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 ± standard deviation 24 ± 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 (χ² = 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

Cardiovascular disease (CVD) is the leading cause of death and a major cause of disability worldwide.¹ In the United States, CVD produces immense health and economic burdens.² Atherosclerotic changes in the carotid arteries generally reflect and predict systemic atherosclerotic diseases.³,⁴ A growing body of evidence indicates that the process of atherosclerosis begins at a young age.⁵ The first clinical manifestation of CVD often arises in a stage of well-advanced atherosclerosis.⁶ Carotid intima-media thickness (IMT) is a surrogate measure of atherosclerosis disease.⁷ Thus, measuring IMT is generally accepted as an early assessment method of subclinical atherosclerosis.⁸,⁹ Numerous epidemiologic studies have shown that IMT is also predictive of CVD.¹⁰,¹¹ 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.¹¹,¹² 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,¹³ which may due to the different methods of measuring IMT.¹⁴ 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...
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). Recruitment and evaluation of participants have been described in detail elsewhere. 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.

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: ≤11, 12 to 15, and ≥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 B-mode 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_mean_l=left-side mean IMT; IMT_max_l=left-side maximum IMT.

Statistical Analysis

Continuous variables are presented as mean±SD, whereas categorical variables are presented as cases (n) and percentage
The growth of IMT was assessed by use of individual growth curve modeling within a multilevel framework 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. 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 (range 20-36). The \( \text{IMT}_{\text{mean}}_r, \text{IMT}_{\text{max}}_r, \text{IMT}_{\text{mean}}_l, \text{and IMT}_{\text{max}}_l \) were 0.53±0.08, 0.70±0.10, 0.54±0.07, and 0.70±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 \( \text{IMT}_{\text{mean}}_r \) was higher in males.

Growth-Curve Models for Left-Side IMT

Results of growth-curve modeling for \( \text{IMT}_{\text{mean}}_l \) and \( \text{IMT}_{\text{max}}_l \) 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 \( \text{IMT}_{\text{mean}}_l \) (\( \beta=0.0213, P<0.001 \)) and \( \text{IMT}_{\text{max}}_l \) 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 \( \text{IMT}_{\text{mean}}_l \) and \( \text{IMT}_{\text{max}}_l \) 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 \( \text{IMT}_{\text{mean}}_l \), 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 \( \text{IMT}_{\text{mean}}_l \) (\( \beta=0.0171, P=0.001 \)) remained significant, but not \( \text{IMT}_{\text{max}}_l \) (\( \beta=0.0075, P=0.233 \)). 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 \( \text{IMT}_{\text{mean}}_l \) and for \( \text{IMT}_{\text{max}}_l \), 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 \( \text{IMT}_{\text{mean}}_r \) and \( \text{IMT}_{\text{max}}_r \). The unconditional growth model with fixed and random linear effects (age) provided the best fit for \( \text{IMT}_{\text{mean}}_r \), and with fixed and random linear effects (age) it provided the best fit for \( \text{IMT}_{\text{max}}_r \). Race/ethnicity had significant effects on \( \text{IMT}_{\text{mean}}_r \) (\( \beta=0.0281, P<0.001 \)) and \( \text{IMT}_{\text{max}}_r \) levels (\( \beta=0.0185, P=0.004 \)), also indicating higher levels in black than in white subjects. As shown in

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Effects on IMT_mean_r and IMT_max_r (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 and IMT_max_r levels; that is, right side IMT increased with increasing BMI, systolic BP, and PP but with decreasing.

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.
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.21,22

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.21,23 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 2. Results of Growth Curve Modeling for Left-Side Carotid IMT

