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Peri-aortic Fat, Cardiovascular Disease Risk Factors, and Aortic Calcification: The Framingham Heart Study

Sam J. Lehman, MBBS FRACP[1,2], **Joseph M. Massaro, PhD**[3], **Christopher L. Schlett, BA**[1], **Christopher J. O'Donnell, MD MPH**[4], **Udo Hoffmann, MD MPH**[1], and **Caroline S. Fox, MD MPH**[4,5]

[1]Massachusetts General Hospital Department of Cardiac MR PET CT and Harvard University, Boston MA

[2]Flinders University Department of Cardiology, Australia

[3]Boston University Department of Mathematics, Boston MA

[4]National Heart, Lung, and Blood's Framingham Heart Study, Bethesda MD and Framingham MA

[5]Brigham and Women's Hospital Division of Endocrinology and Harvard Medical School, Boston MA

Abstract

Objective—Perivascular fat through the secretion of paracrine and pro-inflammatory mediators may play a role in obesity-mediated vascular disease. We sought to examine associations between adipose tissue depots immediately surrounding the thoracic aorta, metabolic risk factors, and vascular calcification.

Methods—In participants free of cardiovascular disease (CVD) from the Framingham Heart Study Offspring cohort who underwent computed tomography (n=1067, mean age 59 years, 56.1% women), thoracic peri-aortic fat depots were quantified. Visceral abdominal tissue (VAT) and calcification of the thoracic and abdominal aorta were also measured.

Results—Peri-aortic fat depots were correlated with body mass index, waist circumference (WC), VAT (all p<0.0001), hypertension (p<0.007), lower HDL (p<0.0001), serum triglycerides (p<0.0001), impaired fasting glucose (p<0.005), and diabetes (p=0.02). These associations generally remained significant after adjustment for BMI and WC (all p-values<0.05), but not after VAT adjustment. Thoracic aortic fat was associated with thoracic calcification in models containing VAT (OR 1.31, 95% CI 1.01–1.71, p=0.04), but was not significant after adjustment for CVD risk factors (OR 1.16, 95% CI 0.88–1.51, p=0.30). Thoracic aortic fat, however, was associated with abdominal

Address for Correspondence: Caroline S. Fox MD MPH, 73 Mt Wayte Ave Suite #2, Framingham MA 01702, foxca@nhlbi.nih.gov, Phone: (508) 935-3447, Fax: (508) 626-1262.

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Disclosures

Dr. Fox, Hoffmann, Schlett and Lehman conceived the study, performed analysis, drafted and revised the manuscript. Dr. Massaro performed analysis, drafted and revised the manuscript. Dr. O'Donnell provided critical revisions to the manuscript and analysis. All authors have approved the manuscript as written. There are no conflicts of interest to disclose. Drs. Fox and Lehman had full access to the data, and take responsibility for its integrity.

aortic calcification (OR 1.48, 95% CI 1.11–1.98, p=0.008) and coronary artery calcification (OR 1.47, 95% CI 1.09–1.98, p=0.001) even in models including CVD risk factors and VAT.

Conclusions—Thoracic peri-aortic fat is associated with measures of adiposity, metabolic risk factors, and coronary and abdominal aortic calcification.

Keywords

Obesity; atherosclerosis; calcium; risk factors

Introduction

There is increasing evidence of an association between specific adipose tissue depots and cardiovascular disease, including cardio-metabolic risk factors and sub-clinical atherosclerosis [1–5]. Fat deposits immediately surrounding blood vessels (perivascular adipose tissue) are metabolically active and may play a pathogenic role in mediating local vascular disease [3,6–10].

We and others have shown that pericardial fat is associated with coronary artery calcification (CAC), suggesting a local toxic effect on the vasculature [5,11,12]. Perivascular fat is known to be highly metabolically active, secreting substances with known vascular actions [3,13, 14]. Further, mediastinal fat, which encases the thoracic aorta, has been associated with abdominal aortic but not coronary calcification [5]. Calcification of the aorta is an important cardiovascular disease risk marker, predicting future events and mortality [15,16]. Therefore, uncovering an association between local peri-aortic fat deposits and sub-clinical atherosclerosis is of great interest to test the hypothesis of a local pathogenic effect of adipose tissue on the vessel wall.

Therefore, the aim of this study is to examine the correlation of adipose tissue immediately surrounding the thoracic aorta with other clinical and radiographic measures of adiposity; metabolic and cardiovascular disease risk profiles; and the extent of thoracic and abdominal aortic calcification in a large community based cohort.

