

Subclinical Atherosclerosis and Metabolic Risk: Role of Body Mass Index and Waist Circumference

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Abstract

Background: Carotid artery intima-media thickness (IMT) is greater in adults with elevated metabolic risk profiles. However, the influence of body mass index (BMI) or waist circumference (WC) on the relationship between IMT and metabolic risk is unclear.

Methods: Adults from the Bogalusa Heart Study were classified as normal weight, overweight, or obese and into WC categories (men, low <94 cm, moderate 94–101.9 cm, high ≥ 102 cm; women, low <80 cm, moderate 80–87.9 cm, high ≥ 88 cm). Elevated metabolic risk was defined by cardiovascular risk factor clustering (≥ 2 abnormal risk factors or insulin resistance (upper quartile of homeostasis model of insulin resistance)). Carotid ultrasound measurements were obtained and mean IMT was calculated. General linear models compared IMT between elevated versus normal metabolic risk groups, adjusting for sex, age, race/ethnicity, and either BMI or WC category.

Results: Adults were 24–43 years of age ($n = 991$) and 41% had elevated metabolic risk (42% male, 28% African American, 38% obese). IMT (mm) was greater in adults with elevated metabolic risk (0.83 ± 0.007) versus normal risk (0.80 ± 0.006) whether adjusted by BMI or WC (both $P < 0.0005$). IMT was greater in adults with elevated compared to normal metabolic risk within normal-weight (0.84 ± 0.016 vs. 0.79 ± 0.008 ; $P = 0.002$), and obese adults (0.86 ± 0.009 vs. 0.80 ± 0.01 ; $P = 0.03$), but not significantly different between risk groups in overweight adults. Similar results were found when stratified by WC category.

Conclusion: Adults with elevated metabolic risk have greater IMT than those with normal risk in normal-weight, overweight, low WC, and high WC, but not significant for overweight or moderate WC categories.

Introduction

MEASUREMENT OF INTIMA MEDIA thickness (IMT) is assessed by a noninvasive ultrasound imaging technique that can measure the extent of generalized atherosclerosis detected in the arterial wall. IMT reflects cardiovascular disease development in asymptomatic, healthy individuals. IMT is positively associated with the number of abnormal cardiovascular disease risk factors,¹ presence of metabolic syndrome,^{2–5} insulin resistance,^{6,7} diabetes,^{8–10} and occurrence of myocardial infarction and stroke.^{11–13} Thus, IMT is an important early screening tool to assess subclinical manifestation of cardiovascular and metabolic diseases.

Despite the known relationship between IMT and cardiovascular disease and diabetes, the influence of anthropometric markers of obesity, such as body mass index (BMI) and waist circumference (WC), is not well understood.

Higher IMT has been shown to be associated with both elevated BMI and WC,^{6,14–18} although this relationship is not always significant.^{7,19–21} Possible reasons for this inconsistency may be due to the influences of existing chronic disease, insulin resistance, or cardiometabolic risk on both IMT and the surrogate measures of adiposity. Due to its possible influence, BMI is often controlled for in studies that examine the relationship of cardiometabolic risk on IMT,^{22–25} but few studies explicitly explore the relationship of IMT and metabolic risk on BMI. Some evidence suggests that obese individuals with insulin resistance have greater IMT compared to their obese, normal metabolic risk counterparts²⁶; however, whether this relationship is consistent across the other BMI groups has not yet been investigated. Furthermore, when participants were matched for BMI and waist-to-hip circumference, there were no differences in IMT between those with normal versus impaired glucose tolerance,²⁷ possibly suggesting some interactions of BMI and WC on the

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relationships between IMT and metabolic risk. Thus, the purpose of this study is to examine IMT between elevated and normal metabolic profiles within BMI (normal weight, overweight, and obese) and WC (low, moderate, and high) groups.

Methods

Study population

The Bogalusa Heart Study is a long-term community-based epidemiologic study of the early natural history of cardiovascular disease in children and young adults from the semirural, biracial (65% white, 35% black) community of Bogalusa, Louisiana.²⁸ The present study sample includes adults measured in the 2001–2002 survey ($n=1,144$) who had IMT measurements. Participants were excluded from the analysis if they were underweight ($BMI \leq 18.5$) ($n=12$), nonfasted ($n=14$), pregnant ($n=7$), had missing variables ($n=18$), or had values greater than ± 3 standard deviations (SD) from the mean for IMT, BMI, WC, systolic blood pressure (SBP), diastolic blood pressure (DBP), triglycerides, high-density lipoprotein cholesterol (HDL-C), insulin, and glucose ($n=102$). The final sample for this particular analysis included 991 (87% of total sample) adults (24–43 years of age; mean 36.2 ± 4.4). Institutional review board (IRB) approval was given from both Tulane University for the data collection, and from Pennington Biomedical Research Center for data analysis.

