

# Growth of Carotid Intima-Media Thickness in Black and White Young Adults

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**Background**—There are few longitudinal studies that have comprehensively examined the intima-media thickness (IMT) growth pattern and its determinants among racial population groups.

*Methods and Results*—Mean and maximum IMT were measured by B-mode ultrasonography up to 3 times in 253 white and 268 black participants, aged 13 to 36 years (mean age $\pm$ standard deviation 24 $\pm$ 3.2 years old). The development of IMT was assessed using individual growth curve modeling. A total of 521 participants with 1015 IMT measurements were eligible for this study. We found higher IMT in both left and right sides in blacks compared to whites (*P*<0.001) in young adulthood. Both whites and blacks showed a strong linear increase in mean IMT with age. Body mass index and father's education level were associated with mean IMT, and only body mass index was associated with maximum IMT (*P*<0.05). We did not observe an interaction between age and race/ethnicity on the growth of IMT, suggesting that blacks and whites developed IMT in similar patterns. Interestingly, we found a faster increase in mean left-side IMT than mean right-side IMT ( $\chi^2$ =11.5, *P*<0.001) in both black and white subjects as well as in males and females.

*Conclusions*—Our findings provide compelling prospective evidence that blacks may have thicker IMT compared to whites as young adults. These racial differences could not be explained by traditional risk factors. This implies that differences in this precursor of atherosclerosis may explain racial disparity in cerebrovascular disease. (*J Am Heart Assoc.* 2016;5:e004147 doi: 10.1161/JAHA.116.004147)

Key Words: carotid intima-media thickness • race/ethnicity • growth curve • longitudinal cohort study

**G** ardiovascular disease (CVD) is the leading cause of death and a major cause of disability worldwide.<sup>1</sup> In the United States, CVD produces immense health and economic burdens.<sup>2</sup> Atherosclerotic changes in the carotid arteries generally reflect and predict systemic atherosclerotic diseases.<sup>3,4</sup> A growing body of evidence indicates that the process of atherosclerosis begins at a young age.<sup>5</sup> The first clinical manifestation of CVD often arises in a stage of well-

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advanced atherosclerosis.<sup>6</sup> Carotid intima-media thickness (IMT) is a surrogate measure of atherosclerosis disease.<sup>7</sup> Thus, measuring IMT is generally accepted as an early assessment method of subclinical atherosclerosis.<sup>8,9</sup> Numerous epidemiologic studies have shown that IMT is also predictive of CVD.<sup>10,11</sup> Understanding of the development of IMT patterns is important because early identification of high-CVD-risk individuals would aid in prevention efforts.

Previous cross-sectional studies in both adult and pediatric populations have shown a thicker IMT in blacks and males compared with whites and females.<sup>1,12</sup> These studies also have shown some associations of IMT with several anthropometric variables (eg, age, sex, race, BMI), chronic stress (eg, socioeconomic status), and hemodynamic variables (eg, blood pressure and pulse pressure). It is not clear to what extent these variables account for IMT variability over time. In addition, the associations between IMT and CVD remain controversial,<sup>13</sup> which may due to the different methods of measuring IMT.<sup>14</sup> Thus far, there are no longitudinal studies that have comprehensively assessed IMT (ie, left/right, mean/maximum) growth pattern and its determinants in a multiracial cohort over a longer period of time from young

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adulthood through middle age. The present study aims to evaluate IMT growth patterns at a critical period of human life when CVD starts to express itself.

# Methods

# **Study Subjects**

The participants were from the Georgia Stress and Heart (GSH) study, an ongoing longitudinal study designed to evaluate the development of cardiovascular (CV) risk factors in youth and young adults, with evaluations conducted annually from 1989 to 2000 (visits 1-10), every 1.5 years from 2000 to 2006 (visits 11-14), and every 2 years from 2008 to 2012 (visits 15-16).<sup>15</sup> Recruitment and evaluation of participants have been described in detail elsewhere.<sup>15-17</sup> Briefly, participants who met the following criteria were recruited: (1) aged 5 to 16 years in 1989, (2) African or European ancestry, (3) normotensive for age and sex based on BP screening, and (4) apparently healthy based on parental reports of the child's medical history. All participants were recruited using family health history questionnaires obtained from a county-wide (Richmond County, Georgia) public school screening of children in kindergarten through grade 8 whose families were interested in health research. A high participation rate was obtained, with 96.3% of those contacted agreeing to participate. This is a substudy of GSH initiated at visit 12 (555 participants): measurements were performed 3 times (visits 12, 14, and 15) during 2001-2011 with the median follow-up period of 7 years (range 5.1-9.7 years). About 80% of 555 participants were followed up 2 or 3 times with IMT measurements, in which there was a higher compliance rate in blacks than that in whites (84.9% vs 76.4%, P=0.010). A total of 521 participants with both left and right IMT measurements were eligible for analysis in this study. The Institutional Review Board at the Medical College of Georgia gave approval for the study. Informed consent was provided by all subjects, or by parents if participants were <18 years.

