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Pericardial Fat Volume Correlates with Inflammatory Markers: The Framingham Heart Study:

Pericardial Fat and Inflammation

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Abstract

The objective of this study was to determine whether systemic inflammatory and oxidative stress marker concentrations correlate with pericardial and intrathoracic fat volumes. Participants of the Framingham Offspring Study (n=1175; 53% women; mean age 59±9 years) had pericardial and intrathoracic fat volumes assessed by multidetector computed tomography (MDCT) scans, and provided fasting blood and urine samples to measure concentrations of fourteen inflammatory markers: C-reactive protein (CRP); interleukin-6; monocyte chemoattractant protein-1 (MCP-1); CD40 ligand; fibrinogen; intracellular adhesion molecule-1; lipoprotein-associated phospholipase A₂ activity and mass; myeloperoxidase; osteoprotegerin; P-selectin; tumor necrosis factor-α; tumor necrosis factor receptor 2; and urinary isoprostanes. Multivariable linear regression models were used to determine the association of log-transformed inflammatory marker concentrations with fat volumes, using fat volume as the dependent variable. Due to smaller sample sizes, models were rerun after adding urinary isoprostanes (n=961) and tumor necrosis factor-α (n=813) to the marker panel. Upon backward elimination, four of the biomarkers correlated positively with each fat depot: CRP ($P<0.0001$ for each fat depot); interleukin-6 ($P<0.05$ for each fat depot); MCP-1 ($P<0.01$ for each fat depot); and urinary isoprostanes ($P<0.01$ for pericardial fat; $P<0.001$ for intrathoracic fat). Even after adjusting for body mass index, waist circumference, and abdominal visceral fat, CRP ($P=0.0001$) and urinary isoprostanes ($P=0.02$) demonstrated

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significant positive associations with intrathoracic fat, but not with pericardial fat. Multiple markers of inflammation and oxidative stress correlated with pericardial and intrathoracic fat volumes, extending the known association between regional adiposity and inflammation and oxidative stress.

INTRODUCTION

Mediators of inflammation and oxidative stress play a role in the pathogenesis of cardiovascular disease (1,2), and are elevated in people with obesity (3). Studies have demonstrated that not only total adiposity but also regional distribution of body fat – in particular, abdominal visceral fat – is an important correlate of inflammation and oxidative stress (4), metabolic risk (5,6), and cardiovascular disease (7). Pericardial and intrathoracic fat are visceral fat depots as well. Pericardial fat shares a common embryonic origin with abdominal visceral fat – the splanchnic mesoderm (8) – and intrathoracic fat originates from the thoracic mesoderm (9).

We previously published that intrathoracic fat volume quantified by multidetector computed tomography (MDCT) scan correlated with hypertension, impaired fasting glucose, and metabolic syndrome even after adjusting for body mass index (BMI) (10). Further, pericardial and intrathoracic fat volumes correlated with coronary and aortic calcium, respectively (10). Other studies have shown that pericardial fat volume (11-13), area (14,15), and thickness (16-20) measured by CT scan (13,17), magnetic resonance imaging (12,14,15), echocardiography (16,18-20), and autopsy (11) correlate with blood pressure (14,15,19), coronary artery calcium (17), insulin resistance (15,19), early left ventricular dysfunction (15), and left ventricular mass (11,20). There are conflicting results regarding the correlation between pericardial fat and angiographically-measured coronary artery disease (13,16).

Given the correlation of pericardial and intrathoracic fat with metabolic and cardiovascular diseases, we hypothesized that systemic markers of inflammation and oxidative stress are associated with pericardial and intrathoracic fat volumes in the community.

METHODS AND PROCEDURES

Our cross-sectional study was performed at the Framingham Heart Study, a community-based observational epidemiology investigation that originated in 1948. The participants were members of the Framingham Offspring Study who underwent MDCT scans (n=1418). Participants living in close proximity to Framingham, MA, and those from large Framingham Heart Study families were preferentially selected for the MDCT scan study. Males had to be at least 35 years old, and females had to be at least 40 years old and not pregnant. Body weights less than 352 pounds were required due to scanner limits. Participants were excluded for the following reasons: technically inadequate MDCT scan (n=46); lack of attendance at examination 7 (1998-2001; n=23); incomplete measurement of inflammatory marker panel (excluding tumor necrosis factor-alpha and urinary isoprostanes, which were measured in subsets of 813 and 961 participants, respectively; n=128); lack of one or more covariates (n=2); and history of coronary artery bypass graft surgery, which makes measurement of pericardial and intrathoracic fat volume unreliable (n=44). The study protocol was reviewed by the Institutional Review Boards of Boston University Medical Center and Massachusetts General Hospital.

