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Thoracic Periaortic and Visceral Adipose Tissue and Their Cross-sectional Associations with Measures of Vascular Function

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Abstract

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Disclosures

Dr Mitchell is owner of Cardiovascular Engineering Inc, a company that designs and manufactures devices that measure vascular stiffness. The company uses these devices in clinical trials that evaluate the effects of diseases and interventions on vascular stiffness. The remaining authors report no conflicts.

Objective—Perivascular fat may have a local adverse effect on the vasculature. We evaluated whether thoracic periaortic adipose tissue (TAT), a type of perivascular fat, and visceral adipose tissue (VAT) are associated with vascular function.

Design and Methods—TAT and VAT were quantified in Framingham Heart Study participants using multidetector computed tomography; vascular function was assessed using brachial artery vasodilator function, peripheral arterial tone and arterial tonometry (n= 2735, 48% women, mean age 50 years, mean BMI 27.7 kg/m2). Using multiple linear regression, we examined relations between TAT, VAT, and vascular measures while adjusting for cardiovascular risk factors.

Results—Mean TAT and VAT volumes were 13.2 and 1763 cm3. TAT and VAT were associated with multiple vascular function measures after multivariable adjustment. After BMI adjustment, TAT and VAT remained negatively associated with peripheral arterial tone and inverse carotid femoral pulse wave velocity ($p<0.02$); TAT was negatively associated with hyperemic mean flow velocity ($p=0.03$). Associations of TAT with vascular function were attenuated after VAT adjustment (all $p>0.06$).

Conclusion—Thoracic periaortic and visceral fat are associated with microvascular function and large artery stiffness after BMI adjustment. These findings support the growing recognition of associations between ectopic fat and vascular function.

Keywords

obesity; vascular function; arterial stiffness; perivascular adipose tissue; visceral adipose tissue

Introduction

Abnormal vascular function may be a biologic intermediary between obesity, CVD risk factors, and clinical vascular disease.(1) Prior studies have demonstrated an association between obesity and measures of vascular function,(2, 3, 4, 5, 6) but mechanisms by which increasing adiposity might contribute to vascular dysfunction are incompletely understood. Adipose tissue inflammation is believed to be important to any link between obesity and vascular function.(7, 8, 9) One theory is that inflammation in perivascular fat, which surrounds blood vessels, may have a local toxic effect on the vasculature.(10, 11) Possible mechanisms include perivascular adipose tissue-mediated recruitment of inflammatory cells to the arterial wall, diffusion of adipokines/cytokines into the arterial wall, or release of adipokines/cytokines into the vasa vasorum.(10, 11, 12, 13) These inflammatory adipokines and reactive oxygen species are known determinants of vascular function.(11, 12, 14, 15) Alternatively, central fat deposition may be more important than local perivascular fat in obesity-mediated vascular disease. Visceral adipose tissue (VAT), a large systemic fat depot, expresses inflammatory adipokines and has a volume nearly 100 times greater than TAT. VAT has previously been shown to be associated with certain measures of vascular function,(16) cardiometabolic risk factors,(17, 18) and clinical cardiovascular disease.(18, 19, 20)

Thoracic periaortic fat (TAT) is a type of perivascular fat that can be reproducibly measured using multidetector computed tomography and may serve as a marker of perivascular fat throughout the vascular tree. In the present study, we sought to determine whether TAT was

associated with measures of vascular function after adjustment for BMI (a measure of generalized adiposity) and whether TAT remained associated with vascular function measures after adjustment for VAT (a measure of central obesity). In addition, building upon prior work examining the association between VAT and brachial artery measures,(16) we sought to determine whether VAT was associated with measures of microvascular function and arterial stiffness. We hypothesized that both fat depots would be associated with multiple measures of vascular function. We further hypothesized that given TAT's location adjacent to the aorta, associations with vascular function, particularly aortic stiffness, would persist after adjustment for VAT.