General examination

Duplicate measurements of height and weight were obtained to the nearest 0.1 cm and 0.1 kg, respectively, and averaged for analysis. BMI was calculated as weight in kilograms divided by the height in meters squared (kg/m^2). WC was measured with a flexible tape midway between the lowest rib and the superior border of the iliac crest. SBP and 5th phase DBP were measured from the right arm with a mercury sphygmomanometer and averaged from six readings performed by two randomly assigned nurses.

Laboratory analyses

All participants were requested to fast for a minimum of 12 h for venipuncture. Blood sample assays were performed in the Core Lipid Laboratory in New Orleans, Louisiana. Blood lipids were measured by a VP instrument (Abbott Laboratories, North Chicago, IL) using enzymatic procedures^{29,30} under quality controls by the Centers for Disease Control and Prevention (Atlanta, GA). Serum triglyceride concentrations were measured with enzymatic procedures, and serum HDL-C was measured using a heparin–calcium precipitation in combination with an agar–agarose gel electrophoresis.³¹ Plasma glucose was measured using an enzymatic procedure, whereas insulin was measured with a commercial radioimmunoassay kit (Phadebas, Pharmacia Diagnostics, Piscataway, NJ).

Carotid ultrasonography

Carotid ultrasound measurements were performed with a Toshiba Ultrasound instrument (Power Vision Toshiba SSH-380 ultrasound system, Toshiba American Medical Systems, Carrollton, TX), using a 7.5-MHz linear array transducer recording images at the common carotid (CC), carotid bulb (CB) (bifurcation), and internal carotid (IC) arteries. Images

were obtained bilaterally according to previously developed protocols for the Atherosclerosis Risk in Communities study.³² Images were recorded on super VHS videotapes and read by certified readers from the Vascular Ultrasound Research Laboratory in Wake Forest Medical Center, North Carolina, using semiautomatic ultrasound imaging. The maximum carotid IMT readings of left and right far walls were averaged for each segment; if bilateral images could not be obtained, one side was used in lieu of the average. Mean carotid IMT was calculated as the average carotid IMT from available measures for CC, CB, and IC segments. Due to some missing data for individual carotid segments, the total n differed between the groups for mean IMT ($n=991$), CC ($n=991$), CB ($n=949$), and IC ($n=974$).

Data treatment

Participants were classified as normal weight (BMI, 18.5–24.9 kg/m^2), overweight (BMI, 25–29.9 kg/m^2), or obese (BMI, ≥ 30 kg/m^2), and were also placed into sex-specific low, moderate, or high WC categories (men, low <94 cm, moderate 94–101.9 cm, high ≥ 102 cm; women, low <80 cm, moderate 80–87.9 cm, high ≥ 88 cm).³³

“Elevated” metabolic risk was defined by meeting the criteria for either cardiovascular risk factor clustering and/or insulin resistance. Cardiovascular risk factor clustering was defined by having two or more abnormal cardiometabolic risk factors: (1) triglycerides ≥ 150 mg/dL, or on drug treatment; (2) HDL-C <40 mg/dL for men; <50 mg/dL for women, or on drug treatment; (3) blood pressure $\geq 130/85$ mmHg, or on drug treatment; and (4) fasting glucose ≥ 100 mg/dL, or on drug treatment.³⁴ Insulin resistance was estimated by the homeostasis model of insulin resistance (HOMA-IR), which is calculated by [(fasting glucose * fasting insulin)/22.5].³⁵ Elevated metabolic risk from insulin resistance was estimated as the top quartile of HOMA-IR (≥ 3.2) or on insulin or glucose drug treatment. Similar definitions combining insulin resistance and clustering of cardiovascular risk factors have been used in other studies to identify metabolic risk profiles.^{36–39}

Statistical analysis

Differences between elevated and normal metabolic risk profiles were analyzed with t -tests for normally distributed cardiovascular disease risk factors, and nonnormally distributed variables (triglycerides, insulin, HOMA-IR) were analyzed with Wilcoxon–Mann–Whitney tests. General linear models were used to compare mean IMT as well as each individual carotid segment (CC, CB, IC) among those classified as elevated versus normal metabolic risk adjusting for sex, age, and race/ethnicity and either BMI group or WC group. Additional analyses were stratified by BMI and WC categories. BMI and WC were also analyzed continuously in the models to compare consistency of results.