#### Measurements

On each laboratory visit, demographic information was collected. Participants' height and weight were measured with a Healthometer medical scale that was calibrated daily. BMI was calculated as weight in kilograms divided by the square of height in meters. Blood pressure (BP) was measured with an automated oscillatory BP system (Dinamap Vital Signs Monitor, Model 1846 SX; Criticon Incorporated, Tampa, FL), using an appropriately sized BP cuff that was placed on the subject's right arm. BP measurements were taken at the end of the 11th, 13th, and 15th minutes during a 15-minute

relaxation period in which participants were instructed to relax as completely as possible while lying (supine) with their head resting on a pillow. The average of the last 2 readings (at 13 and 15 minutes) was used to represent resting systolic BP and diastolic BP, respectively. In addition to systolic BP and diastolic BP, pulse pressure was also chosen because pulse pressure measured in adolescence was significantly related to IMT in adulthood.<sup>18</sup>

Smoking was defined as smoking at least on 1 day and at least 1 cigarette per day during the past 30 days. Alcohol drinking was defined as drinking at least on 1 day and at least 1 drink of alcohol per day during the past 30 days. Exercise was defined as at least once a week engaging in any regular physical activity such as brisk walking or jogging long enough to work up a sweat. Childhood socioeconomic status (SES) was represented by father's education level, which was grouped in 3 classes:  $\leq 11$ , 12 to 15, and  $\geq 16$  years of schooling.

#### Assessments of IMT

A Hewlett-Packard Sonos 5500 (Andover, MA) equipped with a 7.5-MHz linear array probe was used to measure the common carotid artery IMT. Left and right common carotid, carotid bulb, internal carotid, and external carotid were first visualized in transverse and then in longitudinal planes with Bmode and color mode. Arterial walls were scanned longitudinally and perpendicular to the ultrasound beam. Measurements were made at a point 10 mm below the beginning of the carotid bulb on both near and far wall that showed the intima-media boundaries most clearly. Both walls of the common carotid artery were measured on a 10-mm straight arterial segment.

Images were saved on high-quality VHS tapes. IMT were derived from a computer program Vascular Tool (Medical Imaging Application, Iowa City, IA). This system uses an automated method for near and/or far wall border detection. The common carotid's IMT was measured as the distance from the leading edge of the first echogenic line to that of the second echogenic line. Ten frames of common carotid artery were analyzed by an experienced sonographer. The measurements were averaged to determine the mean IMT and maximum IMT for left and right common carotid artery. For each individual the following average of near- and far-wall carotid IMT was determined: IMT\_mean\_r=right-side mean IMT; IMT\_max\_r=right-side maximum IMT; IMT\_max\_l=left-side maximum IMT.

#### **Statistical Analysis**

Continuous variables are presented as mean $\pm$ SD, whereas categorical variables are presented as cases (n) and percentage

rate (%). All descriptive analyses were performed using Stata software version 12.1 (STATA Corp, College Station, TX).

The growth of IMT was assessed by use of individual growth curve modeling within a multilevel framework<sup>19</sup> that was designed to explore hierarchical data. In the present study repeated observations (level 1) are nested within subjects (level 2). Individual growth curve modeling accounts for the dependency of the data on this clustering and fits a curve for each individual. These individual growth curves (eg, IMT development with age) are characterized by their intercept (or level) and slope (rate of change). The addition of independent variables (sex, race/ethnicity, and father's education level were treated as time-invariant variables; others were treated as time-dependent variables) to the model was aimed at explaining between-subject variation (in level and slope) of the IMT growth curves.

MLwiN software was used to construct the multivariate multilevel model.20 A 2-level model was performed, with subjects at level 2 (between-subject level) and repeated measurements (or visits) at level 1 (within-subject level). We first specified the unconditional growth model, in which fixed and random linear relationships were fitted by the addition of age to the intercept-only model. Race/ethnicity and sex were then added to the unconditional growth model to test the effects on IMT intercept and on the rate of change. In the next step, height, BMI, systolic BP, diastolic BP, pulse pressure, smoking, alcohol drinking, exercise, and father's education were added separately to the model to estimate the effect of these variables on the development of the IMT pattern in time. In addition to the main effect, the interaction among age, sex, race/ethnicity, and BMI was also tested. In the final step, all variables that had significant effects on the IMT pattern in the previous models were entered simultaneously in a model, and then each parameter was removed from the model, and a maximum-likelihood method was used to examine whether a fixed effect was significant in this model. At last, all the variables that remained statistically significant or marginally significant were entered into the full model to obtain estimates of race/ethnicity and sex effects. A multivariate multilevel model was used to compare the difference between the coefficients of fixed parameters for left and right IMT. Two-sided P<0.05 was considered statistically significant.