Methods

Study Sample

In 1971, the Framingham Offspring Study enrolled spouses and children of the original Framingham Heart Study cohort [17,18]. Between June 2002 and April 2005, there were 1,418 subjects from the Framingham Offspring Study that underwent chest and abdominal multi-detector computed tomography (MDCT). Our study includes these participants from the Framingham Heart Study Offspring cohort who were free of established cardiovascular disease. An interpretable scan for peri-aortic fat depots was available in 1,235 participants. Of these, 1,111 were free of CVD, 1,092 attended exam 7, and 1,067 had a complete covariate profile.

The study protocol was approved by the institutional review board of the Boston University Medical Center and Massachusetts General Hospital. All subjects provided written informed consent.

Multi-detector Computed Tomography (MDCT) Scan Protocol

MDCT of the chest and abdomen was performed using 8-slice MDCT technology (LightSpeed Ultra, General Electric, Milwaukee, Wisconsin). In the chest, 2.5 mm slices were acquired from the carina to the diaphragm during a single inspiratory breath hold using prospective ECG

triggering at 70% of the cardiac cycle (120 kVp, 320 mA). For the abdomen, 2.5 mm slices (120 kVp, 320 mA) were obtained of a 125 mm abdominal segment using the upper edge of the S1 vertebrae as the anatomic landmark of the lower field.

Measurement of Peri-aortic Fat Volume

All image analyses were performed on a dedicated workstation (Aquarius 3D, TeraRecon, San Mateo, California) as previously described [19]. Adipose tissue quantification was performed in a semi-automated method that required manual definition of borders. CT attenuation thresholds were used to identify fax pixels (window width −195 to −45 HU; window centre −120 HU) to calculate adipose volumes. Thoracic peri-aortic fat was defined as the area immediately surrounding the thoracic aorta anteriorly by a horizontal line through the esophagus, connected to the left costo-vertebral joint, posteriorly by the anterior edge of the vertebral body, and the right lateral border of the vertebral body [19]. In total, a 6.75 cm column (comprised of 27 slices) around the thoracic aorta was quantified. We also conducted a measure of abdominal aortic peri-aortic fat. However, due to technical limitations including the close relationship with aortic diameter, the inability to visualize the retroperitoneal lining, and the lack of anatomic separation with the visceral fat compartment, these measurements are difficult to interpret and not included here. Excellent intra- and inter-reader reproducibility for the measurement of thoracic peri-aortic fat (intra-class correlation coefficient 0.99 and 0.98 respectively) was demonstrated in a random subset of 100 participants [19]. Visceral abdominal fat (VAT) and subcutaneous abdominal fat (SAT) were quantified as previously described [20].

Measurement of Aortic Calcification in the Thoracic Aorta (TAC), Abdominal Aorta (AAC), and Coronary Arteries (CAC)

MDCT scans were read by an experienced observer for the presence and quantity of thoracic aortic, abdominal aortic and coronary calcium using a dedicated workstation (Aquarius, Terarecon). A calcified lesion was defined by the presence of at least 3 connected pixels with attenuation >130 HU. In addition, an Agatston score was calculated by multiplying the lesion area by the attenuation score (in HU). Presence of thoracic aortic, abdominal aortic and coronary artery calcium was based on age and sex-specific 90^{th} percentile cut points derived from a healthy referent sample.

Risk Factor and Covariate Assessment

Cardiovascular disease and metabolic risk factors were measured at the 7^{th} Framingham Offspring Study Examination (1998–2001) using standardized definitions. Body mass index (BMI) was defined as the weight in kilograms divided by the square of the height in meters. Waist circumference was measured at the level of the umbilicus. For the measurement of blood lipids and glucose, fasting morning samples were collected. Diabetes was defined by fasting plasma glucose of ≥ 126 mg/dL or treatment with either oral hypoglycaemic medication or insulin. Impaired fasting glucose was defined by fasting plasma glucose of 100 to 125mg/dL in the absence of diabetes treatment. Current smoking was defined as smoking at least one cigarette per day in the year prior to exam attendance. Alcohol intake was recorded and categorized as greater to or less than 14 drinks per week for men and 7 drinks per week for women. Post menopausal status was defined by the absence of menstrual periods for more than one year. Hypertension by either the use of anti-hypertensive medication, systolic blood pressure ≥ 140 mm Hg, or diastolic blood pressure ≥ 90 mm Hg. Metabolic syndrome was based on criteria from the Modified National Cholesterol Education Program Adult Treatment Panel III [21].

