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Relations among Adiposity and Insulin Resistance with Flow-Mediated Dilation, Carotid Intima-Media Thickness, and Arterial Stiffness in Children

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Abstract

Objective—To determine the associations of adiposity and insulin resistance with measures of vascular structure and function in children.

Study design—A cross-sectional study included 252 children (age 15.1±2.4 yrs; body mass index (BMI)-percentile 68.2±26.5%; Tanner 2–5). Measurements of body fat percentage (BF%) were obtained with dual-energy X-ray absorptiometry (DXA) and visceral fat (VAT) with computed tomography (CT). Insulin resistance was measured with hyperinsulinemic euglycemic clamp. Vascular measurements for endothelial function (brachial artery flow-mediated dilation [FMD]), vascular structure (carotid intima-media thickness [cIMT]), vascular stiffness (carotid incremental elastic modulus [cIEM]), and pulse wave velocity (PWV) were analyzed by tertiles of adiposity and insulin resistance. Additional analyses with ANCOVA and linear regression, were adjusted for Tanner, sex, race, and family relationship; FMD was also adjusted for baseline artery diameter.

Results—FMD was positively associated with high adiposity (BMI, BF%, and VAT) ($p<0.01$ all). Insulin resistance was not associated with FMD. cIMT was significantly, positively related to obesity, VAT, and insulin resistance ($p<0.05$ all). No differences in cIEM and PWV were observed in relation to adiposity or insulin resistance.

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The other authors declare no conflicts of interest.

Conclusions—The findings suggest that adiposity is associated with higher FMD, and insulin resistance and VAT are associated with higher cIMT in children. Further research is needed to clarify the progression of these relations.

Keywords

Adiposity; Obesity; Insulin Resistance; Pediatric; Flow-mediated Dilation; Carotid Intima-Media Thickness; Cardiovascular Disease Risk

Studies in adults have shown adiposity and insulin resistance to be associated with vascular dysfunction and adverse thickening of the vascular wall, measured by carotid intima-media thickness (cIMT)[1–5]. Although these relations are less clear in children, several studies have reported the same adverse relations for adiposity with vascular measures [6–12], and others observed no significant relations.[13–15] However, a recent population based cohort of pre-pubertal children provided data suggesting that adiposity tends to be associated with both an increase in brachial artery flow mediated dilation (FMD) and decrease in arterial stiffness as measured by pulse wave velocity (PWV).[15] Thus, the relationship between adiposity with FMD, cIMT, and arterial stiffness (PWV) remains to be fully defined.

Insulin resistance is associated with obesity and cardiovascular risk factors, beginning in childhood.[16] Studies are needed to examine the relation between insulin resistance, and FMD, cIMT, and arterial stiffness in children. Given that total body and visceral adipose tissue (VAT) play significant, and potentially different roles in relation to insulin resistance and the pathophysiology of cardiovascular disease (CVD),[17] body fat measurements will improve our understanding of the role it plays in the early changes in FMD, cIMT, and arterial stiffness. Furthermore, studying the associations of insulin resistance and adiposity with measures of vascular structure and function, while controlling for pubertal maturation, may yield information toward the understanding of the complex relations between obesity and vascular function and structure in children.

The purpose of this study was to examine the relationship of FMD, cIMT, and arterial stiffness with multiple measures of adiposity and insulin resistance measured by hyperinsulinemic euglycemic clamp in a cohort of healthy children.

Methods

The study protocol was approved by the University of Minnesota Institutional Review Board, and consent/assent was obtained from parents/participants. Data for this study were collected from participants recruited from the Minneapolis - St. Paul Metro area, for two longitudinal studies conducted at the University of Minnesota: 1) a community-based study evaluating cardiometabolic risk in healthy children (2006–2011; n=141; age 9–18 years); and 2) healthy siblings serving as a control group for a cohort of childhood cancer survivors (2007–2012; n=111; age 8–20 years). Participants were included if they were Tanner stage 2–5, normotensive, non-diabetic, free from chronic diseases, and were not taking medications known to influence vascular function and/or glucose metabolism. Both studies were conducted in the Clinical Research Center using similar personnel, equipment, and protocols.