# Results

Our study enrolled 747 individuals among whom 521 participants with 1015 IMT measurements (69.48% participants with at least 2 measurements) were eligible for analysis. There were 268 (51.4%) black and 253 (48.6%) white subjects. As shown in Table 1, black participants had a significantly higher BMI, systolic BP, diastolic BP, and lower childhood SES compared to whites (P<0.01). However, more

white participants were smoking and drinking alcohol (P<0.01). Females had higher BMIs but lower systolic BPs than males. Females also had higher childhood SES and lower rates of smoking and alcohol drinking compared to males (P<0.01). All participants were relatively young at their last visit, with mean age of 28 years (age range 20-36). The IMT\_mean\_r, IMT\_max\_r, IMT\_mean\_I, and IMT\_max\_I were 0.53 $\pm$ 0.08, 0.70 $\pm$ 0.10, 0.54 $\pm$ 0.7, and 0.70 $\pm$ 0.10 mm, respectively. Both left- and right-side IMTs were higher in blacks compared to whites. There were no significant differences between males and females except that IMT\_mean\_r was higher in males.

#### Growth-Curve Models for Left-Side IMT

Results of growth-curve modeling for IMT mean I and IMT max\_I are presented in Table 2. The unconditional growth model with fixed and random linear effects (age) provided the best fit. Race/ethnicity had significant effects on IMT\_mean\_l  $(\beta=0.0213, P<0.001)$  and IMT\_max\_l level  $(\beta=0.0134,$ P=0.035), indicating higher levels for black than white subjects (Table 2, model 1). As shown in Table 2 (models 4-7), BMI, systolic BP, pulse pressure (PP), and father's education level had significant effects on both IMT\_mean\_I and IMT\_max\_I levels; that is, left-side IMT increased with increasing BMI, SBP, and PP, but with decreasing father's education level (P < 0.05). BMI showed an interaction with age ( $\beta$ =0.0002, *P*=0.043) on growth of IMT\_mean\_l, indicating that participants with higher BMI had thicker IMT compared to the lean at similar age. In the full model, after adjusting for BMI, systolic BP, and father's education level, the racial effects on IMT\_mean\_I ( $\beta$ =0.0171, P=0.001) remained significant, but not IMT\_max\_I ( $\beta=0.0075$ , P=0.233). The full model, including age, sex, race/ethnicity, BMI, and father's education level, explained in total 31.03% of the between-subject variance in IMT\_mean\_l; and for IMT\_max\_I, full model including age, sex race/ethnicity, and BMI explained in total 47.95% of the between-subject variance. We did not observe any interactions of age with race/ethnicity or sex on the growth of mean and maximum IMT in the left side, suggesting that the growth patterns were similar between blacks and whites, as well as males and females (Table 2).

#### Growth-Curve Models for Right-Side IMT

Table 3 presents the results of growth-curve modeling for IMT\_mean\_r and IMT\_max\_r. The unconditional growth model with fixed and random linear effects (age) provided the best fit for IMT\_mean\_r, and with fixed and random linear effects (age) it provided the best fit for IMT\_max\_r. Race/ethnicity had significant effects on IMT\_mean\_r ( $\beta$ =0.0281, *P*<0.001) and IMT\_max\_r levels ( $\beta$ =0.0185, *P*=0.004), also indicating higher levels in black than in white subjects. As shown in

	White American		Black American		P Value		
	Males	Females	Males	Females	Sex	Race/ethnicity	
N	134	119	113	155			
Participants with $\geq$ 2 visits, %	73.9	57.1	71.7	73.6			
Age, y	22.1±3.6	22.8±3.6	23±3.8	22.5±3.3	0.84	0.06	
Height, cm	177.9±7.6	164.9±6.1	177.0±6	164.7±6.7	<0.01	<0.01	
BMI, kg/m <sup>2</sup>	25.7±4.9	27.9±8.6	28.4±7.3	30.2±9.3	<0.01	<0.01	
SBP, mm Hg	115.4±10.6	106.1±9.1	120.4±11.4	112.7±12.3	<0.01	<0.01	
DBP, mm Hg	61.2±7.1	61.5±6.0	65.4±8.0	66.3±8.5	0.30	<0.01	
Pulse pressure, mm Hg	54.2±10.0	44.6±7.0	55.0±9.7	46.4±9.2	<0.01	0.14	
Exercise (%)	97 (72.4)	76 (63.9)	66 (58.4)	114 (73.5)	0.38	0.78	
Smoking (%)	73 (54.5)	52 (43.7)	44 (38.9)	64 (41.3)	<0.01	<0.01	
Alcohol drinking (%)	110 (82.1)	80 (67.2)	70 (61.9)	91 (58.7)	<0.01	<0.01	
Father's education level (%)					<0.01	<0.01	
≤11 years	15 (11.2)	10 (8.4)	24 (21.2)	34 (21.9)			
12 to 15 years	67 (50.0)	83 (69.8)	76 (67.3)	103 (66.5)			
≥16 years	52 (38.8)	26 (21.9)	13 (11.5)	18 (11.61)			
IMT, mm							
IMT_mean_r	0.53±0.07	0.52±0.07	0.56±0.07	0.54±0.07	0.03	<0.01	
IMT_max_r	0.69±0.10	0.69±0.08	0.72±0.09	0.71±0.09	0.35	<0.01	
IMT_mean_l	0.53±0.07	0.52±0.06	0.56±0.08	0.54±0.07	0.20	<0.01	
IMT_max_l	0.68±0.10	0.68±0.09	0.71±0.11	0.70±0.08	0.78	0.01	