Methods

Study Sample

Participants from the present study were drawn from the Framingham Heart Study Offspring and Third Generation cohorts who underwent multidetector computed tomography (MDCT) assessment of adipose tissue depots as well as assessment of vascular function. The study designs have been previously described.(5, 21, 22, 23, 24, 25, 26, 27, 28) Briefly, participants underwent MDCT of the thorax and abdomen using an eight-slice scanner. Fat volumes were measured by a semi-automatic technique requiring manual definition of tissue borders and identification of adipose tissue by its characteristic Hounsfield units. Vascular function measures included brachial artery flow mediated dilation, brachial artery hyperemic mean flow velocity, peripheral arterial tone ratio, and arterial tonometry measures (carotid femoral pulse wave velocity, forward wave amplitude, and augmentation index). Full details of the MDCT assessment of adipose tissue volumes and the noninvasive vascular hemodynamic protocols and analyses have been previously published and are summarized in the online-only Data Supplement. As reported previously, reproducibility has been high with both adipose tissue and vascular function measures.(5, 24, 25, 26, 27)

Between June 2002 and April 2005, 3529 participants (2111 Third Generation, 1418 Offspring) underwent MDCT assessment of adipose tissue depots. Brachial artery ultrasound studies were performed at the seventh examination (1998–2001) in the Offspring participants and the first examination (2002–2005) of the Third Generation participants. Peripheral arterial tone and arterial tonometry measurements were performed at the eighth examination (2005–2008) in Offspring participants and the first examination (2002–2005) of Third Generation participants.

For the brachial artery vasodilatory analyses, of the 3529 participants who underwent MDCT, 269 did not have brachial measures available, 64 were missing covariates, 348 had missing information on adipose tissue measures, 28 had unusable brachial flow-mediated dilation (FMD) data, and 293 had unusable or unavailable brachial flow velocity data, resulting in a sample size of 2735 for FMD analyses and 2470 for brachial flow velocity analyses. For the peripheral arterial tone and tonometry analyses, of the 3529 participants who underwent MDCT, 79 were missing covariate data, 367 had missing information on either adipose tissue measure, 1336 did not have peripheral arterial tone performed, and 299 did not have tonometry performed, resulting in a sample size of 1679 for peripheral arterial tone analyses and 2716 for tonometry analyses.

The study protocol was approved by the Institutional Review Boards of Boston University Medical Center and Massachusetts General Hospital. All participants provided written informed consent.

Covariate Assessment

For each analysis, covariates were used from the same examination at which the vascular function test was performed. BMI was defined as weight (in kilograms) divided by the square of the height (in meters). Current smoking was defined as smoking at least 1 cigarette per day in the past year. Alcohol use was dichotomized on the basis of consumption of > 14 drinks per week (in men) or 7 drinks per week (in women). Serum triglycerides, total and high-density lipoprotein cholesterol, and fasting plasma glucose were measured on fasting morning samples. Fasting plasma glucose ≥ 126 mg/dL or treatment with a hypoglycemic agent or insulin was used to define diabetes mellitus. If periods had stopped for >1 year, women were considered postmenopausal. Hypertension was defined as a systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or treatment with an antihypertensive agent. Cardiovascular disease included coronary heart disease, stroke, intermittent claudication and heart failure.(29) Participants in the Offspring Study without contraindication underwent a 6 minute walk test at the seventh examination.

Statistical Analysis

The primary “exposures” of interest were TAT and VAT. The primary dependent variables of interest for TAT were flow-mediated dilation (FMD), hyperemic mean flow velocity, peripheral arterial tone ratio, CFPWV, forward wave amplitude, and mean arterial pressure. Because the peripheral arterial tone ratio had a heteroscedastic error structure, we used a natural logarithmic transformation. Because CFPWV had a heteroscedastic error structure, it was transformed to 1000/CFPWV. Because the association between VAT and brachial artery measures in the Framingham Heart Study has previously been published,(16) for the VAT analysis, the primary dependent variables of interest were peripheral arterial tone ratio, CFPWV, forward wave amplitude and mean arterial pressure. We examined the association between both fat depots and baseline vascular function measures to allow appropriate interpretation of our main findings.

Partial Pearson correlations (adjusted for age, sex and cohort) were examined to assess relations between clinical and MDCT adiposity measures and vascular function measures. Multivariable linear regression was performed to assess the significance of covariate-adjusted relations between MDCT adiposity measures and vascular function measures. All adipose tissue measurements were standardized within sex to a mean of 0 and a standard deviation of 1; estimated regression coefficients are presented per 1 standard deviation increment.