All testing was performed in the morning after an overnight fast (including no caffeine consumption) of at least 8 hours. Height and weight were measured using a wall-mounted stadiometer and an electronic scale, respectively. BMI was calculated as body weight in kilograms divided by the height in meters squared. BMI-percentiles were determined using age and sex based Centers for Disease Control definitions.[18] Normal-weight was defined as >5th to <85th percentile, overweight ≥85th to < 95th percentile, and obesity ≥ 95th percentile. Tanner staging for pubertal maturation was performed by a trained nurse or physician.[19, 20] Blood pressure was measured twice on the right arm after participants were sitting in a quiet room for at least five minutes using a digital blood pressure monitor and the average of the two values was reported for systolic (SBP) and diastolic blood pressure (DBP). A fasting lipid profile [total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG)], and fasting insulin were measured using standard procedures at the Fairview Diagnostic Laboratories at the Fairview-University Medical Center (Minneapolis, MN), a Centers for Disease Control and Prevention–certified laboratory.

Insulin resistance was measured by hyperinsulinemic euglycemic clamp, as previously described.[21] Insulin was infused at a constant rate of 1 μU/kg/min for 3 hours, and glucose was infused at a variable rate to maintain euglycemia (100mg/dl). Insulin resistance (M) was expressed as the amount of glucose required to maintain euglycemia in the last 40 minutes of the clamp (mg/kg/min of glucose) with adjustment for lean body mass (M_{lbm}). Lower M_{lbm} represents greater insulin resistance.

Body fat percentage (BF%) was measured using dual-energy X-ray absorptiometry (DXA) (Lunar Prodigy, General Electric Medical Systems) and analyzed using its enCoreTM software (platform version 13.6, GE Healthcare, Madison, WI, USA). Estimates of abdominal VAT were obtained by CT using a Siemens Sensation 16 (Siemens Medical Solutions, Malvern, PA, USA) with two separate 10 mm slices obtained at the L4–L5 interspace. The two images were subdivided into 5 mm slices and the first and third 5 mm slices were combined and analyzed for VAT. The upper limit of adipose tissue density was −30 Hounsfield units and the lower limit was −190 Hounsfield units. Image slices were individually analyzed by one trained technician using a computer program (Fat Scan version 3.0; N2 System, Osaka, Japan).

Endothelial function was evaluated using brachial artery flow-mediated dilation (FMD) measured with standard ultrasound using a 8–15 MHz linear array transducer held at a constant pressure on the skin and at a fixed point over the imaged artery by a stereotactic arm to obtain B-mode images (Siemens, Sequoia 512, New York, NY) following current guidelines.[22] An electronic wall-tracking software program (Medical Imaging Applications, Coralville, IA) was used for the measurement of brachial artery diameter and blood flow. Following baseline measurements, a blood pressure cuff was placed on the forearm (distal to the imaged area) and inflated to a suprasystolic level (>200mmHg) for 5 minutes. After 5 minutes, cuff occlusion was released and B-mode ultrasound images were captured for approximately three minutes after release. The maximum diameter recorded following reactive hyperemia was reported relative to baseline vessel diameter (FMD = peak diameter – baseline diameter/baseline diameter). An area under the curve (AUC) for FMD was

calculated using the trapezoidal method. All measurements were conducted by the same group of sonographers, under the supervision of the same laboratory director. Our laboratory has previously documented satisfactory FMD reproducibility with the same individual tested one week apart having a mean difference of 0.53±0.28%.[23]

Vascular structure was evaluated using carotid intima-media thickness (cIMT). Images for determining cIMT were obtained at end-diastole (gated by R wave on ECG) using B-mode images of the far wall of the left common carotid artery. Measurements were obtained at the distal 10 mm of the common carotid artery as recommended by pediatric guidelines.[24] An electronic wall-tracking software program was used for the analysis of cIMT. Our laboratory has previously documented satisfactory reproducibility for measurement of cIMT, with the mean difference for repeated measurements on separate days in the same subjects of 0.02 ± 0.03 mm.[25]