#### Table 1. Demographic Characteristics of Participants at the Visit IMT Were First Measured

BMI indicates body mass index; IMT, intima-media thickness; IMT\_max\_I, left-side maximum IMT; IMT\_max\_r, right-side maximum IMT; IMT\_mean\_I, left-side mean IMT; IMT\_mean\_r, right-side mean IMT; SBP, systolic blood pressure.

Table 3 (models 4-7), BMI, systolic BP, PP, and father's education level had significant effects on both IMT\_mean\_r and IMT\_max\_r levels; that is, right side IMT increased with increasing BMI, systolic BP, and PP but with decreasing father's education level (P<0.05). In the full model, adjusting for BMI, systolic BP, and father's education level, the racial effects on IMT\_mean\_r and IMT\_max\_r ( $\beta$ =0.0249, *P*<0.001)  $(\beta=0.0137, P=0.030)$  remained significant. The full model, including age, sex, race/ethnicity, BMI, and father's education level, explained in total 30.08% of the between-subject variance in IMT\_mean\_r; and for IMT\_max\_r, the full model including age, sex, race/ethnicity, and BMI explained in total 51.02% of the between-subject variance. Similar to the left side, we did not observe any interactions of age with race/ ethnicity or sex on the growth of mean and max IMT in the right side (Table 3).

# Comparison of IMT Growth Curves Between Left and Right

Figures 1A and 1B illustrate the growth curves of mean and max left-side IMT by race/ethnicity and sex groups,

respectively. It is shown that the left-side IMT exhibits a linear increase with age for both mean and maximum measurements. Overall, blacks and whites showed similar slopes of the curves, but blacks had higher levels of IMT compared to whites. Figure 2A presents growth curves showing a linear increase of the right-side IMT with age for the mean measurement, whereas Figure 2B illustrates a quadratic increase with age for the right-side max IMT. Similar slopes of the growth curves were found between blacks and whites, although blacks had higher levels of IMT than whites. However, we found a bigger slope of the growth curve for the mean IMT in the left side than that in the right side (0.0021 vs 0.00002,  $\chi^2=11.5$ , *P*<0.001), suggesting a faster increase in the mean IMT in the left side (Figures 1A and 2A). Of note, this difference was across both race/ethnicity and sex groups.

# Discussion

To the best of our knowledge, this is first study to explore the IMT growth pattern during young adulthood in a multiracial cohort. We found that blacks have thicker IMT than whites, although they show similar growth patterns with age.

	Mean IMT				Max IMT			
			Explained Variance				Explained Variance	
	В	P Value	Between	Within	β	P Value	Between	Within
Model 1 (unconditional growth model)			19.81	4.17			29.54	7.69
Age	0.0026	< 0.001			0.0048	< 0.001		
Model 2			20.22	4.05			29.62	7.68
Model 1+sex	-0.0050	0.457			-0.0011	0.857		
Model 1+sex×age	-0.0002	0.867			0.0007	0.678		
Model 3			24.37	3.98			29.99	7.82
Model 1+race/ethnicity	0.0213	< 0.001			0.0134	0.035		
Model 1+race/ethnicity × age	0.0000	0.980			-0.0011	0.496		
Model 1+race/ethnicity×sex	-0.0063	0.530			0.0001	0.991		
Model 4			24.09	2.93			53.43	5.44
Model 1+BMI	0.0009	0.007			0.0022	< 0.001		
Model 1+height	0.0005	0.065			0.0006	0.085		
Model 1+BMI×age	0.0002	0.043			0.0002	0.108		
Model 1+BMI×sex	-0.0005	0.478			-0.0021	0.014		
Model 1+BMI×race/ethnicity	0.0004	0.500			0.0004	0.596		
Model 5			24.85	2.91			36.14	6.62
Model 1+SBP	0.0004	0.020			0.0005	0.020		
Model 1+DBP	0.0003	0.364			0.0002	0.657		
Model 1+PP	0.0005	0.032			0.0007	0.013		
Model 6			_	—			_	—
Model 1+smoking	0.0007	0.879			-0.0098	0.107		
Model 1+alcohol	-0.0045	0.329			-0.0050	0.427		
Model 1+exercise	0.0066	0.133			-0.0064	0.286		
Model 7								
Model 1+father's education	-0.0163	<0.001	24.88	5.00	-0.0107	0.043	30.91	8.26
Model 8 (full model)			31.03	3.52			47.95	5.99
Age	0.0021	<0.001			0.0037	< 0.001		
Sex	-0.0085	0.086			-0.0060	0.329		
Race/ethnicity	0.0171	0.001			0.0075	0.233		
BMI	0.0006	0.070			0.0022	< 0.001		
Father's education level	-0.0121	0.004						