Statistical Analysis

Peri-aortic fat volumes were normally distributed. Age-adjusted Pearson correlation coefficients were examined between these fat volumes and other body fat depots and cardiovascular disease risk factors. The significance of covariate adjusted relationships between perivascular fat and cardiovascular disease risk factors was assessed using multivariable linear and logistic regression. For continuous variables, the covariate-adjusted risk factor per 1-standard deviation (SD) increase in adipose tissue was estimated, while for dichotomous covariates, the odds ratio of the risk factor per 1-SD increase in adipose tissue was estimated. Sex interactions were performed. The multivariable model included the covariates of age, smoking (current/former/never), alcohol use (>14 drinks per week for men and >7 drinks per week for women), menopausal status, and hormone replacement therapy. The presence of therapy for hyperlipidemia, hypertension, and diabetes were included as covariates in models for HDL cholesterol, log triglycerides, systolic and diastolic blood pressure, and fasting plasma glucose, respectively. In addition, the association between peri-aortic fat and risk factor covariates were tested in multivariable models with the inclusion of BMI and WC or VAT. Thoracic peri-aortic fat was not associated with height in women ($r=0.05$, $p=0.25$) or men ($r=0.01$, $p=0.75$)

The association of peri-aortic fat with both thoracic abdominal aortic calcification, and coronary artery calcification was assessed. The presence or absence of calcification was based on age- and sex-adjusted 90^{th} percentile cut points from a healthy referent sample. Logistic regression was performed to assess the beta-coefficients and the odds ratios of calcification per 1-SD increase in thoracic peri-aortic fat. Models are presented adjusted for 1) age and sex; 2) age, sex, and VAT; 3) age, sex, systolic blood pressure, hypertension treatment, diabetes mellitus, total/HDL cholesterol, lipid lowering therapy, smoking, alcohol, menopausal status, and hormone replacement therapy; 4) model 3 plus VAT; 5) model 3 plus VAT, BMI, and WC. All analyses were performed using SAS version 8.0. P-values <0.05 were considered statistically significant.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Study Sample Characteristics

The mean age of the cohort was 59 years, with 56.1% women (Table 1). The mean thoracic peri-aortic fat volume was higher in men (20.3 cm^3) than women (11.9 cm^3, $p<0.05$).

Pearson Correlation Coefficients between Peri-Aortic Fat and CVD Risk Factors

In both men and women, thoracic peri-aortic fat volume was associated with increasing age ($p<0.001$) and clinical and radiographic measures of adiposity (Table 2). In both genders, thoracic peri-aortic fat was correlated with BMI ($p<0.001$), WC ($p<0.001$), and VAT ($p<0.0001$). Modest correlations were observed between thoracic peri-aortic fat and all examined cardio-metabolic risk factors.

Multivariable Regressions relating Thoracic Peri-aortic Fat to CVD Risk Factors

Peri-aortic fat volumes were associated with most cardiovascular risk factors, with a consistently stronger association in women than men (Table 3). Upon further adjustment for BMI and WC, most associations remained significant, although many were attenuated. When VAT was additionally included as a covariate, associations between thoracic peri-aortic fat volume and almost all cardiovascular disease risk covariates were attenuated (all p-

values>0.02). A notable exception was the association between thoracic peri-aortic fat and diabetes in men (OR 2.15 (95% CI 1.40–3.28, p=0.0004).

Peri-aortic Fat and Thoracic Aortic, Abdominal Aortic and Coronary Artery Calcification

Thoracic aortic fat was associated with thoracic calcification in models containing VAT (OR 1.31, 95% CI 1.01–1.71, p=0.04, Table 4), but was attenuated after adjustment for CVD risk factors (OR 1.16, 95% CI 0.88–1.51, p=0.30). However, thoracic peri-aortic fat was associated with abdominal aortic calcification, even in multivariable models that additionally adjusted for CVD risk factors, VAT, BMI, and WC (OR 1.49, p=0.007). There were no significant gender interactions for the association between thoracic perivascular fat and vascular calcification (p-values>. 0.59 for all sex interactions tested).

Thoracic aortic fat was associated with coronary calcification in models adjusted for age and gender (OR 1.35, p=0.001, Table 5). This association persisted in multivariable models with additional adjustment for VAT (OR1.47, p=0.01) and VAT, BMI and WC (OR 1.47, p=0.01).