The multivariable model included age, sex, cohort, smoking (never/former/current), moderate to heavy alcohol use (>14 drinks/week [men], >7 drinks/week [women]), mean arterial pressure (except when the dependent variable was mean arterial pressure), heart rate, walk test (no, before, or after brachial artery vasodilatory function measures to account for any influence of the walk test on brachial artery measures), total/HDL cholesterol, log

triglycerides, fasting glucose level, menopause status, use of hormone replacement therapy, diabetes, hypertension treatment, lipid treatment, and prevalent cardiovascular disease. In secondary analyses, we aimed to disentangle the relative associations of TAT versus VAT with vascular function given the known correlation between the two fat depots. Because both fat depots were associated with measures of microvascular function and arterial stiffness after adjustment for BMI, we compared mean peripheral arterial tone ratio values and mean 1000/CFPWV values within sex-specific VAT and TAT tertiles. In addition, we examined the association of both fat depots with augmentation index, a measure of wave reflection. We adjusted for c-reactive protein in any multivariable models that included BMI and demonstrated significant associations between either TAT or VAT and vascular function measures to assess whether adjustment for inflammation affected the association between fat depots and vascular function. We tested for interactions of sex by fat depots and age by fat depots in multivariable models. We performed a sensitivity analysis limited to the Third Generation cohort in whom MDCT and vascular function measures were performed at the same study visit.

All analyses were performed with SAS version 9.2 for Windows. P-values<0.05 were considered statistically significant for the main analysis. A p<0.001 (0.05/36 tests for interaction) was considered statistically significant in analyses of potential interactions. The authors had full access to and take full responsibility for the integrity of the data.

Results

Participant Characteristics

Participant characteristics and mean values for vascular function measures are presented in Table 1. Age-sex- and cohort-adjusted volumes of VAT and TAT were correlated (r=0.75, p <0.0001). Both fat depots were correlated with BMI (r=0.56, p<0.0001 and r=0.72, p <0.0001, respectively). All vascular function measures were significantly correlated with all adiposity measures, except for the correlation of hyperemic mean flow velocity with waist circumference and BMI (Table 2).

Thoracic Periaortic Fat and Vascular Function Measures

TAT was associated with each of the primary measures of vascular function in minimally adjusted models. There was a negative association between TAT and brachial artery vasodilatory measures, peripheral arterial tone ratio, and 1000/CFPWV and a positive association between TAT and forward wave amplitude and mean arterial pressure (Table 3). These associations remained significant in multivariable models (all p<0.03) with the exception of the association between TAT and forward wave amplitude (p=0.66). After additional adjustment for BMI, TAT remained negatively associated with hyperemic mean flow velocity (p=0.03), peripheral arterial tone ratio (p=0.02) and 1000/CFPWV (p=0.0009). However, after additional adjustment for VAT, TAT was no longer associated with any measure of vascular function (all p>0.06).

The association of TAT with baseline brachial artery diameter, baseline mean flow velocity, and baseline peripheral arterial tone is provided in Supplemental Table 1. TAT was

associated with baseline measures in multivariable models, but not after adjustment for either BMI or VAT.

Visceral Adipose Tissue and Vascular Function Measures

In minimally adjusted models, VAT was negatively associated with peripheral arterial tone ratio and 1000/CFPWV and positively associated with forward wave amplitude and MAP. The significant associations between VAT and peripheral arterial tone ratio and 1000/CFPWV persisted in multivariable models (Table 4). After additional adjustment for BMI, associations were no longer significant except for peripheral arterial tone ratio ($p=0.0007$), and 1000/CFPWV ($p<0.0001$). In multivariable models containing both fat depots, the associations of VAT with peripheral arterial tone and tonometry measures (1000/CFPWV, forward wave amplitude and mean arterial pressure) were significant whereas the associations of TAT with these parameters were no longer significant. For these measures, there was no attenuation of the regression coefficients for VAT after adjustment of multivariable models for TAT. Variance inflation factor was <3.2 for each of these associations, suggesting the lack of severe multicollinearity. The association of VAT with baseline peripheral arterial tone amplitude is provided in Supplemental Table 1; VAT was positively associated with baseline peripheral arterial tone in multivariable models that included BMI.