Model 8 includes age, sex, race/ethnicity, BMI, SBP, and father's education level for IMT\_mean\_l; it includes age, sex, race/ethnicity, and BMI for IMT\_max\_l. For interaction models, both main effects and interaction term were built into the model. BMI indicates body mass index; DBP, diastolic blood pressure; IMT, intima-media thickness; PP, pulse pressure; SBP, systolic blood pressure.

The overall average IMT reported in the present study is consistent with earlier studies focusing on a similar age range. These studies reported IMT range between 0.49 and 0.59 mm for mean IMT and between 0.61 and 0.63 mm for maximum IMT.<sup>21,22</sup>

The present study also showed that IMT levels are higher in blacks than in whites, and the racial differences in IMT could not be explained by differences in BMI, childhood SES, smoking, alcohol drinking, and exercise over time. This is consistent with previous reports that blacks showed greater mean and maximum IMT than South Asians and whites after adjusting for traditional CV risk factors.<sup>21,23</sup> There were no significant differences between males and females except that IMT\_mean\_r was higher in males. A study by Sass et al

Table 3	. Results	of	Growth	Curve	Modeling	for	<b>Right-Side</b>	Carotid	IMT
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	Mean IMT				Max IMT			
		Explained Variance		ariance			Explained Variance	
	β	P Value	Between	Within	β	P Value	Between	Within
Model 1 (unconditional growth model)			8.91	3.33			16.63	5.57
Age	0.0006	0.332			0.0035	< 0.001		
Model 2			10.49	3.17			-	-
Model 1+sex	-0.0075	0.158			-0.0040	0.531		
Model 1+sex×age	-0.0024	0.063			-0.0010	0.576		
Model 3			19.81	2.57			23.11	5.05
Model 1+race/ethnicity	0.0281	< 0.001			0.0185	0.004		
Model 1+race/ethnicity×age	0.0008	0.546			0.0001	0.956		
Model 1+race/ethnicity×sex	-0.0032	0.758			0.0057	0.654		
Model 4			16.90	2.39			50.16	4.39
Model 1+BMI	0.0012	0.001			0.0021	<0.001		
Model 1+height	0.0005	0.115			0.0005	0.125		
Model 1+BMI×age	0.0001	0.078			0.0001	0.378		
Model 1+BMI×sex	-0.0010	0.128			-0.0017	0.054		
Model 1+BMI×race/ethnicity	0.0010	0.150			0.0009	0.307		
Model 5			15.44	2.91			37.88	4.02
Model 1+SBP	0.0006	0.002			0.0007	0.006		
Model 1+DBP	0.0003	0.379			-0.0000	0.967		
Model 1+PP	0.0007	0.002			0.0010	0.001		
Model 6			_	_			-	_
Model 1+smoking	0.0062	0.208			0.0004	0.949		
Model 1+alcohol	-0.0044	0.377			-0.0055	0.399		
Model 1+exercise	0.0016	0.737			-0.0059	0.351		
Model 7								
Model 1+father's education	-0.0144	0.001	13.54	3.55	-0.0120	0.023	16.86	7.17
Model 8 (full model)			30.08	1.78			51.02	4.08
Age	0.00002	0.970			0.0024	0.006		
Sex	-0.0136	0.008			-0.0101	0.105		
Race/ethnicity	0.0249	< 0.001			0.0137	0.030		
BMI	0.0009	0.008			0.0021	< 0.001		
Father's education level	-0.0086	0.049						

Model 8 includes age, sex, race/ethnicity, BMI, and father's education level for mean right intima-media thickness; it includes age, sex, race/ethnicity, and BMI for maximum right intimamedia thickness. For interaction models, both main effects and interaction term were built into the model. BMI indicates body mass index; DBP, diastolic blood pressure; IMT, intima-media thickness; PP, pulse pressure; SBP, systolic blood pressure.

found that, between ages of 10 and 18 years, carotid and femoral artery IMTs were not significantly different between boys and girls, but after the age of 18 years, boys had significantly greater carotid and femoral IMTs than girls.<sup>8</sup> Thus, sex differences in IMT occur only at an adult age; considering the age range of our sample (13-36 years), this result was similar to ours.

