.

Multivariate linear regression analysis was used to examine baseline and longitudinal associates of IMT_{Change} with standardized beta coefficients (Table 2, Models 1–4). Models including and excluding baseline IMT were compared with models including baseline IMT showing better statistical fit based on akaike information criterion and R^2 (data not shown); hence, models were adjusted for baseline IMT. Model included age, sex, and race as covariates. Subsequently (Models 2–4), we examined the association of IMT_{Change} with different covariates,

including those in Model 1, with the addition of baseline and rate of change of SBP and DBP in Model 2, baseline and rate of change of PP and MAP in Model 3, and baseline and rate of change of PWV in Model 4. Models 2 to 4 were also adjusted for baseline and rate of change of BMI, smoking, diabetes mellitus, glucose, LDL, HDL, triglycerides, and hypertension and statin treatments. In alternative analysis, body surface area was used instead of BMI with no significant association with IMT. All analyses were performed via SAS for Windows (Version 9.4; Cary, NC).

RESULTS

Descriptive characteristics of the sample are shown in Table 1. The average age of the participants was 63.0±14.2 years with an average of 3.5±1.6 follow-ups; 47.9% of participants were male, and 25.7% were Black race. About 4% of participants were current smokers, 48.5% were hypertensive, while 13.1% had diabetes mellitus. About 33.4% of the participants were on antihypertensive medications, while 27.0% were on antilipid medications.

Men had a higher baseline IMT (0.76 mm versus 0.70 mm, $P<0.001$) and higher SBP (125.3 mm Hg versus 122.6 mm Hg, $P=0.027$), DBP (74.0 mm Hg versus 70.9 mm Hg, $P<0.001$), PWV (7.7 m/s versus 7.2 m/s, $P<0.001$), and triglycerides (116.5 mg/dL versus 99.4 mg/dL, $P<0.001$) but lower HDL (48.4 mg/dL versus 60.8 mg/dL, $P<0.001$). Compared with women, a greater proportion of men were smokers (53.1% versus 36.2%, $P<0.001$), hypertensives (55.5% versus 43.9%, $P<0.001$), and diabetics (16.0% versus 10.3%, $P=0.015$), and a greater proportion were uncontrolled on hypertension medications (41.9% versus 35.2%) (Table 1).

Regression models examining the potential associations of IMT_{Change} are shown in Table 2. In the basic model (Model 1), IMT_{Change} was positively associated with age ($P<0.001$), indicating that IMT increased at accelerating rates in older participants; the rate of increase of IMT was estimated at 0.02 mm/decade in those who were age 50 years compared with 0.05 mm/decade in those who were age 80 years. Figure illustrates model-predicted cross-sectional differences and longitudinal changes of IMT with advancing age in men and women.

Sex was also associated with greater IMT_{Change} (Table 2, Model 1). On average, IMT in men increased at a rate of 0.01 mm faster per decade than in women ($P=0.001$). Similarly, in addition to having a higher baseline IMT, Black race had a 0.01 mm higher increase of their IMT per decade compared with nonblack race ($P=0.002$).

LDL and LDL_{Change} were independently associated with IMT_{Change} (Models 2–4) (all $P<0.001$). A 1 SD higher baseline LDL (32.7 mg/dL) was associated with 0.007 mm higher increase in IMT over a decade, while an increase in the LDL_{Change} by 1 SD (2.5 mg/dL per year) led to a 0.010 mm higher increase in IMT over a decade. On the other hand, baseline values of HDL, triglycerides, smoking, BMI, and their rates of change were not associated with IMT_{Change}.

IMT_{Change} was associated with baseline SBP and SBP_{Change}, and inversely associated with baseline DBP and DBP_{Change} (all $P<0.050$). Greater baseline SBP of 1 SD (19.8 mm Hg) was associated with a 0.008 mm higher increase in IMT over a decade, while an increase in SBP_{Change} by 1 SD (1.1 mm Hg/year) led to a greater increase in IMT of 0.011 mm/decade. Similarly, a 1 SD higher DBP (13.2 mm Hg) was associated with a 0.013 mm lesser increase in IMT over a decade, while a 1 SD (0.8 mm Hg/y) increase in the DBP_{Change} was associated with a 0.017 mm lesser increase in IMT over a decade. When pressure was expressed as PP and MAP, IMT_{Change} was positively associated with PP and PP_{Change} and inversely associated with baseline MAP and rate of change of MAP. IMT_{Change} showed no statistically significant associations with PWV or PWV_{Change} (Table 2, Model 4). MAP terms became nonsignificant in the model including PWV, likely reflecting collinearity between the 2 variables. A separate model (data not shown) was fitted with PWV alone, showing similar results with no significant association with PWV baseline and Change.