Secondary Analyses

Association of TAT and VAT with Augmentation Index—TAT was positively associated with augmentation index in multivariable models and this association remained significant after adjustment for either BMI or VAT (all $p<0.05$, Supplemental Table 1). There was no association between VAT and augmentation index in either multivariable-adjusted or multivariable and BMI-adjusted models (all $p>0.05$, Supplemental Table 1).

Mean Values of Peripheral Arterial Tone Ratio and 1000/CFPWV on the Basis of Tertiles of TAT Within Tertiles of VAT—To further investigate the association between higher TAT relative to VAT with vascular function measures, we compared mean peripheral arterial tone ratio values and mean 1000/CFPWV values stratified by sex-specific VAT and TAT tertiles (Figure 1). Mean peripheral arterial tone ratio values were lower across TAT tertiles within VAT tertiles 1 and 3 ($p<0.05$). For 1000/CFPWV, levels across TAT tertiles were also lower in VAT tertiles 1 and 3.

Additional Adjustment of Models for C-reactive Protein (CRP)—We performed exploratory analyses to examine the effect of additional adjustment for CRP levels in multivariable models of both TAT and VAT with vascular function measures that had retained significance after BMI adjustment. We found that the negative association between VAT and peripheral arterial tone ratio was no longer significant after CRP adjustment (regression estimate 0.03, $p=0.10$) whereas the negative association of VAT and 1000/CFPWV remained significant (regression estimate −3.58, $p=0.0002$). TAT remained significantly negatively associated with hyperemic mean flow velocity (regression estimate −1.14, $p=0.02$), pulse arterial tone ratio (regression estimate −0.03, $p=0.03$), and 1000/CFPWV (regression estimate −1.54, $p=0.003$) after adjustment for CRP.

Age and Sex Interactions—In multivariable models, there was no evidence of effect modification by sex in the associations of either fat depot with vascular function measures. Evidence of effect modification by age was found in the negative associations of both fat depots with peripheral arterial tone ratio and forward wave amplitude in multivariable models; the negative association between TAT and forward wave amplitude was stronger in older participants, whereas the negative association between VAT and forward wave amplitude was stronger in younger individuals. In contrast, the positive associations of both fat depots with mean arterial pressure were consistently stronger in younger individuals (data not shown).

Analyses limited to the Third Generation Cohort—In analyses of the association of TAT with vascular function measures limited to the Third Generation cohort (in whom MDCT scans and vascular function measures were performed at the same study visit), the results were generally similar (Supplemental Table 2). TAT was associated with most vascular measures in multivariable models, with some residual association after adjustment for BMI, and full attenuation of the associations upon VAT adjustment. The results for the association of VAT and vascular function, limited to the Third Generation, were also generally similar. Of note, the estimated beta coefficient of the association of VAT and mean arterial pressure was higher in the Third Generation cohort. This may reflect the previously documented age interaction (p, interaction <0.0001) in which results for the association of VAT and mean arterial pressure were stronger in younger as opposed to older individuals.

Discussion

In our community-based sample, TAT, a local perivascular fat depot, and VAT, a measure of central adiposity, were associated with multiple measures of vascular function that are believed to reflect distinct biologic pathways that may contribute to the development of cardiovascular disease. TAT, which may serve as a marker of perivascular fat throughout the vasculature, was negatively associated with hyperemic mean flow velocity and peripheral arterial tone response (measures of microvascular function) as well as 1000/CFPWV (a measure of aortic stiffness with a lower value of 1000/CFPWV corresponding to a stiffer aorta). In addition, VAT was negatively associated with peripheral arterial tone and inverse CFPWV. These findings suggest an association of both of these fat depots with microvascular function and aortic stiffness beyond that of generalized adiposity.

Our findings are largely consistent with the small number of previous studies that have examined either perivascular or visceral adiposity and measures of vascular function. Perivascular fat surrounding the brachial artery has previously been found to be associated with hyperemic mean flow volume, but not flow-mediated dilation.(30) Hyperemic mean flow volume is closely related to our measure of hyperemic mean flow velocity. In contrast to our findings with TAT, the association of peri-brachial adipose tissue and hyperemic mean flow volume persisted after adjustment for VAT. We extend these findings by examining TAT, a different sub-type of perivascular fat and also examining the association with measures of pulse arterial tone and arterial stiffness. Likewise, prior studies, including those from the Framingham Heart Study as well as the Health ABC study, found

associations between VAT and both brachial artery flow mediated dilation and CFPWV. We now additionally describe the association of VAT and both pulse arterial tone and various measures of arterial stiffness.