A number of cross-sectional studies have demonstrated that IMT increases with advancing age,<sup>21,24</sup> which is consistent with our results even after adjustment for the other CV risk factors over time. However, we did not find a difference between males and females. As in the Young Finn study, sex differences in the IMT were mostly explained by differences in risk factors and vessel size.<sup>21</sup> In line with previous findings



Figure 1. The increase of left-side mean (A) and maximum (B) intima media thickness with age by race/ethnicity and sex.

IMT increased with increasing BMI,<sup>25</sup> and childhood SES played a significant role early in the atherosclerotic disease process.<sup>26-28</sup>

Contrary to numerous previous studies we did not find an association between IMT and exercise, smoking, and alcohol drinking.<sup>29-32</sup> Consistent with our result, the association between smoking status and IMT has been reported by Sass and colleagues in middle-aged but not in young adults.<sup>8</sup> The short smoking duration in the younger population may be 1 possible reason to explain this paradox. Several studies have reported an association between systolic BP and IMT in a

middle-aged population,<sup>10,33</sup> but some studies in children and young adults have not found such an association.<sup>8,10</sup> We also did not find an association between blood pressure and IMT in the present study. This discrepancy may be due to differences in study protocols (eg, age range of study cohort and portion of the carotid artery that is studied).<sup>8,10,34</sup>

Interestingly, we found a faster increase in the mean IMT on the left side than that on the right side. Kollias and colleagues reported that the left-side IMT was higher and more closely related to CV risk factors (mainly systolic BP) than that on the right side in children.<sup>35</sup> Several other studies



Figure 2. The increase of right side mean (A) and maximum (B) intima media thickness (IMT) with age by race/ethnicity and sex.

also demonstrated that IMT is higher on the left side than the right side in middle-aged or older populations.<sup>36,37</sup> These results were consistent with our study to some extent. Atherosclerotic processes at different artery segments are a result of differing mechanisms associated with the specific structure. The artery segments differ in geometry, cellular composition, and function and are exposed differently to shear stress.<sup>38,39</sup> Hernandez and colleagues found a higher left IMT than right IMT in untreated hypertensive patients, and this finding has been attributed to the higher crosssectional area of the intima-media complex and higher flow velocity at the left side.<sup>14</sup> Our results suggest that changes in the left-side IMT might be better indicators of atherosclerotic processes in young adults. Whether the observed differences reflect a natural course of adaptive vascular injury on different shear stress conditions requires further study.

#### Limitations

Our study has several limitations. First, our cohort just included black and white Americans, and the results may not be generalizable to other populations. Second, IMT was measured only in the common carotid artery, making it difficult to compare with other studies using different segments of the carotid artery. Here we consistently scanned the common carotid artery, and it is possible that including the carotid bifurcation and the internal carotid artery may enhance the prediction of atherosclerotic disease.40 Third, we only have 3 visit measurements, and not all participants were measured 3 times in our study; having more visits could improve the estimation of the growth curves. Fourth, other IMT-related factors, such as serum lipids and glucose, were not available in our study. Finally, our young and healthy population did not have asymptomatic or symptomatic arthrosclerosis, preventing us from making clinical inferences.

# Conclusions

Our findings provide compelling prospective evidence that blacks have thicker IMT compared to whites during young adulthood. These racial differences could not be explained by traditional risk factors. This implies that differences in IMT may explain racial disparity in the burden of cerebrovascular disease. Our study also found a faster increase in mean leftside IMT than mean right-side IMT with age, which indicates that left-side IMT might be a better screen indicator of atherosclerosis in young adults. These results underscore the importance of probing IMT alterations as end-target organ damage and the need for future studies to consider the effects of IMT growth on clinical endpoints.

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## **Disclosures**

None.