Results

Descriptive characteristics of the Bogalusa Heart Study sample ($n=991$) are presented in Table 1. The mean (\pm SD) age of the sample was 36.2 ± 4.4 years and mean BMI was 29.0 ± 6.4 kg/m^2 . A total of 38% of the sample was obese, 42% were male, and 28% were African American. Significant differences were present between normal and elevated metabolic

TABLE 1. DESCRIPTIVE CHARACTERISTICS OF THE BOGALUSA HEART STUDY SAMPLE (N=991)

	Total (n=991)	Normal risk (n=585, 59%)	Elevated risk (n=406, 41%)	P value ^a
Male (n, %)	417 (42)	223 (38)	194 (48)	0.002
White (n, %)	717 (72)	438 (75)	279 (69)	0.03
Age (years)	36.2 ± 4.4	36.1 ± 4.3	36.4 ± 4.6	0.32
BMI (kg/m ²)	29.0 ± 6.5	26.4 ± 5.0	32.7 ± 6.6	< 0.0001
Normal weight, n (%)	309 (31)	263 (45)	46 (11)	
Overweight, n (%)	306 (31)	204 (35)	102 (25)	< 0.0001 ^b
Obese, n (%)	376 (38)	118 (20)	258 (64)	
Waist circumference (cm)	92.5 ± 16.3	85.5 ± 12.7	102.6 ± 15.5	< 0.0001
Low, n (%)	402 (41)	333 (57)	69 (17)	
Moderate, n (%)	192 (19)	124 (21)	68 (17)	< 0.0001 ^b
High, n (%)	397 (40)	128 (22)	269 (66)	
Triglycerides (mg/dL) ^c	102 (73–146)	85 (64–113)	147 (102–204)	< 0.0001
Systolic blood pressure (mmHg)	115.5 ± 12.3	111.7 ± 10.5	121.1 ± 12.5	< 0.0001
Diastolic blood pressure (mmHg)	78.2 ± 9.0	75.3 ± 7.9	82.4 ± 8.9	< 0.0001
HDL-C (mg/dL)	47.3 ± 12.0	50.9 ± 11.8	42.2 ± 10.2	< 0.0001
Glucose (mg/dL)	83.3 ± 10.9	79.9 ± 7.8	88.2 ± 12.8	< 0.0001
Insulin (μU/mL) ^c	10 (7–15)	8 (6.0–11.0)	17 (11–22)	< 0.0001
HOMA-IR ^c	2.0 (1.3–3.2)	1.5 (1.1–2.1)	3.6 (2.2–5.0)	< 0.0001
IMT (mm)	0.80 ± 0.13	0.78 ± 0.12	0.83 ± 0.14	< 0.0001

^aP value represents the comparison of the unadjusted t-tests between normal and elevated risk.

^bP value represents the chi-squared comparison between normal and elevated risk.

^cDue to nonnormal distribution, nonparametric Wilcoxon rank sum tests were used to compare values between normal and elevated risk.

BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; IMT, intima media thickness.

risk groups for BMI, WC, triglycerides, SBP, DBP, HDL-C, glucose, insulin, HOMA-IR, and IMT (all *P* < 0.0001).

Effect of metabolic risk by individual carotid artery segments and mean IMT

Overall, adults with elevated metabolic risk had higher mean IMT values than adults with normal metabolic risk, whether adjusting for BMI category (0.83 ± 0.007 versus 0.80 ± 0.006; *P* = 0.0001) (Fig. 1) or WC group (0.83 ± 0.007 versus 0.80 ± 0.006; *P* = 0.0004) (Fig. 2). Significant effects of

race/ethnicity and sex were also found for both WC- and BMI-adjusted models whereby men had higher IMT values than women (*P* < 0.0001) and African-American adults had higher IMT than white adults (*P* = 0.02). The statistical significance of these results did not change when BMI or WC were included as a continuous rather than a categorical covariate.