Given established sex differences in BP changes with aging, SBP and DBP models were subsequently stratified by sex (Table 3). IMT_{Change} was positively associated with SBP, SBP_{Change}, and inversely associated with DBP and DBP_{Change} in women, while in men IMT_{Change} was only inversely associated with DBP and DBP_{Change} (all $P<0.050$) (Table 3). Similarly, after stratifying the PP and MAP model on sex, IMT_{Change} was associated with PP, PP_{Change}, and rate of change of MAP in women, and in men IMT_{Change} was associated only with MAP in an inverse direction ($P<0.050$) (Table 3).

Presence of hypertension, diabetes mellitus and hyperlipidemia, or their treatment status, was not associated with IMT_{Change} in any of the models. Similarly, menopausal status and history of ever being on hormone replacement therapy were not associated with IMT_{Change}.

DISCUSSION

Principal Findings

As far as we know, this is the first analysis examining the rates of change in IMT in a community-dwelling population over a broad age range. We report that in both men and women free of cardiovascular disease, IMT increases with aging across a wide age range.

Table 1. Descriptive Baseline Characteristics of the Study Population

	Total, n=1067	Men (n=512)	Women (n=555)	*P* Value
Demographics				
Age, y	63.0±14.2	64.7±13.7	61.3±14.5	<0.001
Follow-ups, y	3.5±1.6	3.5±1.6	3.5±1.6	0.757
Male, %	48	NA	NA	NA
Black, %	25.8	20.7	30.4	<0.001
Cardiovascular variables				
IMT, mm	0.73±0.17	0.76±0.18	0.70±0.15	<0.001
IMT_{change}, mm/decade	0.034±0.062	0.035±0.053	0.032±0.070	0.369
SBP, mm Hg	123.9±19.8	125.3±18.9	122.6±20.5	0.027
DBP, mm Hg	72.4±13.2	74±12.8	70.9±13.3	<0.001
PP, mm Hg	51.4±14.6	51.1±13.4	51.7±15.8	0.533
MAP, mm Hg	94±14.4	95.5±14.1	92.6±14.5	0.001
PWV, m/s	7.5±2.0	7.7±2.0	7.2±2.0	<0.001
Laboratory variables				
LDL, mg/dL	110.0±32.7	108.3±32.1	111.5±33.2	0.121
HDL, mg/dL	54.9±16.1	48.4±13.8	60.8±15.7	<0.001
Triglycerides, mg/dL	107.6±76.9	116.5±92.4	99.4±58.3	<0.001
Glucose, mg/dL	89.5±19.8	91.0±23.3	88.1±15.7	0.066
Body habitus				
Body mass index	26.7±4.3	27.1±3.8	26.2±4.7	<0.001
Body surface area, m^2	1.9±0.2	2.0±0.2	1.8±0.1	<0.001
Waist circumference	89.3±12.4	95.7±10.8	83.4±10.7	<0.001
Medical conditions and medications				
Ever smoker, %	44.3	53.1	36.2	<0.001
Hypertension, %	49.5	55.5	43.9	<0.001
Diabetes mellitus, %	13.1	16	10.3	0.015
Hyperlipidemia, %	53.8	52.8	54.9	0.609
Antihypertensive medication, %				0.004*
None	39.8	35.3	44	
Meds, controlled	21.6	22.6	20.7	
Meds, uncontrolled	38.4	41.9	35.2	
Diabetic medication, %				0.087*
None	89.1	85.3	87.3	
Meds, controlled	2.8	4.3	3.5	
Meds, uncontrolled	9.1	10.3	7.9	
Lipid-modifying medication, %				0.469*
None	42	35.1	38.7	
Meds, controlled	39.1	44.5	34.1	
Meds, uncontrolled	22.1	20.3	23.8	

Data are presented as mean±SD or proportions. DBP indicates diastolic blood pressure; HDL, high-density lipoprotein; IMT, intimal medial thickness; LDL, low-density lipoprotein; MAP, mean arterial pressure; NA, not applicable; PP, pulse pressure; PWV, pulse wave velocity; ROC, rate of change; and SBP, systolic blood pressure.

*The *P* values reported for treatment status variables are for the groupwise differences between men and women. *T* tests were used for comparison of continuous variables, and χ^2 for comparison of categorical variables.

Male and Black participants had higher baseline IMT and experienced steeper progression over time. Beyond those demographics, blood pressure parameters and LDL cholesterol were the main determinants of IMT progression. A novel finding of this study was the steeper IMT progression associated with greater PP but lower mean pressure. In sex-stratified analysis, these associations were evidenced in women rather than men. Interestingly, PWV, a measure of arterial stiffening, was not associated with IMT progression.