Discussion

Principal Findings

We describe a novel body fat depot, thoracic peri-aortic fat, that can be quantified with high reproducibility using CT. In participants free of CVD, thoracic peri-aortic fat was correlated with several CVD risk factors despite adjustment for clinical measures of obesity. In addition, peri-aortic fat was correlated with VAT, a well established body fat depot with important implications for cardiovascular disease. Lastly, thoracic peri-aortic fat was associated with abdominal aortic and coronary calcification.

In the Context of Current Literature

The association between peri-aortic fat and cardiovascular disease risk factors is similar to prior observations relating VAT and pericardial fat to cardiometabolic risk [1,5]. In addition, consistent with other body fat depots, correlations between perivascular fat and adverse cardiovascular risk profiles were stronger in women than men, highlighting potential differences in obesity related cardiovascular disease in women [1,5].

Prior research shows that VAT, BMI, and pericardial fat are associated with coronary calcification, but only pericardial fat remained significant following risk factor adjustment, suggesting a locally toxic effect [5,11,12]. We now extend these findings and report an association between thoracic peri-aortic fat and both coronary and abdominal aortic but not local thoracic aortic calcification. There are several potential reasons for the lack of association between thoracic peri-aortic fat and local vascular calcification. Firstly, the expression profiles of body fat depots vary by anatomic location [3]. Pericardial fat is known to secrete lower levels of anti-inflammatory adiponectin and higher levels of pro-inflammatory cytokines (interleukin-6, interleukin-8, and monocyte chemoattractant protein-1) than other fat depots [3,7,8]. While there is evidence of the chemotatic properties of peri-aortic white adipose tissue in humans as a source of local vascular inflammation, the specific metabolic profile of pericardial fat may explain its differential association with vascular calcification as compared to other fat depots [9]. Our thoracic calcification measurement was limited by the lack of inclusion of the aortic arch. Lastly, we can not rule out that the lack of association was due to chance. Nonetheless, the association between thoracic peri-aortic fat and both abdominal aortic and coronary calcification in the absence of an association with local thoracic aortic calcification is of interest and should stimulate interest in the expression profiles of this fat depot.

Potential Mechanisms

Yudkin has hypothesized a pathogenic role of peri-vascular fat in local atherosclerosis via "vasocrine" pathways has been described in the vascular supply to the rat cremaster muscle [6]. This hypothesis states that fat deposits surrounding arteries supplying metabolically active tissue such as muscle (nutritive arteries) release substances that affect vascular tone and hence limit substrate delivery to tissues in times of calorie excess. These mechanisms as well as the high pro-inflammatory cytokine expression of pericardial fat may not operate in fat deposits surrounding other arteries, particularly those not immediately supplying end organs such as the aorta. Differences in secretory products and gene expression profiles for leptin, adiponectin, IL-6, IL-8, and MCP-1 have been demonstrated for subcutaneous fat, VAT and pericardial fat [3,7,10,26–29]. While animal research has demonstrated vaso-active substances expressed in aortic perivascular fat and up-regulation of pro-inflammatory gene expression in response to a high fat diet, complete expression profiles from this tissue in humans have not been described [3,13,14]. The composition of adipose tissue in specific deposits may also be responsible for regional differences. While pericardial fat is white adipose tissue, brown adipose tissue is known to be present in the thorax, and may not exert similar pro-inflammatory or vaso-active properties [3,22].

Clinical and Research Implications

Future research should aim to identify differences in cytokine expression profiles between fat depots that exhibit a local association with atherosclerosis and those that do not to identify potentially causative mediators.

Strengths and Limitations

Strengths of the study are the large community based nature of the cohort, with measured cardiovascular risk factors. In addition to cardiovascular risk factors, we were able to account for VAT in multivariable models. Certain limitations warrant mention. The Framingham offspring study is predominantly a white cohort and this limits the ability to generalize findings to other ethnic groups. Our study described the correlation of multiple covariates and perivascular fat. A limitation of performing multiple tests is the possibility of associations achieving statistical significance by chance alone. In addition, our study was cross-sectional in nature. As such, we can not infer causality regarding the relationship between volume of perivascular fat and vascular calcification. Furthermore, our study used the presence of calcification as a surrogate for atherosclerotic vascular disease. As such, we do not assess the relationship of perivascular fat with other non-calcified atherosclerotic plaque components.

Conclusions

Peri-aortic fat depots are associated with cardiovascular disease risk profiles and existing measures of adiposity. Thoracic peri-aortic fat is associated with coronary and abdominal aortic calcification.