These results were also consistent for the individual carotid artery segments. In the analysis adjusted by BMI group, adults with elevated metabolic risk had a higher CC (mean difference, 0.02 ± 0.008, *P* = 0.003), IC (mean difference, 0.03 ± 0.013, *P* = 0.01), and CB (mean difference, 0.04 ± 0.02, *P* = 0.005) than

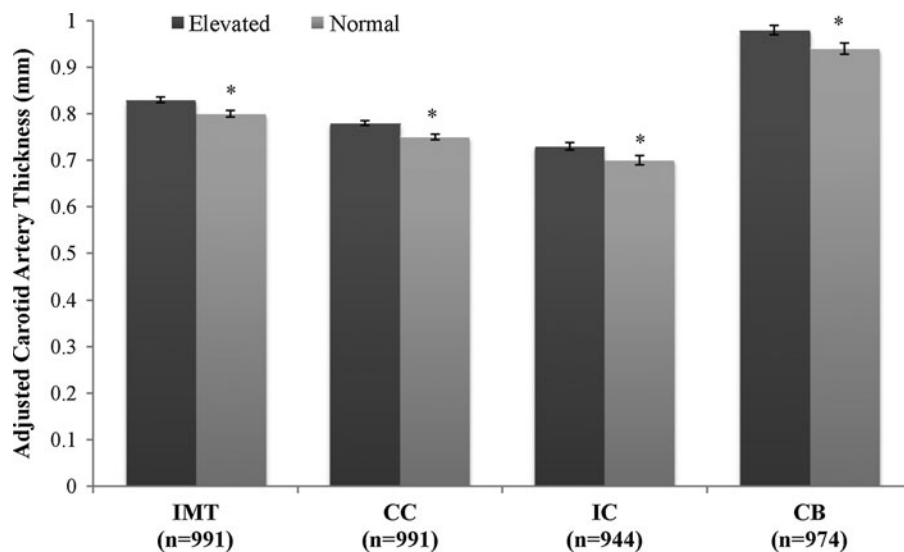


FIG. 1. Individual carotid segment thickness [mean ± standard error (SE)] between metabolic risk profiles adjusted for body mass index (BMI) group. Adjusted for age, sex, race, and BMI group (normal weight, overweight, and obese). (*) Significant difference between elevated and normal metabolic risk profile (*P* < 0.05). IMT, mean intima media thickness; CC, common carotid segment; IC, internal carotid segment; CB, carotid bulb segment.

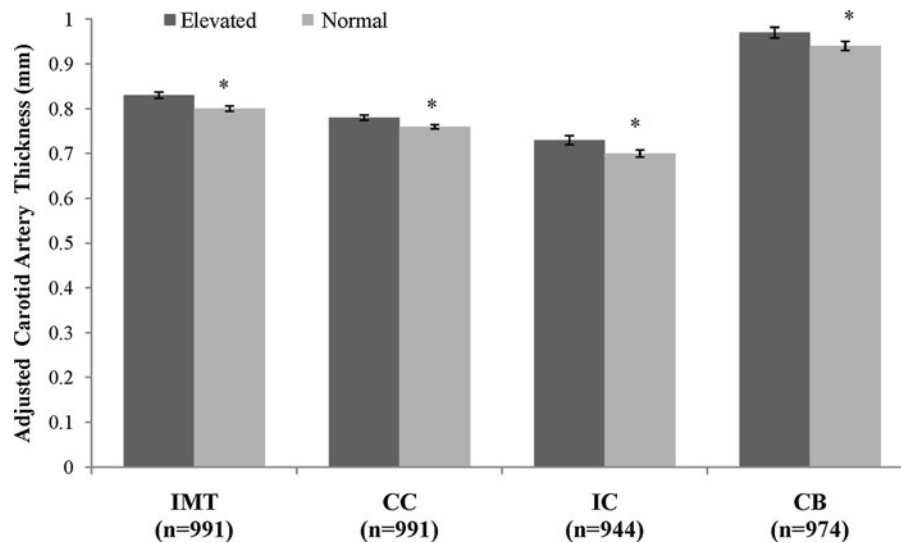


FIG. 2. Individual carotid segment thickness [mean \pm standard error (SE)] between metabolic risk profiles adjusted for waist circumference (WC) group. Adjusted for age, sex, race, and WC group (sex-specific low, moderate, and high). (*) Significant difference between elevated and normal metabolic risk profile ($P < 0.05$). IMT, Mean intima media thickness; CC, common carotid segment; IC, internal carotid segment; CB, carotid bulb segment.

adults in the normal metabolic risk group (Fig. 1). When adjusted by WC group, adults with elevated metabolic risk had a higher CC (mean difference, 0.02 ± 0.008 , $P = 0.01$), IC (mean difference, 0.03 ± 0.01 , $P = 0.006$), and CB (mean difference, 0.04 ± 0.02 , $P = 0.02$) than adults with normal metabolic risk (Fig. 2). Statistical significance did not change whether BMI or WC was analyzed as continuous versus categorical variables, except in the case of WC-adjusted CC. When waist circumference was added as a continuous variable, differences between elevated and normal metabolic risk groups were no longer significant for CC ($P = 0.15$).