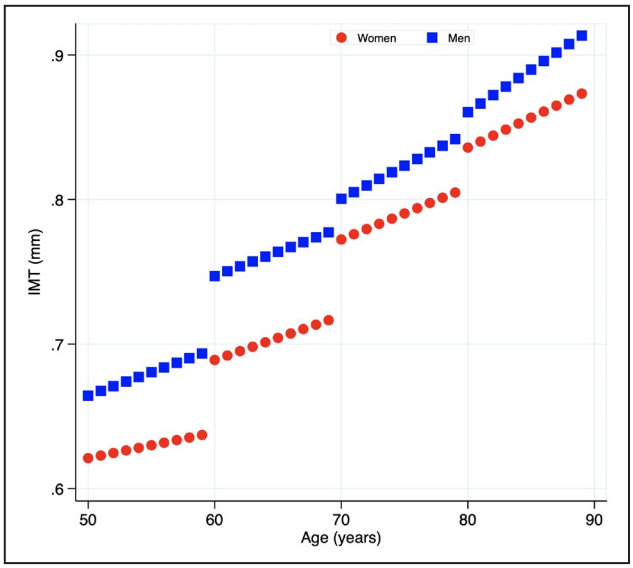

Figure 1. Cross-sectional differences and longitudinal changes of IMT in men and women.
Cross-sectional differences and longitudinal changes of IMT in men and women across decades, from age 50 to 90 years. IMT increases cross-sectionally across decades as indicated by the higher starting point for each decade. The slopes for each decade indicate the rate of increase of IMT in that decade, and the slope is steeper in the older decades. This indicates that IMT increases at higher rates in the older age groups. In summary, IMT starts higher and increases faster in the older decades. IMT indicates intima medial thickness.

Changes in IMT Across the Age Spectrum

Unlike other approaches, we determined rate of change of IMT at varying ages across a wide age range. Our findings of an ongoing longitudinal increase in IMT with advancing age further extend previous research showing a dominant role of aging in IMT progression. We report a rate of change that ranges from 0.02 mm/decade at age 50 years to 0.05 mm/decade at age 80 years. Previous findings from the MESA (Multi-Ethnic Study of Atherosclerosis) study examined the changes in IMT over 10 years and showed an overall rate of change of 0.109 mm/decade; however, no age-specific rates of changes were reported.[8] Other short-term studies have examined IMT progression over time showing an increase in IMT ranging from 0.08 to 0.12 mm/decade.[3,7,8,15–18] It is important to note that many of these studies included plaque burden, whereas we excluded regions with plaque when measuring IMT.

Such information is essential to our understanding of the forces driving IMT increase, and to the design and interpretation of studies aimed at regressing IMT in older adults. The relatively low rates of change reported in our study compared with other studies such as MESA and ARIC (Atherosis Risk in Communities) could be partly because of the overall excellent health of BLSA participants, and in part because of more aggressive blood pressure control observed in the BLSA with average blood pressure dropping from 124 mm Hg at baseline, to 120 mm Hg at the last follow-up.

Sex Differences in IMT Progression

Our results demonstrate that men not only had a higher baseline IMT but also a higher rate of increase of IMT, which further extends previous research on the association of sex with IMT. A previous report from the Young Finns study reported findings similar to ours, but in a much younger population (mean age 10.9 years). However, 2 studies in older populations—the Rotterdam study and the MESA study—showed conflicting findings. While both showed men had a higher baseline IMT, the progression of IMT was not associated with sex in MESA, while men in the Rotterdam study had a lower rate of progression of IMT than women.

Although the reasons for the conflicting results are not clear, results from sex-stratified analyses in our study might shed light on potential causes. In this analysis, the increase in IMT in men and women appears to be driven by different components of blood pressure (cf. the section on Hemodynamic Determinants below). Hence, differences in blood pressure profiles and changes over time could contribute to the conflicting results among studies.

Racial Differences in IMT Changes

In our analysis, Black participants had higher baseline IMT and progression of IMT compared with other non-Black participants, and this finding remained significant after adjustment for confounders. In the MESA study, Black race was also associated with higher baseline IMT, but not with IMT progression. In the ARIC study, Black race had a higher baseline IMT, but 5-year progression was higher in White race than Black race. The reasons for discrepancy of these findings between different studies are unclear and may be simply explained by the different studied population. However, it is important to note that the BLSA is not a population-representative sampling cohort, and differences in recruitment of subjects among these studies might have contributed to variation between studies. In addition, the fact that other studies did not adjust for baseline values might have contributed to the decline seen among those with higher baseline values (regression to the mean). Our findings of concordantly higher baseline and rate of increase in IMT among Black race appear to be more consistent with the