Fat volume measurements

Thoracic and abdominal MDCT scans were performed between June 2002 and April 2005. On average, forty-eight 2.5-millimeter slices were taken from the superior border of the aortic arch inferiorly to the diaphragm. A pre-defined image display was set at -120 Hounsfield Units, with window width -195 to -45 Hounsfield Units used to identify adipose tissue from the level of the right pulmonary artery inferiorly to the diaphragm, and from the chest wall posteriorly to the descending aorta. A semi-automatic segmentation technique was used, requiring the reader to trace the thoracic structures manually. Fat volume (measured in cubic centimeters) was quantified by multiplying areas of fat times each contiguous 2.5-mm slice. A subset of 100 MDCT scans was read by the same reader twice and by two readers to determine intra- and inter-observer variability. The interclass correlation coefficients for intra- and inter-observer readings of pericardial fat were 0.97 and 0.95, respectively; and for total thoracic fat, they were 0.99 and 0.98, respectively.

Fat nomenclature

Fat within the pericardium was termed “pericardial fat,” and fat within the thorax – including the pericardial fat – was termed “total thoracic fat.” “Intrathoracic fat” was calculated as the difference between total thoracic fat and pericardial fat in order to create two distinct (non-overlapping) fat depots; this is different from our prior definition of intrathoracic fat (10). Nomenclature varies among experts. Intrathoracic fat in our present study is synonymous with mediastinal fat, or, paracardial fat. It is composed of all fat external to the pericardial sac within the mediastinum, including paraaortic, paravertebral, and substernal fat. Pericardial fat in our present study is used interchangeably with epicardial fat. However, we are unable to separate the true epicardial fat (fat within the visceral pericardium) from fat between the visceral pericardium and the pericardial sac on our CT scans. Measurement of abdominal visceral and subcutaneous fat volume has been described previously (4).

Covariate assessment

Participants presented to the Framingham Heart Study between 1998 and 2001, at which time covariates were assessed by physician history and physical examination, participant questionnaires, and available medical records from outpatient and hospital visits. Smoking was defined as one or more cigarettes per day within the last 12 months. Heavy alcohol consumption was defined as ≥ 14 drinks per week for men and ≥ 7 drinks per week for women. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. Obesity was defined as BMI ≥ 30 kilograms/meter squared. Waist circumference was measured by trained technicians according to standard protocol. Lipid profile and blood glucose were measured from morning fasting blood samples. Aspirin use was defined as ≥ 3 doses per week. Menopause was defined as lack of menses for ≥ 1 year. Diabetes mellitus was defined as fasting blood glucose ≥ 126 mg/dL or treatment with hypoglycemic agent(s). Cardiovascular disease was defined as history of angina pectoris, coronary insufficiency, myocardial infarction, congestive heart failure, transient ischemic attack, stroke, or intermittent claudication determined by an expert panel of 3 physicians.

Measurement of inflammatory and oxidative stress marker concentrations

Participants provided fasting blood and urine samples. Samples were frozen at -80 degrees Celsius until testing. Serum concentrations of the following markers were measured: C-reactive protein (CRP); interleukin-6; intracellular adhesion molecule-1; monocyte chemoattractant protein-1 (MCP-1); myeloperoxidase. Plasma concentrations of the following markers were measured: CD40 ligand; fibrinogen; lipoprotein-associated phospholipase A₂ activity and mass; osteoprotegerin; P-selectin; and tumor necrosis factor

receptor 2. Urine isoprostanes concentrations indexed to urinary creatinine were measured as well. All the intra-assay coefficients of variation were $\leq 9.1\%$. Details regarding marker measurements have been reported previously (4).

Statistical analyses

Inflammatory and oxidative stress marker concentrations were natural log-transformed to account for skewed distribution for all analyses. Pearson's correlation coefficients were calculated to determine correlation between fat volume and inflammatory marker concentrations in age- and sex-adjusted models.

Four multivariable, sex-pooled linear regression models were executed for fat volume versus inflammatory marker concentrations, using fat volumes as the dependent variables. Separate models were executed for pericardial and intrathoracic fat depots. Model 1 adjusted for age, sex; current smoking; heavy alcohol use; aspirin use; menopausal status; and hormone replacement therapy. Model 2 adjusted for Model 1 plus BMI and waist circumference. Model 3 adjusted for Model 2 plus abdominal visceral fat volume. Model 4 adjusted for Model 2 plus the following: systolic and diastolic blood pressure; lipid treatment; total cholesterol/HDL ratio; triglycerides; diabetes mellitus; and cardiovascular disease. Covariates and adjustments were chosen based on their associations with inflammatory and oxidative stress marker concentrations in our previous studies (3,21). Hierarchical models were used because we hypothesized that, due to interrelations among regional fat depots, BMI, and waist circumference (10), adjustments for the other adiposity measurements would obfuscate the correlations of inflammatory markers with pericardial and intrathoracic fat. For each fat volume and model, the regression first simultaneously included all inflammatory markers as independent variables. If one overall omnibus statistical test – assessing whether at least one marker was related to the given fat variable in the given model – yielded statistical significance at the $P < 0.05$ level, then backward elimination of inflammatory markers was performed and model R^2 values were calculated for those markers that were significantly correlated with fat volume.

Secondary analyses

Tumor necrosis factor- α and urinary isoprostanes were added to the marker panel in the linear regression models in separate analyses because a smaller subset of participants had measurements for these markers ($n=813$ for tumor necrosis factor- α ; $n=961$ for urinary isoprostanes). Tests for effect modification by sex, age (<60 versus ≥ 60 years old), and obesity (BMI <30 versus ≥ 30 kg/m²) were performed for all fourteen markers, adjusting for the Model 2 covariates and using a significance threshold of $P < 0.01$.