Effect of metabolic risk by BMI and WC groups

The prevalence of elevated metabolic risk was 41% overall, and 11%, 25%, and 64% in normal-weight, overweight, and

obese groups, respectively, and 17%, 17%, and 66% in low, moderate, and high WC groups, respectively (Table 1). When regression analyses were stratified by BMI category, adjusted IMT was greater in those with elevated metabolic risk compared to normal metabolic risk within normal-weight (0.84 ± 0.016 vs. 0.79 ± 0.008 ; $P = 0.002$) and obese adults (0.86 ± 0.009 vs. 0.80 ± 0.01 ; $P = 0.03$), but not in the overweight adults (0.83 ± 0.012 vs. 0.80 ± 0.009 ; $P = 0.06$). Figure 3 presents the analysis stratified by BMI groups.

When regression analyses were stratified by WC category, adjusted IMT was greater in those with elevated metabolic risk compared to normal metabolic risk in the low WC (0.83 ± 0.013 vs. 0.79 ± 0.007 ; $P = 0.003$), and high WC group (0.84 ± 0.009 vs. 0.80 ± 0.012 ; $P = 0.003$), but not in the moderate WC group (0.81 ± 0.012 vs. 0.82 ± 0.015 ; $P = 0.79$). Figure 4 presents the analysis stratified by WC groups.

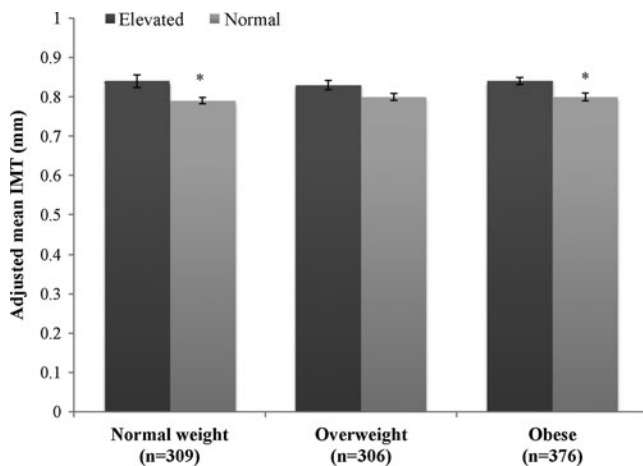


FIG. 3. Mean intima media thickness (IMT) [mean \pm standard error (SE)] between metabolic risk profiles within body mass index (BMI) groups. Adjusted for age, sex, and race. (*) Significant difference between elevated and normal metabolic risk profile ($P < 0.05$).

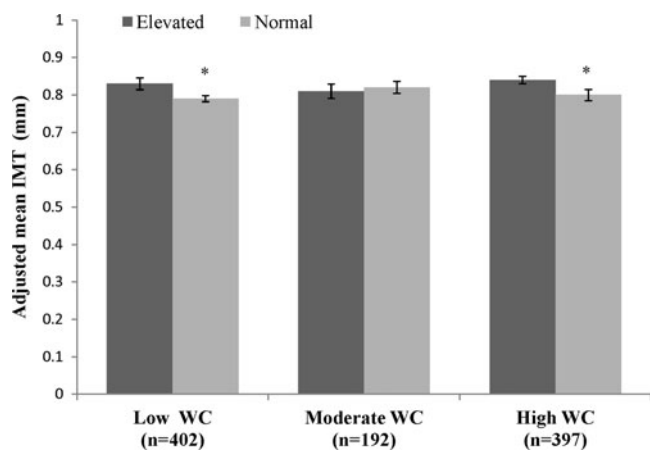


FIG. 4. Mean intima media thickness (IMT) [mean \pm standard error (SE)] between metabolic risk profiles within waist circumference (WC) groups. Adjusted for age, sex, and race. (*) Significant difference between elevated and normal metabolic risk profile ($P < 0.05$).