Table 2. Determinants of the Longitudinal Rates of Changes in IMT (SD IMT_{Change} [mm/decade])

Variables	SD of Variable	Model 1		Model 2		Model 3		Model 4	
		STβ	*P* Value	STβ	*P* Value	STβ	*P* Value	STβ	*P* Value
Baseline IMT	0.175 mm	−0.458	<0.001	−0.443	<0.001	−0.448	<0.001	−0.454	<0.001
Age	14.284 y	0.153	<0.001	0.12	0.002	0.129	0.001	0.159	<0.001
Sex	0.500 (proportion)	0.092	0.001	0.134	<0.001	0.133	<0.001	0.099	0.001
Race	0.438 (proportion)	0.089	0.002	0.101	0.001	0.1	0.001	0.094	0.002
Baseline LDL	32.741 mg/dL			0.121	<0.001	0.119	<0.001	0.127	<0.001
LDL_{Change}	2.554 mg/dL			0.169	<0.001	0.177	<0.001	0.191	<0.001
Baseline SBP	19.828 mm Hg			0.126	0.023				
SBP_{Change}	1.191 mm Hg			0.199	<0.001				
Baseline DBP	13.217 mm Hg			−0.222	<0.001				
DBP_{Change}	0.841 mm Hg			−0.294	<0.001				
Baseline PP	14.699 mm Hg					0.12	0.008		
PP_{Change}	0.883 mm Hg					0.174	<0.001		
Baseline MAP	14.461 mm Hg					−0.111	0.012	−0.009	0.827
MAP_{Change}	0.786 mm Hg					−0.156	<0.001	−0.011	0.772
Baseline PWV	2.035 m/s							0.015	0.656
PWV_{Change}	0.061 m/s							−0.003	0.910

Standardized regression coefficients (STβ) indicate the association of 1 SD difference between the particular variable and IMT_{Change}. Subscript Change indicates the rate of change of the particular variable. Model 1 was the baseline model examining only demographic variables such as age, sex, and race. Models 2 to 4 examined the relationship between IMT_{Change} and various measures/surrogates of arterial pressure—SBP and DBP in Model 2, PP and MAP in Model 3, and PWV in Model 4. Each of these measures was expressed in terms of their baseline values and their rate of change. Additionally, Models 2 to 4 were adjusted for baseline values and rate of change of body mass index, smoking, diabetes mellitus, glucose, LDL, high-density lipoprotein, triglycerides, and hypertension and statin treatments. DBP indicates diastolic blood pressure; IMT, intima medial thickness; LDL, low-density lipoprotein; MAP, mean arterial pressure; PP, pulse pressure; PWV, pulse wave velocity; and SBP, systolic blood pressure.

universal finding of higher IMT among Black race at baseline. Further examination of the causes of such racial differences beyond confounders measured in this study is needed.

Traditional Cardiovascular Risk Factors and IMT

Our analysis showed that among traditional metabolic cardiovascular risk factors (obesity, smoking, glucose,

Table 3. Sex-Specific Associations of Rate of Change of IMT With Blood Pressure (SD IMT_{Change} [mm/decade])

Characteristic	SD of Variable	Model 1				Model 2			
		Women		Men		Women		Men	
		STβ	*P* Value	STβ	*P* Value	STβ	*P* Value	STβ	*P* Value
Baseline IMT	0.175 mm	−0.487	<0.001	−0.422	<0.001	−0.497	<0.001	−0.421	<0.001
Age	14.284 y	0.144	0.008	0.133	0.015	0.148	0.006	0.150	0.005
Race	0.438 (proportion)	0.123	0.002	0.075	0.086	0.126	0.002	0.072	0.099
Baseline LDL	32.741 mg/dL	0.111	0.012	0.155	0.002	0.105	0.018	0.158	0.001
LDL_{Change}	2.554 mg/dL	0.186	<0.001	0.145	0.003	0.198	0.001	0.147	0.003
Baseline SBP	19.828 mm Hg	0.149	0.047	0.076	0.364				
SBP_{Change}	1.191 mm Hg	0.214	0.001	0.087	0.325				
Baseline DBP	13.217 mm Hg	−0.198	0.009	−0.22	0.014				
DBP_{Change}	0.841 mm Hg	−0.282	<0.001	−0.199	0.029				
Baseline PP	14.699 mm Hg					0.143	0.022	0.073	0.275
PP_{Change}	0.883 mm Hg					0.217	<0.001	0.036	0.573
Baseline MAP	14.461 mm Hg					−0.077	0.182	−0.147	0.033
MAP_{Change}	0.786 mm Hg					−0.140	0.013	−0.115	0.100