Contrary to our hypothesis, we did not observe an association between TAT and vascular function measures after accounting for VAT. These findings have multiple potential explanations. First, TAT and VAT are highly correlated; although statistical testing was not consistent with severe multicollinearity, we cannot rule out the possibility that conjoint statistical adjustment may still attenuate true associations. In an attempt to disentangle the specific associations of TAT versus VAT with measures of vascular function, we examined the association of TAT with 1000/CFPWV and peripheral arterial tone within VAT tertiles, and observed a trend of lower pulse arterial tone ratio (more adverse microvascular function) and lower 1000/CFPWV (higher stiffness) across tertiles of TAT. These findings are of particular interest given TAT directly surrounds the thoracic aorta and CFPWV is a measure of aortic stiffness.

A second explanation for the lack of association of TAT and measures of vascular function after adjustment for VAT is that our measure of TAT only captures fat in the descending aorta; it is possible that the lack of inclusion of periaortic fat surrounding the ascending aorta may have precluded identification of an association of TAT and vascular function after adjustment for VAT. Third, the aorta is an elastic artery that does not directly supply metabolically active tissues.(31) Although TAT may serve as a marker of the total volume of perivascular fat elsewhere in the body, it is possible that associations of TAT with vascular function do not reflect associations of smaller perivascular fat depots with vascular function. Smaller muscular arteries and arterioles undergo greater dynamic modulation, and are likely most important in regulating blood flow.(31) In contrast to TAT, VAT encases small muscular arteries and arterioles of the mesentery, and may actually itself serve as a marker of perivascular fat. Therefore, taken together, our findings do not rule out the existence of a local effect of perivascular fat.

The evidence for a role of perivascular fat in vascular regulation stems largely from basic science and small clinical studies.(11, 12, 32, 33) In both mice and humans, obesity leads to perivascular fat inflammation and changes in adipokine secretion, both of which have been associated with vascular dysfunction.(12, 32, 33) In addition, perivascular fat in lean individuals appears to convey anti-contractile properties on the vasculature that are lost with the development of obesity.(11, 34) Consistent with a potential local influence of periaortic fat on the vasculature, inflammation in abdominal periaortic fat has been shown to be associated with angiotensin II-induced aortic aneurysm formation in obese mice,(35) and TAT was associated with clinical lower extremity peripheral artery disease in humans despite adjustment for VAT.(36)

Strengths and Limitations

Strengths of our study include the large community based nature of the cohort and sophisticated assessment of fat depots and vascular function measures. In addition, detailed assessment of covariates strengthened our multivariable analysis. Certain limitations warrant discussion. The cross-sectional design of the analysis prevents inferences of causality or

temporality. The Framingham Heart Study is predominantly white and results may not be generalizable to other ethnic/racial groups. There were temporal differences between the CT scans and the vascular measures. However, our sensitivity analysis limited to the Generation-3 cohort (in which MDCT scans and vascular function measures occurred during the same study visit) demonstrated overall similar findings. In addition, our primary aim was to assess whether there were differential associations between VAT as compared to TAT with vascular function. Importantly, VAT and TAT were measured at the same time, reducing the risk of affecting our ability to examine the relative association of each with vascular function. Nitroglycerin was not administered to this community-based cohort, preventing us from having a measure of non-endothelium dependent brachial artery vasodilation. Our measure of periaortic fat is limited to the descending thoracic aorta. Forward wave amplitude and mean arterial pressure rely on properties of the ascending aorta, and this limitation may explain the lack of association of TAT and these measures. We were not able to measure abdominal periaortic fat, and this prevents us from speculating whether differences in the association between TAT and VAT with vascular function measures were related to different anatomical locations (chest versus abdomen) versus the different structures they surround (aorta versus viscera). Finally, adjustment of multivariable models for CRP does not exclude inflammation as a potential mediator of the association of ectopic fat and vascular function since circulating levels of CRP do not necessarily reflect local inflammatory mediators.