## References

- Gersh BJ, Sliwa K, Mayosi BM, Yusuf S. Novel therapeutic concepts: the epidemic of cardiovascular disease in the developing world: global implications. *Eur Heart J.* 2010;31:642–648.
- 2. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Despres JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER, 3Ro, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB, American Heart Association Statistics C, Stroke Statistics S. Heart Disease and Stroke Statistics—2015 update: a report from the American Heart Association. *Circulation*. 2015;131:e29–e322.
- Simon A, Gariepy J, Chironi G, Megnien JL, Levenson J. Intima-media thickness: a new tool for diagnosis and treatment of cardiovascular risk. J Hypertens. 2002;20:159–169.
- Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. *Circulation*. 1997;96:1432–1437.
- Hong YM. Atherosclerotic cardiovascular disease beginning in childhood. Korean Circ J. 2010;40:1–9.
- Poredos P. Intima-media thickness: indicator of cardiovascular risk and measure of the extent of atherosclerosis. Vasc Med. 2004;9:46–54.
- Polak JF, Pencina MJ, Pencina KM, O'Donnell CJ, Wolf PA, D'Agostino RB Sr. Carotid-wall intima-media thickness and cardiovascular events. N Engl J Med. 2011;365:213–221.
- Sass C, Herbeth B, Chapet O, Siest G, Visvikis S, Zannad F. Intima-media thickness and diameter of carotid and femoral arteries in children, adolescents and adults from the Stanislas cohort: effect of age, sex, anthropometry and blood pressure. J Hypertens. 1998;16:1593–1602.
- Lee DG, Han JH, Kwon KY, Kim JH, Han KH, Lee EJ. Association of 10-year atherosclerotic cardiovascular disease risk score with carotid intima-media thickness and plaque. *Korean J Fam Med.* 2015;36:310–315.
- Davis PH, Dawson JD, Riley WA, Lauer RM. Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: the Muscatine Study. *Circulation*. 2001;104:2815–2819.
- 11. Baldassarre D, Hamsten A, Veglia F, de Faire U, Humphries SE, Smit AJ, Giral P, Kurl S, Rauramaa R, Mannarino E, Grossi E, Paoletti R, Tremoli E; Group IS. Measurements of carotid intima-media thickness and of interadventitia common carotid diameter improve prediction of cardiovascular events: results of the IMPROVE (carotid intima media thickness [IMT] and IMT-progression as predictors of vascular events in a high risk European population) study. J Am Coll Cardiol. 2012;60:1489–1499.
- Santos IS, Bittencourt MS, Oliveira IR, Souza AG, Meireles DP, Rundek T, Foppa M, Bezerra DC, Freire CM, Roelke LH, Carrilho S, Bensenor IM, Lotufo PA. Carotid intima-media thickness value distributions in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). *Atherosclerosis*. 2014;237:227–235.
- Takiuchi S, Kamide K, Miwa Y, Tomiyama M, Yoshii M, Matayoshi T, Horio T, Kawano Y. Diagnostic value of carotid intima-media thickness and plaque

score for predicting target organ damage in patients with essential hypertension. *J Hum Hypertens*. 2004;18:17–23.

- Rodriguez Hernandez SA, Kroon AA, van Boxtel MP, Mess WH, Lodder J, Jolles J, de Leeuw PW. Is there a side predilection for cerebrovascular disease? *Hypertension*. 2003;42:56–60.
- Dekkers JC, Snieder H, Van Den Oord EJ, Treiber FA. Moderators of blood pressure development from childhood to adulthood: a 10-year longitudinal study. J Pediatr. 2002;141:770–779.
- Wang X, Poole JC, Treiber FA, Harshfield GA, Hanevold CD, Snieder H. Ethnic and gender differences in ambulatory blood pressure trajectories: results from a 15-year longitudinal study in youth and young adults. *Circulation*. 2006;114:2780–2787.
- Su S, Wang X, Pollock JS, Treiber FA, Xu X, Snieder H, McCall WV, Stefanek M, Harshfield GA. Adverse childhood experiences and blood pressure trajectories from childhood to young adulthood: the Georgia Stress and Heart Study. *Circulation*. 2015;131:1674–1681.
- Raitakari OT, Juonala M, Taittonen L, Jula A, Laitinen T, Kahonen M, Viikari JS. Pulse pressure in youth and carotid intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *Stroke*. 2009;40:1519–1521.
- Goldstein H. Multilevel Statistical Models. Chichester, West Sussex: Wiley; 2011.
- Rasbash J, Browne W, Goldstein H, Yang M, Plewis I, Healy M, Woodhouse G, Draper D, Langford I, Lewis T. A User's Guide to MLwiN. London, UK: University of London, Institute of Education; 2009.
- 21. Juonala M, Kahonen M, Laitinen T, Hutri-Kahonen N, Jokinen E, Taittonen L, Pietikainen M, Helenius H, Viikari JS, Raitakari OT. Effect of age and sex on carotid intima-media thickness, elasticity and brachial endothelial function in healthy adults: the Cardiovascular Risk in Young Finns Study. *Eur Heart J.* 2008;29:1198–1206.
- Davis PH, Dawson JD, Blecha MB, Mastbergen RK, Sonka M. Measurement of aortic intimal-medial thickness in adolescents and young adults. *Ultrasound Med Biol.* 2010;36:560–565.
- Bennett PC, Gill PS, Silverman S, Blann AD, Lip GY. Ethnic differences in common carotid intima-media thickness, and the relationship to cardiovascular risk factors and peripheral arterial disease: the Ethnic-Echocardiographic Heart of England Screening Study. *QJM*. 2011;104:245–254.
- Kuller LH, Sutton-Tyrrell K. Aging and cardiovascular disease. Use of subclinical measurements. *Cardiol Clin.* 1999;17:51–65, viii.
- Li S, Chen W, Srinivasan SR, Bond MG, Tang R, Urbina EM, Berenson GS. Childhood cardiovascular risk factors and carotid vascular changes in adulthood: the Bogalusa Heart Study. *JAMA*. 2003;290:2271–2276.
- Lynch J, Kaplan GA, Salonen R, Salonen JT. Socioeconomic status and progression of carotid atherosclerosis. Prospective evidence from the Kuopio Ischemic Heart Disease Risk Factor Study. *Arterioscler Thromb Vasc Biol.* 1997;17:513–519.
- Thurston RC, El Khoudary SR, Derby CA, Barinas-Mitchell E, Lewis TT, McClure CK, Matthews KA. Low socioeconomic status over 12 years and subclinical cardiovascular disease: the study of women's health across the nation. *Stroke*. 2014;45:954–960.