Carotid arteries also were imaged to capture the left common carotid artery diastolic and systolic lumen diameters to determine carotid incremental elastic modulus (cIEM, mmHg), a measure of carotid artery stiffness. Systolic and diastolic blood pressures were recorded with an automated blood pressure sphygmomanometer (Colin Medical Instruments Corp., San Antonio, TX, USA) during the 10-sec measurements. The ultrasound scanning system was interfaced with a standard computer, with images collected at 20 frames/sec for 10-sec (200 frames) to ensure the capture of full arterial diameter change during a cardiac cycle and calculated using a standard formula.[26] Arterial stiffness also was measured by carotid-radial pulse wave velocity (PWV) (SphygmoCor® system, Sydney, Australia). PWV was calculated as distance (m)/transit time (s). The distance was measured between the carotid and radial sites and the sternal notch.

Statistical Analyses

Demographic, anthropometric, and cardiometabolic differences across sex were compared by paired t-test. Data were examined using both continuous and categorical analysis. Data for BF%, VAT, insulin resistance (M_{lbm}), and fasting insulin were split into categorical variables by tertile. The relation between obesity status (normal-weight, overweight, obese), BF%, VAT, insulin resistance, and fasting insulin as categorical variables and both FMD and FMD AUC were assessed by ANCOVA using linear mixed models to adjust for Tanner stage, sex, race, family relationship (ie, siblings), and baseline artery diameter with post-hoc testing for between group differences conducted using Bonferroni correction. Relations to cIMT, cIEM, and PWV were evaluated by ANCOVA using linear mixed models adjusting for Tanner stage, sex, race, and family relationships (siblings). Multiple linear regression analysis was used to examine the association of M_{lbm}, fasting insulin, and BF% on FMD and FMD AUC as continuous variables. Covariates in the analysis were Tanner stage, sex, race, family relationship (siblings), and baseline artery diameter. cIMT, cIEM, and PWV were evaluated similarly using multiple linear regression models adjusting for Tanner stage, sex, race, and family relationships (siblings). All models accounted for sibling relationships (17 families with 2 siblings; 2 with 3 siblings; and 1 with 4 siblings. It has been proposed that simple adjustment for baseline artery diameter may not be sufficient to account for the confounding relationship of artery diameter on FMD, therefore we conducted allometric

scaling in addition to more traditional analysis in order to confirm our findings.[27, 28] Analysis was conducted using SPSS version 22.0 (IBM, Armonk, NY). Data are presented as mean ± SD (except where noted). Significance was set at an alpha level of $p<0.05$.

Results

Demographic and clinical characteristics of the study population divided by sex are presented in the Table. A total of 252 children, age 8–20 years (mean age = 15.1 ± 2.4 yrs; M=121; mean BMI-percentile = 68.2 ± 26.5) were included. No sex-specific differences were observed for age, BMI, BMI – percentile, total cholesterol, LDL-C, HDL-C, TG, DBP, VAT, $M_{lbm,}$ Fasting insulin, cIMT, cIEM, or PWV. Males were taller, had higher SBP, and had larger brachial artery diameter than females. Females had a greater Tanner stage, BF%, FMD, and FMD AUC than males. However, after adjustment for baseline artery diameter, no differences were present between males and females for FMD (P = 0.58) and FMD AUC (P= 0.84). Combined data for males and females examining the relations of adiposity with vascular measures are presented in Figure 1 and 2.