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Table 1
Study sample characteristics among participants without prevalent CVD

Data are presented as mean (standard deviation) or the percentage having the characteristic.

	Women (n=599)	Men (n=468)	Overall (n=1067)
Age, years	59 (9)	58 (9)	59 (9)
Body Mass Index, kg/m^2	27.7 (5.6)	28.7 (4.3)	28.1 (5.1)
Waist Circumference, cm	96 (15)	103 (11)	99 (14)
Triglycerides, mg/dl*	126 (76–161)	143 (79–174)	133 (77–165)
HDL cholesterol, mg/dl	61 (15)	46 (12)	54 (16)
Total cholesterol, mg/dl	207 (36)	195 (33)	202 (35)
Systolic blood pressure, mm Hg	124 (19)	126 (16)	125 (18)
Diastolic blood pressure, mm Hg	73 (9)	77 (9)	75 (9)
Hypertension, %	34.9	37.8	36.2
Fasting plasma glucose, mg/dL	98 (18)	104 (24)	101 (21)
Impaired fasting glucose, %†	25.5	42.8	33.0
Diabetes mellitus, %	7.9	11.1	9.3
Metabolic Syndrome, %	36.6	40.6	38.3
Smoking, %			
Current	9.4	8.6	9.0
Former	51.1	50.6	50.9
Never	39.6	40.8	40.1
Postmenopausal, %	81.1	-	-
Hormone replacement therapy, %	36.6	-	-
Alcohol use, %‡	16.0	15.8	15.9
Thoracic Peri-aortic Fat, cm^3	11.9 (5.8)	20.3 (9.0)	15.6 (8.5)
Visceral Adipose Tissue, cm^3	1615 (870)	2514 (1015)	2009 (1037)
Thoracic Aortic Calcification (prevalence>90%)	31.2	35.3	33.0
Abdominal Aortic Calcification (prevalence>90%)	23.1	16.1	20.0

*Median with 25th–75th percentiles.

†Defined as fasting plasma glucose 100–125 mg/dL (based on participants without diabetes).

‡Defined as ≥14 drinks per week (men), or ≥7 drinks per week (women). HDL indicates high density lipoprotein.

Table 2

Age-Adjusted Pearson Correlation Coefficients Between Metabolic Risk Factors and Thoracic Peri-aortic Fat among participants without prevalent CVD.

	Women Thoracic Peri-Aortic Fat	Men Thoracic Peri-Aortic Fat	Overall Thoracic Peri-Aortic Fat
Age	0.31*	0.30*	0.30*
BMI	0.56*	0.58*	0.53*
WC	0.59*	0.58*	0.54*
VAT	0.77*	0.75*	0.75*
Subcutaneous Adipose Tissue	0.50*	0.47*	0.46*
Log triglycerides	0.36*	0.26*	0.29*
HDL cholesterol	−0.28*	−0.26*	−0.25*
Total cholesterol	0.10‡	−0.01	0.04
Systolic blood pressure	0.24*	0.13*	0.17*
Diastolic blood pressure	0.20*	0.17*	0.18*
Blood glucose	0.32*	0.22*	0.26*

* p<0.001;

† p<0.01;

‡ p<0.05.

BMI, body mass index; WC, waist circumference; VAT, visceral adipose tissue; HDL, high density lipoprotein.

Table 3

Sex-Specific Multivariable-Adjusted (MV) Regressions for Thoracic Peri-aortic fat with Continuous Metabolic Risk Factors and Dichotomous Risk Factors among participants without prevalent CVD

Data presented include effect size (risk factor±SE) per 1 SD of adipose tissue for continuous data, and the odds ratio per 1 SD of adipose tissue with 95% CI for dichotomous data.