|                  | Mean IMT | Max IMT |
|------------------|----------|---------|
|                  | B        | P Value | Explained Variance | β    | P Value | Explained Variance |
|                  |          |         | Between | Within |       | Between | Within |
| Model 1 (unconditional growth model) | 19.81 | 4.17 | 0.0026 | <0.001 | 0.0048 | <0.001 | 29.54 | 7.69 |
| Age              | -0.0050 | 0.457   |         |        | -0.0011 | 0.857 | 29.62 | 7.68 |
| Model 1+sex     | -0.0002 | 0.867   |         |        | 0.0007  | 0.678 | 29.99 | 7.82 |
| Model 3         | 24.37 | 3.98 | 0.0213 | <0.001 | 0.0134 | 0.035 | 53.43 | 5.44 |
| Model 4         | 24.09 | 2.93 | 0.0009 | 0.07   | 0.0022 | <0.001 |       |         |
| Model 5         | 24.85 | 2.91 | 0.0004 | 0.020  | 0.0005 | 0.020 | 36.14 | 6.62 |
| Model 6         |        |        |         |        | 0.0036 | 0.133 | 0.0007 | 0.013 |
| Model 7         | -0.0163 | <0.001 | 24.88 | 5.00 | -0.0107 | 0.043 | 30.91 | 8.26 |
| Model 8 (full model) | 31.03 | 3.52 | 0.0021 | <0.001 | 0.0037 | <0.001 | 47.95 | 5.99 |
| Age              | -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 | -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.
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. 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, 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. In line with previous findings

### Table 3. Results of Growth Curve Modeling for Right-Side Carotid IMT

|                | Mean IMT |                                                                 | Max IMT |                                                                 |
|----------------|----------|-----------------------------------------------------------------|---------|-----------------------------------------------------------------|
|                | β        | P Value             | Explained Variance | β       | P Value             | Explained Variance |
|                |          |                     | Between         |         |                     | Between         |
| Model 1 (unconditional growth model) |          | 8.91                | 3.33            | 0.0035  | <0.001              | 16.63           | 5.57            |
| Age            | 0.0006   | 0.332               |                 |         |                     |                 |
| Model 2        |          | 10.49               | 3.17            |         |                     |                 |
| Model 1+sex    | -0.0075  | 0.158               |                 |         |                     |                 |
| Model 1+sex×age| -0.0024  | 0.063               |                 |         |                     |                 |
| Model 3        |          | 19.81               | 2.57            | 0.0185  | 0.004               |                 |
| Model 1+race/ethnicity | 0.0281  | <0.001              |                 |         |                     |                 |
| Model 1+race/ethnicity×age | 0.0008  | 0.546               |                 |         |                     |                 |
| Model 1+race/ethnicity×sex | -0.0032 | 0.758               |                 |         |                     |                 |
| Model 4        |          | 16.90               | 2.39            | 0.0021  | <0.001              |                 |
| Model 1+BMI    | 0.0012   | 0.001               |                 |         |                     |                 |
| Model 1+height | 0.0005   | 0.115               |                 |         |                     |                 |
| Model 1+BMI×age| 0.0001   | 0.078               |                 |         |                     |                 |
| Model 1+BMI×sex | -0.0010 | 0.128               |                 |         |                     |                 |
| Model 1+BMI×race/ethnicity | 0.0010  | 0.150               |                 |         |                     |                 |
| Model 5        |          | 15.44               | 2.91            | 0.0007  | 0.006               |                 |
| Model 1+SBP    | 0.0006   | 0.002               |                 |         |                     |                 |
| Model 1+PP     | 0.0007   | 0.002               |                 |         |                     |                 |
| Model 6        |          |                     |                 |         |                     |                 |
| Model 1+smoking| 0.0062   | 0.208               |                 |         |                     |                 |
| Model 1+alcohol| -0.0044  | 0.377               |                 |         |                     |                 |
| Model 1+exercise| 0.0016  | 0.737               |                 |         |                     |                 |
| 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            | 0.0024  | 0.006               |                 |
| Age            | 0.00002  | 0.970               |                 |         |                     |                 |
| Sex            | -0.0136  | 0.008               |                 |         |                     |                 |
| Race/ethnicity | 0.0249   | <0.001              |                 |         |                     |                 |
| BMI            | 0.0009   | 0.008               |                 |         |                     |                 |
| 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 intima-media 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.

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IMT increased with increasing BMI, and childhood SES played a significant role early in the atherosclerotic disease process.

Contrary to numerous previous studies we did not find an association between IMT and exercise, smoking, and alcohol drinking. 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. The short smoking duration in the younger population may be one possible reason to explain this paradox. Several studies have reported an association between systolic BP and IMT in a middle-aged population, but some studies in children and young adults have not found such an association. 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).

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. Several other studies

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

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. 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. Hernandez and colleagues found a higher left IMT than right IMT in untreated hypertensive patients, and this finding has been attributed to the higher cross-sectional area of the intima-media complex and higher flow velocity at the left side. 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. 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 artherosclerosis, 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 left-side 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.

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