Obese children had significantly greater FMD (Figure 1, A) and FMD AUC (p=0.01) compared with overweight and normal-weight children. Data analyzed across tertiles of BF % and VAT showed significantly higher FMD (Figure 1, B and C) and FMD AUC (p=0.003 and p<0.001, respectively) in the highest compared with the lowest tertile. There were no significant differences in FMD or FMD AUC between normal weight and overweight children or between low and mid BF% tertiles. No differences in FMD or FMD AUC were seen by tertiles of M_{lbm} (Figure 1, D). Children in the highest tertile of fasting insulin (>12 μU/L) had significantly higher FMD (p=0.029) than the mid (7–12 μU/L) or lowest (<7 μU/L) tertiles. When allometric scaling was conducted the results for any of the measurements and FMD did not meaningfully differ.

Obese children had significantly greater cIMT than normal weight children, and similar results were found in high VAT compared with low VAT tertiles (Figure 2, A and C). No significant differences were seen by BF% tertile (Figure 2, B). Children in the most insulin resistant tertile (low M_{lbm}) had higher cIMT than those in the high M_{lbm} tertile (Figure 2, D). No differences in cIEM or PWV were found for the adiposity or M_{lbm} measures.

Analyses by sex showed some differences between females and males. FMD% in females was significantly higher in the high BF% tertile (p=0.04) and high VAT tertile (p=0.002), cIMT was significantly greater in the highest VAT tertile (p=0.02), but no differences were found by tertiles of M_{lbm} (p=0.35). FMD% in males was significantly higher only in the highest VAT tertile (p=0.046), there were no differences by tertiles of BF% (p=0.29) or M_{lbm} (p=0.38), and there were no differences in cIMT in relation to BF%, VAT or BMI status.

The associations between FMD, cIMT, cIEM, and PWV and BF%, VAT, insulin resistance, and fasting insulin were also assessed in a continuous fashion using multiple linear regression analysis. Insulin resistance was not a predictor of FMD% or FMD AUC. BF% was positively associated with FMD% (β (SE) = 0.07 ± 0.02, p=0.001, R^2 = 0.197) and

FMD AUC (β (SE) = 8.3 ± 2.7, p=0.002, R^2 = 0.155). Fasting insulin was positively associated with FMD% (β (SE) = 0.08 ± 0.03, p=0.016, R^2 = 0.218), independent of BF%. VAT was positively associated with FMD% (β (SE) = 0.09 ± 0.02, p<0.001, R^2= 0.226), FMD AUC (β (SE) = 12.1 ± 2.3, p<0.001, R^2=0.224) and cIMT (β (SE) = 0.01 ± 0.01, p=0.002, R^2= 0.083). There were no significant associations between cIMT, cIEM, or PWV with insulin resistance or fasting insulin. BF% was positively associated with cIMT (β (SE) = 0.01 ± 0.01, p=0.028, R^2= 0.048), but no significant associations were observed between cIEM or PWV and BF%.

When BMI and BMI-percentile replaced BF%, in the ANCOVA and linear regression model(s) the results did not differ. To determine if differences were present between pubertal and post-pubertal children, we compared Tanner stage 2–4 (n=136) versus Tanner stage 5 (n=116). No statistically significant differences were observed between the 2 pubertal groups for any of the outcomes.

Discussion

The findings of this cross-sectional study of children indicate that: (1) obesity, regardless of method used to define it is associated with higher FMD; (2) obesity (BMI) and higher VAT are associated with higher cIMT; (3) insulin resistance measured by hyperinsulinemic euglycemic clamp, within the most insulin resistant tertile group, was associated with higher cIMT, but not with lower FMD or arterial stiffness; (4) fasting insulin was associated with higher FMD independent of BF%; and (5) sex-specific differences were present, however, the current sample size is insufficient to draw firm conclusions about the role of sex.