Standardized regression coefficients (STβ) indicate the association of 1 SD difference between the indexed variable and IMT_{Change}. Subscript Change indicates the rate of change of the indexed variable. DBP indicates diastolic blood pressure; IMT, intima medial thickness; LDL, low-density lipoprotein; MAP, mean arterial pressure; PP, pulse pressure; and SBP, systolic blood pressure.

and lipid levels), only LDL was a significant determinant of IMT and its change over time. The association was significant in men and women and remained after adjusting for covariates. While previous studies have consistently shown that higher LDL is associated with higher incidence of cardiovascular events, the data regarding its association with IMT have been conflicting, often not being associated with IMT progression in longitudinal cohort studies, but associated with baseline IMT.[19,20]

Some of the reasons for the conflicting results might be because of substratification based on different cutoffs, use of hypercholesterolemia or total cholesterol instead of absolute LDL values, and failure of adjustment for statin medication use. The fact that the association between IMT and LDL was significant in a relatively healthy population with lower LDL levels (mean±SD of 110.0±32.7 mg/dL) indicates that the effect of LDL on IMT continues to be maintained at levels traditionally considered to be normal.

The lack of an association among triglycerides, HDL, and IMT in our study is consistent with most studies. HDL has often been significant in analyses looking at carotid plaque progression, but most studies have found no consistent association with progression of IMT in multivariate longitudinal analyses. Similarly, we did not observe a significant association of smoking habit or BMI with either baseline IMT or its progression.

Hemodynamic Determinants of IMT Progression and the Role of Sex

A major and novel finding of our analysis was that higher systolic and pulse pressures, but lower diastolic and mean blood pressures were associated with IMT progression. These associations were evidenced among women only in sex-stratified analysis. Previous studies that examined the role of blood pressure have focused on SBP as a traditional cardiovascular risk factor. Most of these studies have shown a predominant association between IMT and SBP.[8] Our results further expand these findings by confirming SBP association and direct SBP but also suggesting that such an association is because IMT progression is mostly related to rising pulsatility (of which higher SBP is a contributor) rather than simply higher mean pressure. In fact, DBP and mean blood pressure were both inversely associated with IMT progression in this older population.

One cross-sectional study observed that PP was associated more strongly with IMT in men than women.[21] This study, however, was cross-sectional with a relatively younger mean age and a narrower age distribution, likely capturing an association early in life before the more pronounced increase in PP that occurs beyond the fifth decade of age.[22] The stronger association between PP and IMT progression in women is consistent with previous findings that higher PP is associated with increased cardiovascular mortality in women but not men.[23,24]

Considering these potential proposed mechanistic pathways, these findings might suggest that the greater increase in PP in women compared with men makes it an active determinant with women demonstrating greater increase in PP experiencing greater IMT progression. In men, however, PP does not appear to play such an active role in further promoting IMT progression.

IMT Progression and Arterial Aging

Increasing pulsatility and the plateauing of mean pressure are known hemodynamic changes of aging.[25] Hence, our findings of an association of IMT progression with increasing PP and decreasing mean pressure suggest that IMT thickening is linked to exaggerated age-associated hemodynamic changes. It is curious, however, that IMT change was not associated with that of PWV, an established marker of arterial aging. While PWV change is a covariate of age, the lack of association observed between PWV and IMT changes indicate that those who had accelerated IMT beyond what is expected for their age and sex did not have a similarly accelerated increase in PWV, but demonstrated accelerated increase in PP and decline in MAP. The reasons for this dissociation could be because of the different vessels involved with PWV mainly assessing the aorta, while IMT is measured in the carotid artery. Despite this dissociation, however, it is important to note that similar to PWV,[12] IMT progression increased with advancing age and was more pronounced in men than women.

The divergence in the association of IMT with PP and PWV and the sex difference observed in this association appear to be linked to the intriguing dissociation between PP and PWV with advancing age.[26] A previous analysis has shown that while PWV increase accelerates with aging in men more than women, women demonstrated greater increase in PP with advancing age compared with men who demonstrated plateauing PP.[26]

Carotid arterial wall remodeling has been shown to be consistent with Laplace's law, with higher blood pressures leading to IMT progression via smooth muscle hypertrophy and changes in collagen–elastin interactions.[9] Additionally, as people age, a decreasing diastolic blood pressure in combination with an increasing systolic blood pressure leads to PP widening, and this greater difference in blood pressures has been postulated to exert a greater radial stress on the arterial wall.[9,18,19,21,27–30]