Conclusion

Thoracic periaortic fat and visceral adipose tissue are associated with microvascular function and aortic stiffness after adjustment for BMI, suggesting a role for both local ectopic and central fat depots in vascular dysfunction beyond that of generalized adiposity. Associations of TAT and vascular function measures did not persist after adjustment for VAT, but this does not exclude a role for perivascular fat in vascular function. Our results overall support the growing recognition of a potentially adverse association of perivascular fat and vascular function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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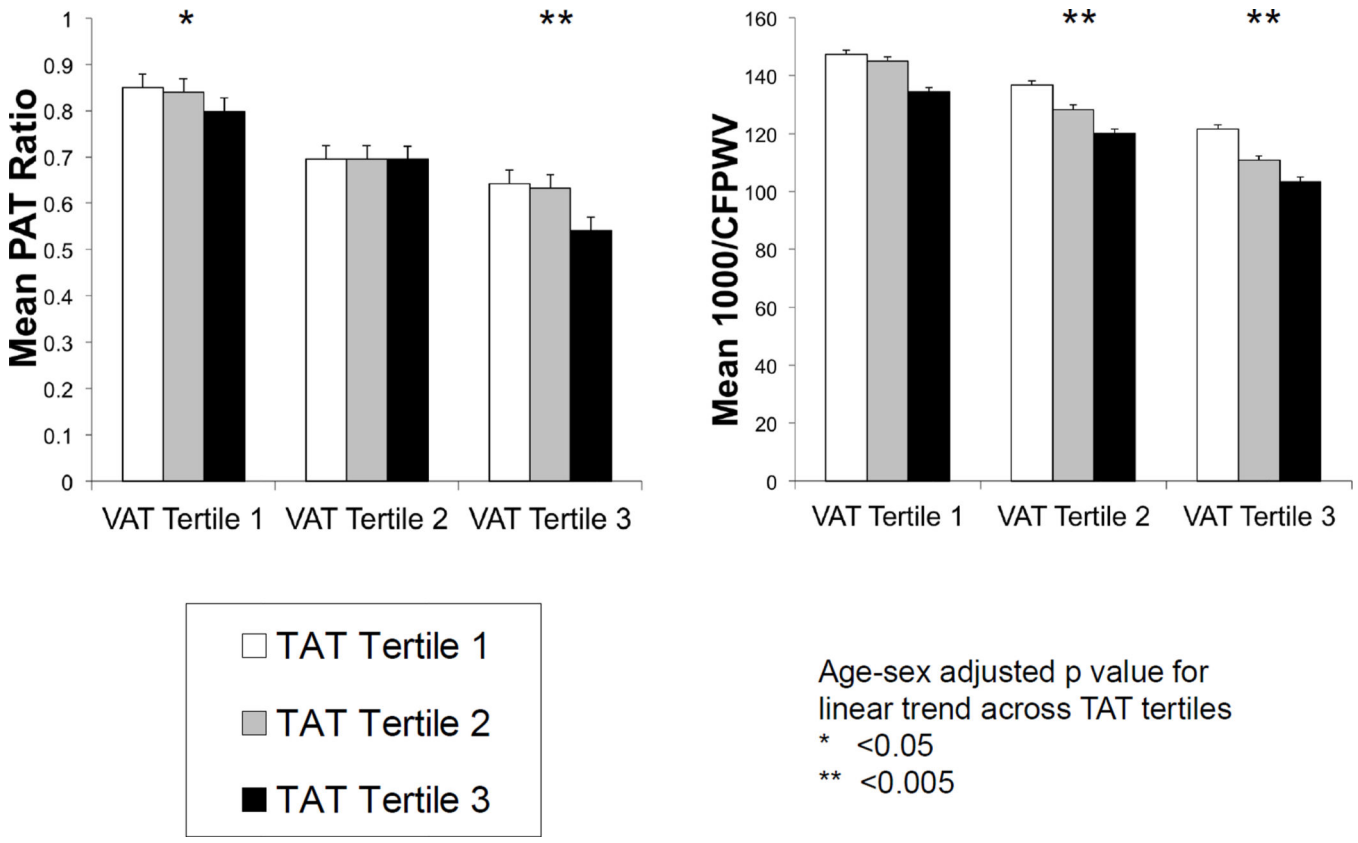

Figure 1.