We acknowledge that these findings for FMD do not agree with a body of literature suggesting that obesity in childhood is associated with reduced FMD [6, 7, 9, 11, 29], or with some studies suggesting no relationship between obesity and FMD.[13, 14] Differences between the present and previous studies should be noted. Our study has a larger sample size, wider age range, and accounts for potential confounding variables (i.e. baseline artery diameter). The lack of controlling for baseline artery diameter highlights a potential serious flaw in other previous studies which found a relationship between lower FMD and obesity without this adjustment. This issue has been raised extensively in other publications as FMD is often partly a function of baseline artery diameter.[15, 27, 28, 30]

Although it is unclear why these findings differ, our data are in agreement with a prior study, showing obesity to be associated with higher FMD: in a large group (n>6000) of pre-pubertal children, it was shown that obese children had larger brachial artery diameters, increased blood flow, and marginally increased FMD compared with normal-weight and overweight children and also showed a significant, positive association of DXA trunk fat with FMD.[15] These findings were replicated in our data (DXA trunk fat vs FMD data not shown), and further expanded upon through our more sensitive and specific VAT data and in a cohort that included pubertal and post-pubertal children.

Our insulin resistance findings are incongruent with previous studies using the homeostasis model assessment index of insulin resistance (HOMA-IR).[29] A recent study in 150 children

(10.4 ± 3.1yr; BMI-percentile = 83.0 ± 23.3%), showed greater HOMA-IR, BMI, and waist circumference to be associated with lower FMD. However, this study did not account for the important contribution of pubertal maturation in their models and the potential confounding contribution of baseline artery diameter, which has been shown to be larger in obese children.[11, 15, 31] Moreover, our measurement of insulin resistance with hyperinsulinemic euglycemic clamp offers a more robust estimation of peripheral insulin sensitivity than HOMA-IR which more relates to basal insulin levels.[32] A number of in vivo and in vitro studies support a role for insulin in the regulation of vascular tone.[5, 33, 34] In association with insulin sensitivity, both fluid shear stress and insulin preferentially stimulate a signaling pathway that induces downstream nitric oxide (NO),[5, 34–36]. However, in the presence of insulin resistance the signaling pathway induces downstream production of endothelin-1 (ET-1), a potent vasoconstrictor.[5, 37] Therefore, it seems reasonable to suggest that the apparent paradoxical relation between adiposity and endothelial function results from still insulin sensitive endothelial cells not yet altered by obesity related insulin resistance.

In contrast to the apparent beneficial effect of obesity on vascular function, measures of adiposity in this study (BMI and VAT) were associated with greater cIMT, but there were no significant relations between any measure of adiposity and arterial stiffness (cIEM or PWV). The association of higher levels of adiposity and greater cIMT thickening has been shown previously.[6, 12, 13, 24]

Sex-specific differences in vascular measures may be important in understanding the discrepancies in the literature. In this study females had higher FMD, but smaller baseline artery diameter than males. When adjustments were made for baseline artery diameter no sex differences in FMD were present. The majority of the current pediatric reports showing FMD to be lower in obese youth failed to adjust for differences in baseline artery diameter,[7, 9–11] and those that did account for baseline artery diameter[13, 15] found no relationship or (similar to the present study) found enhanced FMD with obesity in children.

The current study has a number of strengths. It evaluated a relatively large cohort of children (n=252) with balanced of sex distribution, used gold-standard measurements of body composition, fat depots, insulin resistance, non-invasive assessment of FMD, cIMT, and arterial stiffness (cIEM and PWV), and controlled for confounding variable of baseline artery diameter which issparsely accounted for in previous studies. Limitations of the study include the cross-sectional design, which does not allow inferences about causality. The limited sample size, did not allow a clear interpretation of the differences between males and females regarding vascular measures based upon tertiles adiposity and insulin resistance. Despite our best efforts to standardize the FMD procedure, we were not able to account for a number of other factors which may influence FMD (i.e. physical activity and fitness). We are unable to determine the role body size may play in carotid artery remodeling which may affect cIMT levels in obese youth. There are no validated pediatric thresholds for insulin resistance measured by the hyperinsulinemic euglycemic clamp; therefore, we cannot assign clinical significance to our arbitrary tertile cut-points of insulin resistance.