	MV-adjusted residual effect size	Women MV-adjusted residual effect size after BMI-WC adjustment	MV-adjusted residual effect size after VAT adjustment	MV-adjusted residual effect size	Men MV-adjusted residual effect size after BMI-WC adjustment	MV-adjusted residual effect size after VAT adjustment	P-value for sex interaction
SBP, mm Hg	3.60±0.75*	1.49±0.90	0.67±1.14	1.79±0.73‡	0.87±0.91	1.61±1.10	<0.001
DBP, mm Hg	1.69±0.40*	0.69±0.48	0.32±0.60	1.61±0.45†	0.80±0.55	0.95±0.66	0.02
FPG, mg/dL	4.55±0.61*	1.99±0.74†	0.07±0.92	3.59±1.02†	3.55±1.25†	3.62±1.52‡	0.03
Log TG, mg/dl	0.19±0.02*	0.12±0.024*	0.04±0.03	0.15±0.03*	0.14±0.03*	0.05±0.04	<0.0001
HDL, mg/dl	−4.36±0.63*	−2.49±0.77†	−0.36±0.96	−3.64±0.55*	−2.77±0.68*	−1.85±0.82‡	0.002
Hypertension	1.94(1.57–2.39)*	1.37(1.07–1.75)‡	1.10 (0.81–1.49)	1.52(1.22–1.88)†	1.46(1.12–1.90)†	1.42 (1.03–1.95)‡	0.001
IFG	2.11(1.68–2.64)*	1.63(1.26–2.11)*	1.38 (1.00–1.91)‡	1.51(1.21–1.88)†	1.27(0.98–1.65)	0.94 (0.67–1.31)	0.0007
Diabetes	1.77(1.36–2.31)*	1.35(0.97–1.87)	0.98 (0.64–1.48)	1.90(1.43–2.53)*	1.46(1.03–2.07)‡	2.15 (1.40–3.28)*	0.26
Metabolic Syndrome	3.28(2.54–4.23)*	1.82(1.35–2.44)*	1.26 (0.89–1.79)	2.12(1.69–2.67)*	1.40(1.06–1.83)‡	1.14 (0.83–1.58)	<0.0001

MV indicates the multivariable model, adjusted for age, smoking, alcohol use, menopausal status (women only), and hormone replacement therapy (women only). For blood pressure, FPG, HDL cholesterol, and log triglycerides, and additional covariate of treatment for hypertension, diabetes, or lipid disorders, respectively, was included. l; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TG, triglyceride; HTN, hypertension; IFG, impaired fasting glucose; and DM, diabetes mellitus. VAT, visceral adipose tissue; BMI, body mass index; WC, waist circumference.

P for thoracic fat in the model:

*p<0.001;

†p<0.01;

‡p<0.05.

Table 4

Multivariable-adjusted regressions for Thoracic Peri-aortic Fat with the presence or absence of Thoracic or Abdominal Aortic calcification, with and without adjustment for metabolic risk factors and other measures of adiposity. Data presented as odds ratio of thoracic or abdominal aortic calcification per 1 standard deviation increase of thoracic peri-aortic fat.

	Thoracic Aortic Calcification		Abdominal Aortic Calcification	
Model Adjustments	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Age, Sex	1.06 (0.90–1.26)	0.50	1.46 (1.23–1.75)	<0.0001
Age, Sex, VAT	1.31 (1.01–1.71)	0.04	1.70 (1.30–2.21)	0.0001
Age, Sex, MV†	0.89 (0.73–1.08)	0.23	1.10 (0.90–1.35)	0.36
Age, Sex, MV†, VAT	1.16 (0.88–1.51)	0.30	1.48 (1.11–1.98)	0.008
Age, Sex, MV†, VAT, BMI, WC	1.16 (0.89–1.53)	0.27	1.49 (1.12–1.99)	0.007

†Multivariable (MV) adjusted for systolic blood pressure, hypertension treatment, diabetes, total/HDL cholesterol, lipid treatment, smoking, alcohol, menopausal status, hormone replacement therapy. VAT, visceral adipose tissue; BMI, body mass index; WC, waist circumference.

Table 5

Multivariable-adjusted regressions for Thoracic Peri-aortic Fat with the presence or absence of Coronary Artery Calcification (CAC), with and without adjustment for metabolic risk factors and other measures of adiposity. Data presented as odds ratio of CAC per 1 standard deviation increase of thoracic peri-aortic fat.

	Coronary Aortic Calcification	
Model Adjustments	**OR (95% CI)**	**p-value**
Age, Sex	1.35 (1.12–1.61)	0.001
Age, Sex, VAT	1.62 (1.22–2.13)	<0.001
Age, Sex, MV†	1.11 (0.90–1.36)	0.34
Age, Sex, MV†, VAT	1.47 (1.09–1.98)	0.01
Age, Sex, MV†, VAT, BMI, WC	1.47 (1.09–1.98)	0.01

†Multivariable (MV) adjusted for systolic blood pressure, hypertension treatment, diabetes, total/HDL cholesterol, lipid treatment, smoking, alcohol, menopausal status, hormone replacement therapy. VAT, visceral adipose tissue; BMI, body mass index; WC, waist circumference.