Discussion

In the current study, young adults had IMT values that varied by metabolic risk profile, independently of BMI or WC. Adults classified with elevated metabolic risk, defined as having either cardiovascular risk factor clustering or insulin resistance, showed greater IMT than their normal risk counterparts. These results were consistent across mean IMT and the individual carotid segments (CC, IC, and CB), as well as within BMI and WC groups.

Others have also found IMT to differ by metabolic risk status employing a definition of either insulin resistance⁷ or cardiometabolic risk factor clustering,^{1,4} although few have tested whether this relationship was independent of BMI or WC.⁷ Freedman et al. have suggested that cardiovascular risk factors have a stronger association with IMT than BMI.⁴⁰ Metabolic risk assessment, regardless of BMI, can also predict the development of type 2 diabetes, cardiovascular disease, and death.^{37,41} Kawamoto et al. have shown that IMT is greater in normal-weight adults with metabolic syndrome versus those without metabolic syndrome in a clinical sample of Japanese elderly.⁴² In addition, Stefan et al. found greater IMT in obese adults with insulin resistance versus without in a German sample.²⁶ The current study provides additional evidence that metabolic risk is significantly associated with subclinical atherosclerosis in a large biracial sample of men and women.

Specific differences in IMT were found between metabolic risk groups in normal-weight and obese adults classified by BMI and in low WC or high WC adults. There were no significant differences in elevated versus normal metabolic risk for IMT in either the overweight or moderate WC groups. However the differences between the normal versus elevated metabolic risk in the overweight group approached significance ($P = 0.06$). Possible reasons for nonsignificance in the moderate WC groups are uncertain, but could be due to the lower number of adults classified into this group or the lower amount of variation due to an upper and lower bound category. In addition, there were significant effects of sex within the moderate WC group. When we stratified the analysis by sex (data not shown), we found that women had significant differences in IMT between normal and elevated metabolic risk, whereas men did not. Thus, possible gender/sex influences may also explain the lack of statistical difference within the whole group.

The physiological mechanisms for the relationships between IMT and metabolic risk may relate to insulin levels acting on the arterial wall, resulting in cellular remodeling, or through insulin's association with clustering of multiple cardiovascular disease risk factors.⁴³ Stefan et al. found that ectopic liver fat was the most important predictor of a person's metabolic status, whether they were normal weight, overweight, or obese. However, these findings need to be confirmed in larger population-based studies.²⁶ Possible influences of metabolic status on IMT may relate to lifestyle behaviors, such as dietary intake or physical activity, and future studies are needed to help explain greater IMT in individuals with elevated metabolic risk, regardless of obesity status.

We used WC and BMI as surrogate measures for obesity; however, the Bogalusa Heart Study also has triceps and subscapular skinfold measures that estimate subcutaneous adiposity. Using the sum of the two skinfolds, IMT was

significantly greater in elevated metabolic risk versus normal metabolic risk groups within each tertile of skinfolds (data not shown). These results are consistent with our results for BMI and WC, also suggesting that metabolic risk is related to IMT, independent of adiposity.

A marked strength of this study is the use of the Bogalusa Heart Study data, which includes a large cohort of young adults with IMT measures. We were able to employ measures from three carotid segments for a computed IMT mean, which has been shown to provide a better prediction for cardiovascular-related events.¹³ IMT is known to be influenced by aging,^{20,44} and using this measure in asymptomatic young, healthy asymptomatic adults is indicative of early stages of atherosclerosis. IMT measurement in young adults may reflect the local arterial shear stress and pressure environment influenced by other lipid and metabolic risk factors, as opposed to actual atherosclerotic lesions.²⁰ Furthermore, previous evidence from the Bogalusa Heart Study has shown both sex and racial/ethnic influences of the relationship of BMI to IMT.²⁴ Although we do not have the statistical power to specifically analyze racial/ethnic effects due to smaller number of African-American adults overall, we were able to use the full sample of African-American and white men and women and control for demographic characteristics in our analysis. Finally, because we have performed only cross-sectional analysis, the direction or causality of the observed relationships could not be determined.

In conclusion, IMT is associated with metabolic risk profiles, independent of BMI or WC. These results imply that assessment of metabolic risk, regardless of a person's BMI or WC, can provide valuable information concerning atherosclerosis status, even in young adults. Research is needed to identify the casual links between specific metabolic risk indicators and IMT for given levels of adiposity, and to determine the effects of interventions designed to decrease metabolic risk and their effects on IMT across classes of BMI.

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Author Disclosure Statement

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