The findings of the present study suggest that FMD, is higher in the context of excess adiposity. Although insulin resistance was not associated with FMD, there was a significant

positive relation with fasting insulin, independent of adiposity, suggesting this may explain, in part, the association with adiposity. Although this study does not provide evidence for causation, obesity, VAT, and insulin resistance were associated with thickening in the carotid vascular wall (cIMT), but no differences in arterial stiffness were observed for any adiposity or insulin resistance measure. These data suggest that obesity, insulin, and/or insulin resistance may play a pivotal role in regulating early adaptations within the vascular milieu.

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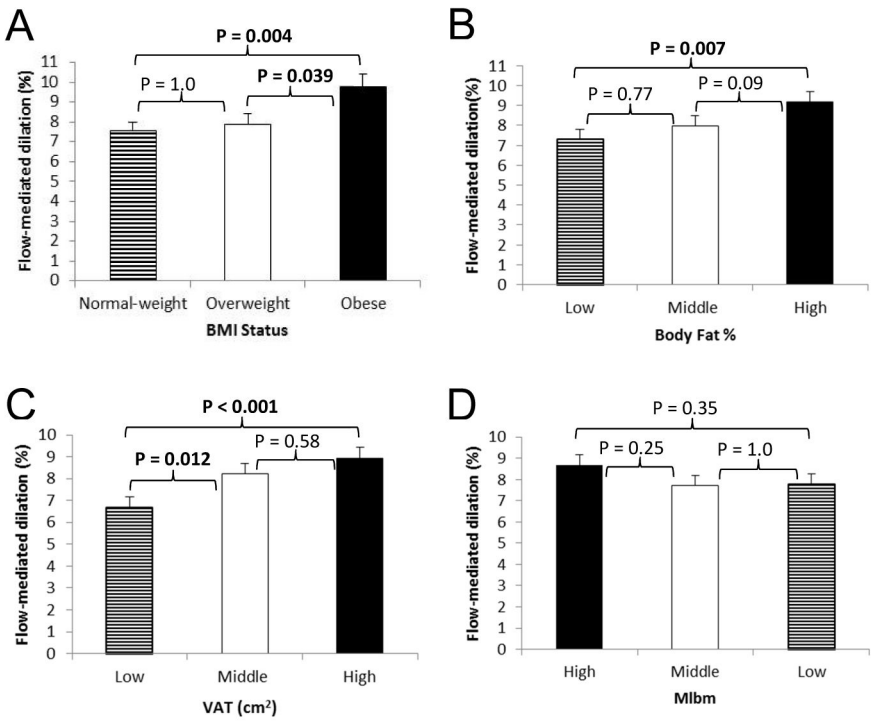

Figure 1.

Association between BMI Status (A), Body Fat (B), VAT (C), and Mlbm (D; Lower Mlbm equals greater insulin resistance) with Flow-mediated Dilation in Children.

Data are means ± SE adjusted for Tanner stage, sex, race, family relationship (siblings), and baseline artery diameter using ANCOVA; p-values determined using Bonferroni post-hoc testing.