Limitations

Our study has a number of limitations. The changes observed in this healthier cohort might be less than those observed in the community; however, we believe our observed changes might be closer to what is considered "normative aging." In the same vein, the healthier condition might have prevented detection of associations with other metabolic cardiovascular risk factors in pathological ranges. The relatively smaller sample size when stratifying by sex may have reduced the power to detect associations in men. However, we believe the samples to be comparable between sexes, implying that the effect of size is greater in women than men. Our analysis did not examine atherosclerotic plaque progression, given the few cases with such plaques on imaging. Further studies are needed to explore the role of the associations observed in plaque progression in cohorts with heavier burden of atherosclerosis. It is important to note that the provided estimates of change are model-predicted; hence and given interperson heterogeneity in longitudinal changes, these estimates manifest shrinkage compared with observed data yielding estimates that are likely lower than latent changes in these variables. Nonetheless, these estimates are valuable in informing the general nature and direction of associations and their strength relative to each other via standardized beta coefficients.

ARTICLE INFORMATION

Received December 11, 2019; accepted May 12, 2020.

Affiliations

From the Longitudinal Studies Section, Translational Gerontology Branch, National Institute on Aging, NIH, Baltimore, MD (A.C.K., M.A., M.T.O., E.P., L.F.); Laboratory of Cardiovascular Science, National Institute on Aging, NIH, Biomedical Research Center, Baltimore, MD (M.A., M.T.O., C.M., J.B.S., E.G.L.); and Department of Medicine, Johns Hopkins School of Medicine, Baltimore, MD (M.A.).

Sources of Funding

This research was supported by the Intramural Research Program of the National Institutes of Health, National Institute on Aging (USA), and Medstar Research Institute.

Disclosures

None.

Supplementary Material

Data S1
Table S1

REFERENCES

1. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises. *Circulation*. 2003;107:346–354.
2. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N Engl J Med*. 1999;340:14–22.
3. Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, Clegg LX. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987–1993. *Am J Epidemiol*. 1997;146:483–494.
4. Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. *Arterioscler Thromb*. 1991;11:1245–1249.
5. Costanzo P, Perrone-Filardi P, Vassallo E, Paolillo S, Cesarano P, Brevetti G, Chiariello M. Does carotid intima-media thickness regression predict reduction of cardiovascular events? A meta-analysis of 41 randomized trials. *J Am Coll Cardiol*. 2010;56:2006–2020.
6. Scuteri A, Najjar SS, Muller DC, Andres R, Hougaku H, Metter EJ, Lakatta EG. Metabolic syndrome amplifies the age-associated increases in vascular thickness and stiffness. *J Am Coll Cardiol*. 2004;43:1388–1395.
7. Pursnani S, Diener-West M, Sharrett AR. The effect of aging on the association between coronary heart disease risk factors and carotid intima media thickness: an analysis of the Atherosclerosis Risk in Communities (ARIC) cohort. *Atherosclerosis*. 2014;233:441–446.
8. Tattersall MC, Gassett A, Korcarz CE, Gepner AD, Kaufman JD, Liu KJ, Astor BC, Sheppard L, Kronmal RA, Stein JH. Predictors of carotid thickness and plaque progression during a decade: the Multi-Ethnic Study of Atherosclerosis. *Stroke*. 2014;45:3257–3262.
9. Liang Y-L, Shiel LM, Teede H, Kotsopoulos D, McNeil J, Cameron JD, McGrath BP. Effects of blood pressure, smoking, and their interaction on carotid artery structure and function. *Hypertension*. 2001;37:6–11.
10. Scuteri A, Chen C-H, Yin FCP, Chih-Tai T, Spurgeon HA, Lakatta EG. Functional correlates of central arterial geometric phenotypes. *Hypertension*. 2001;38:1471–1475.
11. Rice SC, Zonderman AB, Metter EJ, Najjar SS, Waldstein SR. Absence of relation between depressive symptoms and carotid intimal medial thickness in the Baltimore Longitudinal Study of Aging. *Psychosom Med*. 2009;71:70–76.
12. AlGhatrif M, Strait JB, Morrell CH, Canepa M, Wright J, Elango P, Scuteri A, Najjar SS, Ferrucci L, Lakatta EG. Longitudinal trajectories of arterial stiffness and the role of blood pressure: the Baltimore Longitudinal Study of Aging. *Hypertension*. 2013;62:934–951.
13. Najjar SS, Scuteri A, Shetty V, Wright JG, Muller DC, Fleg JL, Spurgeon HP, Ferrucci L, Lakatta EG. Pulse wave velocity is an independent predictor of the longitudinal increase in systolic blood pressure and of incident hypertension in the Baltimore Longitudinal Study of Aging. *J Am Coll Cardiol*. 2008;51:1377–1383.
14. Morrell CH, Brant LJ, AlGhatrif M, Lakatta EG. Estimating subject-specific rates of change from longitudinal data. In: *JSM Proceedings, Biometrics Section*. Alexandria, VA: American Statistical Association; 2018:881–890.
15. Herder M, Johnsen SH, Arntzen KA, Mathiesen EB. Risk factors for progression of carotid intima-media thickness and total plaque area. *Stroke*. 2012;43:1818–1823.81
16. Juonala M, Viikari JSA, Kahonen M, Taittonen L, Laitinen T, Hutri-Kahonen N, Lehtimaki T, Jula A, Pietikainen M, Jokinen E, et al. Lifetime risk factors and progression of carotid atherosclerosis in young adults: the Cardiovascular Risk in Young Finns study. *Eur Heart J*. 2010;31:1745–1751.
17. van der Meer IM, Iglesias del Sol A, Hak AE, Bots ML, Hofman A, Witteman JCM. Risk factors for progression of atherosclerosis measured at multiple sites in the arterial tree. *Stroke*. 2003;34:2374–2379.
18. Zureik M, Touboul P-J, Bonithon-Kopp C, Courbon D, Berr C, Leroux C, Ducimetière P. Cross-sectional and 4-year longitudinal associations between brachial pulse pressure and common carotid intima-media thickness in a general population. *Stroke*. 1999;30:550–555.
19. Chambless LE, Folsom AR, Davis V, Sharrett R, Heiss G, Sorlie P, Szklo M, Howard G, Evans GW. Risk factors for progression of common carotid atherosclerosis: the Atherosclerosis Risk in Communities Study, 1987–1998. *Am J Epidemiol*. 2002;155:38–47.
20. Touboul P-J, Labreuche J, Bruckert E, Schargrodsky H, Prati P, Tosetto A, Hernandez-Hernandez R, Woo K-S, Silva H, Vicaut E, et al. HDL-C, triglycerides and carotid IMT: a meta-analysis of 21,000 patients with automated edge detection IMT measurement. *Atherosclerosis*. 2014;232:65–71.
21. Winston GJ, Palmas W, Lima J, Polak JF, Bertoni AG, Burke G, Eng J, Gottesman R, Shea S. Pulse pressure and subclinical cardiovascular disease in the Multi-Ethnic Study of Atherosclerosis. *Am J Hypertens*. 2013;26:636–642.