Sex and age specific tertiles of VAT by tertiles of TAT for mean peripheral arterial tone ratio and mean 1000/Carotid Femoral Pulse Wave Velocity. Age-adjusted *P* value for linear trend is presented. Error bars reflect standard errors. Peripheral arterial tone ratio is natural log transformed.

Table 1

Participant Characteristics - Data are means ± SD or %[a]

Clinical Characteristics	
n	2763
Age, years	50 ± 10
Women, N (%)	1337 (48)
Offspring, N (%)	988 (36)
Smoking, N (%)	
Never	1364 (49)
Former	1041 (38)
Current	358 (13)
Moderate/heavy alcohol use[b], N (%)	422 (15)
Heart rate, beats/min	63 ± 10
Total/HDL-cholesterol	4.0 ± 1.4
Triglycerides, mg/dl	127 ± 90
Fasting Glucose, mmol/L (mg/dl)	5.5 ± 1.2 (99 ± 21)
Postmenopausal, N (%)	644 (48)
Hormone Replacement Therapy, N (%)	285 (21)
Diabetes, N (%)	168 (6)
Hypertension treatment, N (%)	481 (17)
Lipid treatment, N (%)	358 (13)
Prevalent cardiovascular disease, N (%)	117 (4)
Adiposity Measures	
Body Mass Index, kg/m^2	27.7 ± 5.2
Waist circumference, cm	97 ± 14
Subcutaneous adipose tissue (SAT), cm^3	2868 ± 1387
Visceral adipose tissue (VAT), cm^3	1763 ± 1004
Thoracic periaortic adipose tissue (TAT), cm^3	13.2 ± 7.7
Vascular Measures	
Baseline brachial artery diameter, mm	4.2 ± 0.8
Baseline mean flow velocity, cm/s	7.6 ± 4.4
Baseline pulse amplitude	5.7 ± 0.9
Augmentation index, %	11.8 ± 12.3
Flow mediated dilation, %	4.4 ± 3.5
Hyperemic mean flow velocity, cm/s	57.7 ± 19.7
Peripheral arterial tone ratio [c], unitless	0.71 ± 0.41
Carotid-femoral pulse wave velocity, (m/s)	8.4 ± 2.7
1000/Carotid-femoral pulse wave velocity, (ms/mm)	127 ± 30
Forward-wave amplitude, mm Hg	49.0 ± 14.2

Clinical Characteristics	
Mean arterial pressure, mm Hg	94 ± 11

[a] Clinical characteristics were assessed for the Offspring participants at exam 7. Adiposity measures were assessed for the Offspring participants between exams 7 and 8. Peripheral arterial tone and arterial tonometry variables were assessed for the Offspring participants at exam 8. Generation 3 participants had clinical characteristics and all vascular function measurements assessed at exam 1.

[b] Defined as >14 drinks weekly for men and >7 drinks weekly for women

[c] Peripheral arterial tone measures are natural logarithm transformed

Table 2

Partial Pearson correlation coefficients between adiposity measures and vascular function measures adjusted for cohort, sex and age

	N	Thoracic periaortic fat		Visceral Adipose Tissue		Body Mass Index		Waist Circumference	
		r	P-value	r	P-value	r	P-value	r	P-value
Flow mediated dilation (%)	2735	−0.07	0.0005	−0.08[b]	<0.0001	−0.10	<0.0001	−0.10	<0.0001
Hyperemic mean flow velocity (cm/sec)	2470	−0.04	0.04	−0.04[b]	0.03	−0.03	0.10	−0.03	0.19
Peripheral arterial tone ratio	1679	−0.22	<0.0001	−0.27	<0.0001	−0.25	<0.0001	−0.23	<0.0001
1000/CFPWV[a] (ms/mm)	2716	−0.21	<0.0001	−0.29	<0.0001	−0.22	<0.0001	−0.24	<0.0001
Forward wave amplitude (mm Hg)	2716	0.07	0.0007	0.07	0.0002	0.06	0.0009	0.06	0.0009
Mean arterial pressure (mm Hg)	2716	0.17	<0.0001	0.23	<0.0001	0.24	<0.0001	0.24	<0.0001

[a] CFPWV, carotid femoral pulse wave velocity

[b] The correlation between visceral adipose tissue and flow mediated dilation and hyperemic mean flow velocity in the Framingham Heart Study has previously been published (Parikh, N et al. *Obesity* 2009;17:2054–2059). In some cases, r values differ slightly from those reported by Parikh, et al. due to small differences in the sample size.