- Rosvall M, Ostergren PO, Hedblad B, Isacsson SO, Janzon L, Berglund G. Occupational status, educational level, and the prevalence of carotid atherosclerosis in a general population sample of middle-aged Swedish men and women: results from the Malmo Diet and Cancer Study. *Am J Epidemiol.* 2000;152:334–346.
- Lamont D, Parker L, White M, Unwin N, Bennett SM, Cohen M, Richardson D, Dickinson HO, Adamson A, Alberti KG, Craft AW. Risk of cardiovascular disease measured by carotid intima-media thickness at age 49-51: lifecourse study. *BMJ*. 2000;320:273–278.
- Raitakari OT, Juonala M, Kahonen M, Taittonen L, Laitinen T, Maki-Torkko N, Jarvisalo MJ, Uhari M, Jokinen E, Ronnemaa T, Akerblom HK, Viikari JS. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. JAMA. 2003;290:2277–2283.
- Johnson HM, Douglas PS, Srinivasan SR, Bond MG, Tang R, Li S, Chen W, Berenson GS, Stein JH. Predictors of carotid intima-media thickness progression in young adults: the Bogalusa Heart Study. *Stroke*. 2007;38:900–905.
- 32. Juonala M, Viikari JS, Kahonen M, Laitinen T, Taittonen L, Loo BM, Jula A, Marniemi J, Rasanen L, Ronnemaa T, Raitakari OT. Alcohol consumption is directly associated with carotid intima-media thickness in Finnish young adults: the Cardiovascular Risk in Young Finns Study. *Atherosclerosis*. 2009;204:e93–e98.
- Lakka TA, Salonen R, Kaplan GA, Salonen JT. Blood pressure and the progression of carotid atherosclerosis in middle-aged men. *Hypertension*. 1999;34:51–56.
- 34. Rubba P, Panico S, Bond MG, Covetti G, Celentano E, lannuzzi A, Galasso R, Belisario MA, Pastinese A, Sacchetti L, Mancini M, Salvatore F. Site-specific atherosclerotic plaques in the carotid arteries of middle-aged women from southern Italy: associations with traditional risk factors and oxidation markers. *Stroke*. 2001;32:1953–1959.
- Kollias A, Psilopatis I, Karagiaouri E, Glaraki M, Grammatikos E, Grammatikos EE, Garoufi A, Stergiou GS. Adiposity, blood pressure, and carotid intimamedia thickness in Greek adolescents. *Obesity (Silver Spring)*. 2013;21:1013– 1017.
- Chaubey S, Nitsch D, Altmann D, Ebrahim S. Differing effect of modifiable cardiovascular risk factors on intima-media thickening and plaque formation at different sites of the arterial vasculature. *Heart.* 2010;96:1579–1585.
- Allan PL, Mowbray PI, Lee AJ, Fowkes FGR. Relationship between carotid intima-media thickness and symptomatic and asymptomatic peripheral arterial disease—the Edinburgh Artery Study. *Stroke*. 1997;28:348–353.
- Dietrich M, Jacques PF, Polak JF, Keyes MJ, Pencina MJ, Evans JC, Wolf PA, Selhub J, Vasan RS, D'Agostino RB. Segment-specific association between plasma homocysteine level and carotid artery intima-media thickness in the Framingham Offspring Study. J Stroke Cerebrovasc Dis. 2011;20:155– 161.
- Luo X, Yang Y, Cao T, Li Z. Differences in left and right carotid intima-media thickness and the associated risk factors. *Clin Radiol.* 2011;66:393–398.
- Peters SA, Bots ML. Carotid intima-media thickness studies: study design and data analysis. J Stroke. 2013;15:38–48.