22. Franklin SS, Gustin W, Wong ND, Larson MG, Weber MA, Kannel WB, Levy D. Hemodynamic patterns of age-related changes in blood pressure: the Framingham Heart Study. *Circulation*. 1997;96:308–315.
23. Regnault V, Thomas F, Safar ME, Osborne-Pellegrin M, Khalil RA, Pannier B, Lacolley P. Sex difference in cardiovascular risk. *J Am Coll Cardiol*. 2012;59:1771–1777.
24. Casiglia E, Spolaore P, Mazza A, Ginocchio G, Colangeli G, Onesto C, Di Menza G, Pegoraro L, Ambrosio GB. Effect of two different therapeutic approaches on total and cardiovascular mortality in a Cardiovascular Study in the Elderly (CASTEL). *Jpn Heart J*. 1994;35:589–600.
25. AlGhatrif M, Wang M, Fedorova OV, Bagrov AY, Lakatta EG. The pressure of aging. *Med Clin North Am*. 2017;101:81–101.
26. Scuteri A, Morrell CH, Orrù M, Strait JB, Tarasov KV, Ferreli LAP, Loi F, Pilia MG, Delitala A, Spurgeon H, et al. Longitudinal perspective on the conundrum of central arterial stiffness, blood pressure, and aging. *Hypertension*. 2014;64:1219–1227.
27. Zanchetti A, Crepaldi G, Bond MG, Gallus GV, Veglia F, Ventura A, Mancia G, Baggio G, Sampieri L, Rubba P, et al. Systolic and pulse blood pressures (but not diastolic blood pressure and serum cholesterol) are associated with alterations in carotid intima-media thickness in the moderately hypercholesterolaemic hypertensive patients of the Plaque Hypertension Lipid Lowering Italian Study. PHYLLIS study group. *J Hypertens*. 2001;19:79–88.
28. Tartière J-M, Kesri L, Safar H, Girerd X, Bots M, Safar ME, Blacher J. Association between pulse pressure, carotid intima–media thickness and carotid and/or iliofemoral plaque in hypertensive patients. *J Hum Hypertens*. 2004;18:325–331.
29. García-Ortiz L, Gómez-Marcos MA, Martín-Moreiras J, González-Elena LJ, Recio-Rodriguez JI, Castaño-Sánchez Y, Grandes G, Martínez-Salgado C. Pulse pressure and nocturnal fall in blood pressure are predictors of vascular, cardiac and renal target organ damage in hypertensive patients (LOD-RISK study). *Blood Press Monit*. 2009;14:145–151.
30. Neisius U, Bilo G, Taurino C, McClure JD, Schneider MP, Kawecka-Jaszcz K, Stolarz-Skrzypek K, Klima Ł, Staessen JA, Kuznetsova T, et al. Association of central and peripheral pulse pressure with intermediate cardiovascular phenotypes. *J Hypertens*. 2012;30:67–74.

SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

MEASUREMENTS OF IMT

Prior to 2000, IMT measurements were made directly by the sonographer (OIMT). From 2000 onwards, imaging software by QLAB - Microvascular Imaging (MVI) (Philips; Andover,MA) was used to obtain 5 measurements of IMT using edge detection technology. These measurements were averaged to obtain the mean IMT (NIMT).

We checked for any systematic difference between OIMT and NIMT, the "machine effect". We selected participants who had at least one IMT reading in each of the two time periods. We then selected their last OIMT and their first NIMT, so that the intervening time between the 2 readings would be as short as possible. Using mixed models, we predicted the NIMT from the OIMT, including covariates (Entry-age), time, gender, race, SBP and DBP, and a variable "machine" for the machine effect.

The coefficient of "machine" was then used to adjust the OIMT. Mixed models of all IMT, including all IMT readings pre-2000 and post-2000 IMT were then run with age, gender, race, SBP and DBP, again including "machine" as a covariate. We tested to see that it was not significant, as this would indicate that any differences in IMT purely due to the machine effect were accounted for. We ran several models, and the best fit was a logarithmic model, with the coefficient for "machine" being a multiplicative term that we then used to correct the older IMT.

Estimating Subject-Specific Rates of Change

Linear mixed-effects (LME) models have become a standard statistical model for analyzing the repeated-measures data that derives from longitudinal studies.[1–3] These models handle unbalanced data while including any relevant explanatory variables that need to be taken into account. The models contain both fixed- and random-effects. The fixed effects allow for the estimation of population average trajectories and rates of change while the inclusion of the subject-specific random effects enables the variability in these quantities among subjects to be investigated. The estimates of the subject-specific random effects are shrinkage estimators as the estimates for each individual "borrow strength" from the other subjects in the study to obtain "better" subject-specific estimates resulting in subject-specific estimates that are shrunken towards the overall mean. The amount of shrinkage depends on the amount of data for the subject and the relative between and within subject error variances.

Due to the shrinkage, the subject specific rates of change can appear to have too little variability compared to what is expected. On the other hand, if linear regression models are fit to each subject's data individually, there will be too much variability due to the small number of observations for each subject. Here we estimate the subject-specific rate of change as a weighted average of the LME estimate and the regression estimate.

First, let the fitted LME model for subject *i* be $\hat{y}_{i,LME} = \hat{\beta}_0 + \hat{b}_{i0} + (\hat{\beta}_1 + \hat{b}_{i1})Time$. Then the estimated rate of change for subject *i* is $\widehat{Rate}_{i,LME} = (\hat{\beta}_1 + \hat{b}_{i1})$. Next, let the usual ordinary least squares regression model for the data from only subject *i* be $\hat{y}_{i,OLS} = \hat{\theta}_0 + \hat{\theta}_{1i}Time$ with rate of change for subject *i* given by $\widehat{Rate}_{i,OLS} = \hat{\theta}_{1i}$. To combine the two estimates, $\widehat{Rate}_{i,LME}$ and $\widehat{Rate}_{i,OLS}$, a weighted average is used.

$$\widehat{Rate}_{i,Comb} = \lambda_i \widehat{Rate}_{i,LME} + (1 - \lambda_i) \widehat{Rate}_{i,OLS}$$

where we need to determine the weights, λ_i. A good choice is to use the reciprocal of the variances of each of the two estimates to obtain the weights as this will minimize the variance of the resulting weighted average.[4] Then the estimate with the smaller variance (SE) will be weighted more heavily. That is:

$$\lambda_i = \frac{{}^{1}/_{Var(\widehat{Rate}_{i,LME})}}{{}^{1}/_{Var(\widehat{Rate}_{i,LME})} + {}^{1}/_{Var(\widehat{Rate}_{i,OLS})}}$$

where the variances are the squares of the standard errors (SEs) of the estimates discussed above.

Table S1. Distribution of IMT pre- and post-2000.

IMT period	Pre-2000	Post-2000	P value
Before correction (age-adjusted)	0.5452 ± 0.0916	0.7306 ± 0.1227	<0.05
After Correction for Machine (age-adjusted)	0.7306 ± 0.1227	0.7448 ± 0.0797	NS