Table 3

Multivariable-adjusted[a] regression for thoracic periaortic fat with vascular function measures. Data presented as beta-coefficients per 1 standard deviation increase of thoracic periaortic fat

	n	Model 1: MV* Adjusted		Model 2: MV* + BMI Adjusted		Model 3: MV* + VAT Adjusted	
		Regression Coefficient (95% C.I.)	P-value	Regression Coefficient (95% C.I.)	P-value	Regression Coefficient (95% C.I.)	P-value
Flow mediated dilation (%)	2735	−0.26 (−0.42, −0.10)	0.002	−0.14 (−0.33, 0.04)	0.13	−0.15 (−0.37, 0.07)	0.19
Hyperemic mean flow velocity (cm/sec)	2470	−1.03 (−1.94, −0.11)	0.03	−1.20 (−2.26, −0.15)	0.03	−1.00 (−2.27, 0.28)	0.13
Peripheral arterial tone ratio	1679	−0.06 (−0.09, −0.04)	<0.0001	−0.03 (−0.06, 0.00)	0.02	−0.01 (−0.04, 0.02)	0.46
1000/CFPWV[b] (ms/mm)	2716	−1.85 (−2.70,−0.99)	<0.0001	−1.69 (−2.69, −0.69)	0.0009	0.32 (−0.87, 1.51)	0.60
Forward wave amplitude (mm Hg)	2716	−0.11 (−0.62, 0.40)	0.66	0.52 (−0.08, 1.11)	0.09	0.69 (−0.02, 1.40)	0.06
Mean arterial pressure (mm Hg)	2716	1.06 (0.59, 1.53)	<0.0001	0.10 (−0.45, 0.65)	0.72	−0.12 (−0.78, 0.53)	0.71

BMI, body mass index; VAT, visceral adipose tissue

[a]Multivariable models adjusted for age, sex, cohort, smoking, alcohol intake, mean arterial pressure (not included in models with mean arterial pressure as dependent variable), heart rate, walk test (no, before, after), total/HDL cholesterol, log triglycerides, fasting glucose level, menopause, hormone replacement therapy, diabetes, hypertension treatment, lipid treatment, and prevalent cardiovascular disease

[b]CFPWV, carotid femoral pulse wave velocity

Table 4

Multivariable-adjusted[a] regression for visceral adipose tissue with vascular function measures. Data presented as beta-coefficients per 1 standard deviation increase of visceral adipose tissue[b]

	n	Model 1: MV* Adjusted		Model 2: MV* + BMI Adjusted	
		Regression Coefficient (95% C.I.)	P-value	Regression Coefficient (95% C.I.)	P-value
Peripheral arterial tone ratio	1679	−0.08 (−0.11, −0.06)	<0.0001	−0.05 (−0.08, −0.02)	0.0007
1000/CFPWV[c] (ms/mm)	2716	−2.93 (−3.79, −2.07)	<0.0001	−3.83 (−4.98, −2.68)	<0.0001
Forward wave amplitude (mm Hg)	2716	−0.67 (−1.18, −0.16)	0.01	−0.05 (−0.74, 0.64)	0.88
Mean arterial pressure (mm Hg)	2716	1.64 (1.17, 2.11)	<0.0001	0.63 (0.00, 1.26)	0.05

[a] Multivariable models adjusted for age, sex, cohort, smoking, alcohol intake, mean arterial pressure (not included in models with mean arterial pressure as dependent variable), heart rate, walk test (no, before, after), total/HDL cholesterol, log triglycerides, fasting glucose level, menopause, hormone replacement therapy, diabetes, hypertension treatment, lipid treatment, and prevalent cardiovascular disease

[b] The association of visceral adipose tissue and flow mediated dilation and hyperemic mean flow velocity in the Framingham Heart Study has previously been published (Parikh, N et al. *Obesity* 2009;17:2054–2059

[c] CFPWV, carotid femoral pulse wave velocity