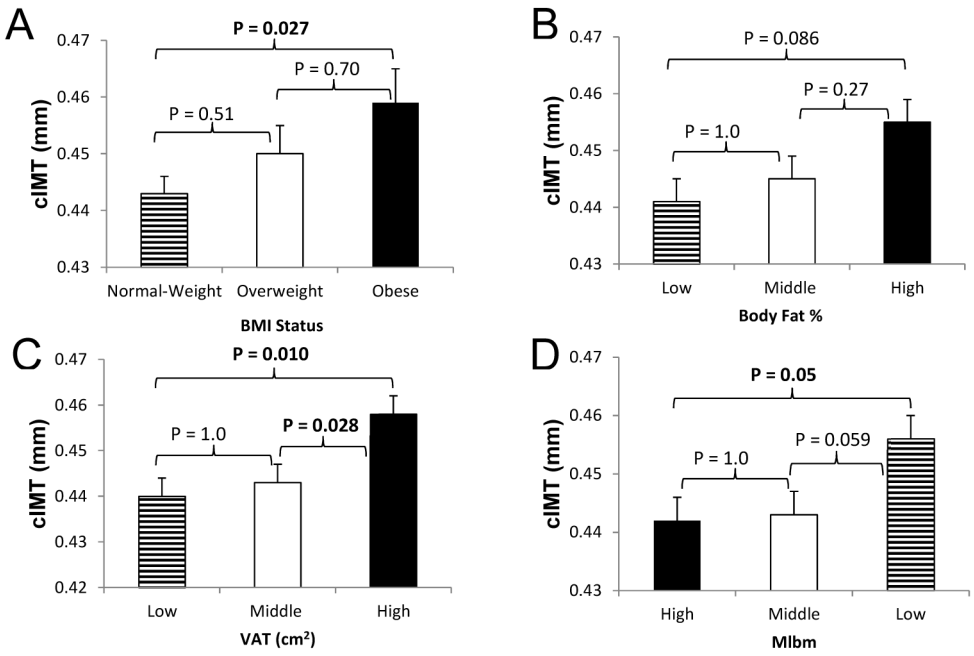

Figure 2.

Association between BMI Status (A), Body Fat % (B), VAT (C), and Mlbm (D; Lower Mlbm equals greater insulin resistance) with cIMT in Children.

Data are means ± SE adjusted for tanner stage, sex, race, and family relationship (siblings) using ANCOVA; p-values determined using Bonferroni post-hoc testing.

Table 1

Descriptive and clinical characteristics split by sex.

	Male	Female	Difference
Overall n = 252	*n* = 121	*n* = 131	
Age (years)	14.9 ± 2.3	15.3 ± 2.5	0.199
Tanner	3.9 ± 1.2	4.2 ± 0.9	0.004
Height (cm)	168.6 ± 12.1	161.7 ± 8.6	<0.001
Weight (kg)	66.3 ± 21.2	61.8 ± 17.4	0.061
BMI (kg/m^2)	22.9 ± 5.1	23.4 ± 5.5	0.433
BMI - percentile (%)	67.5 ± 27.9	68.7 ± 25.1	0.721
Cholesterol (mg/dL)	147 ± 26	148 ± 24	0.778
LDL-c (mg/dL)	83 ± 23	83 ± 21	0.918
HDL-c (mg/dL)	48 ± 11	49 ± 10	0.347
TG (mg/dL)	77 ± 40	80 ± 39	0.482
SBP (mmHg)	112 ± 9	107 ± 9	<0.001
DBP (mmHg)	58 ± 8	59 ± 7	0.376
BF%	21.6 ± 9.9	32.5 ± 9.0	<0.001
Visceral Fat (cm^2)	21.4 ± 13.6	20.8 ± 8.5	0.654
Mlbm ($mg/kg_{LBM}/min$)	12.7 ± 4.3	12.4 ± 4.1	0.527
Fasting insulin (μU/L)	10.2 ± 7.8	11.1 ± 6.6	0.346
Brachial artery diameter (mm)	3.6 ± 0.6	3.1 ± 0.4	<0.001
cIMT (mm)	0.45 ± 0.04	0.44 ± 0.04	0.079
cIEM	1018 ± 560	969 ± 314	0.390
PWV (m/s)	6.9 ± 1.2	7.1 ± 1.1	0.223
FMD%	7.0 ± 3.3	8.3 ± 3.8	0.002
FMD (AUC)	669 ± 406	774 ± 433	0.048

*Data are Mean ± SD

Group difference determined by paired t-test.

BMI = Body Mass Index; BF = Body Fat; LDL-C = Low-density lipoprotein cholesterol; HDL-C = High-density lipoprotein cholesterol; TG= Triglycerides; SBP = systolic blood pressure; DBP = diastolic blood pressure; M_{lbm} = insulin sensitivity/resistance (adjusted for lean body mass); cIMT = Carotid intima-media thickness; cIEM = carotid incremental elastic modulus; PWV = Pulse wave velocity; FMD = Flow-mediated dilation.