RESULTS

Of the 1175 participants in the study, 53% were women, the mean age was 59 ± 9 years, and the mean BMI was 28.2 ± 5.2 kg/m². The mean pericardial and intrathoracic fat volumes were $124 (\pm 51)$ cm³ and $114 (\pm 62)$ cm³, respectively. See Table 1 for study sample characteristics.

Age- and sex-adjusted Pearson's correlation coefficients for pericardial fat with inflammatory marker concentrations revealed statistically significant positive correlations of pericardial fat with CRP, fibrinogen, intracellular adhesion molecule-1, interleukin-6, isoprostanes, MCP-1, P-selectin, and tumor necrosis factor receptor-2. The same markers, as well as myeloperoxidase, had significant positive Pearson's correlation coefficients for intrathoracic fat (Table 2).

Results of sex-pooled multivariable linear regression models with backwards elimination of inflammatory markers are presented in Table 3. For pericardial fat, backwards elimination in Model 1 revealed significant correlations with concentrations of CRP ($P<0.0001$), interleukin-6 ($P<0.02$), and MCP-1 ($P<0.01$); the overall R^2 of Model 1 was 0.244. After further adjusting for BMI and waist circumference (Model 2), interleukin-6 was no longer significant; and after further adjusting for abdominal visceral fat volume (Model 3), none of the inflammatory markers were retained in the model. In Model 4, which adjusted for additional covariates but not abdominal visceral fat volume, CRP ($P<0.01$) and MCP-1 ($P<0.05$) remained correlated with pericardial fat.

Similarly for intrathoracic fat, backwards elimination in Model 1 revealed significant correlations with CRP ($P<0.0001$), interleukin-6 ($P=0.03$), and MCP-1 ($P<0.01$) (R^2 of Model 1 was 0.425); with loss of significance of interleukin-6 after further adjusting for BMI and WC (Model 2). However, CRP remained significantly correlated with intrathoracic fat even after additional adjustment for abdominal visceral fat in Model 3 ($P<0.0001$) and the additional covariates in Model 4 ($P<0.0001$). Examining age- and sex-adjusted mean CRP by tertiles of intrathoracic and abdominal visceral fat, the trend for higher CRP concentrations across intrathoracic fat tertiles was significant ($P<0.05$) within all 3 abdominal visceral fat tertiles (Figure 1).

Secondary analyses

We examined the addition of tumor necrosis factor- α and urinary isoprostanes to the marker panel in the subset of subjects with these markers. Backwards elimination revealed that urinary isoprostanes were significantly correlated with intrathoracic fat even after adjustment for BMI, waist circumference, and abdominal visceral fat ($P=0.02$), as well as the covariates in Model 4 ($P<0.001$). Examining age- and sex-adjusted mean urinary isoprostanes concentrations by tertiles of intrathoracic and abdominal visceral fat, the trend for increased urinary isoprostanes across intrathoracic fat tertiles was significant ($P<0.05$) in the middle abdominal visceral fat tertile (Figure 2).

For intrathoracic fat, the test for statistical interaction between sex and marker concentrations was significant for CRP ($P<0.0001$), fibrinogen ($P=0.0007$), and isoprostanes ($P=0.0001$). Effect sizes were larger for men than women. There was no statistical interaction between intrathoracic fat and age or obesity. For pericardial fat, the test for statistical interaction between sex and marker concentrations was significant for fibrinogen ($P=0.007$) and isoprostanes ($P=0.009$); and that between obesity and marker levels was significant for MCP-1 ($P=0.008$) and P-selectin ($P=0.004$). Effect sizes were larger for men than women, and for obese versus non-obese participants. There was no statistically-significant interaction between pericardial fat and age.

DISCUSSION

Principal findings

Pericardial and intrathoracic fat volumes correlated with multiple markers of inflammation and oxidative stress, including CRP, fibrinogen, intracellular adhesion molecule-1, interleukin-6, MCP-1, P-selectin, tumor necrosis factor receptor-2, and urinary isoprostanes. In multivariable-adjusted backwards elimination of the inflammatory markers, CRP, interleukin-6, MCP-1, and urinary isoprostanes were significantly correlated with both pericardial and intrathoracic fat. After adjusting for other markers of adiposity – including BMI, waist circumference, and abdominal visceral fat – CRP and urinary isoprostanes remained significantly correlated with intrathoracic fat volume.

Comparison with previous literature

Animal models have shown that epicardial fat (analogous to pericardial fat in our study) has a high rate of fatty acid synthesis and release, and significantly higher protein content than subcutaneous fat (22). Proteins released by periaortic adipocytes (analogous to intrathoracic fat in our study) from obese rats (compared with non-obese controls) induce significantly more in vitro smooth muscle cell proliferation (23), supporting a local role for perivascular fat in obesity-related atherosclerosis. Upregulation of multiple inflammation-related genes in human pericardial versus subcutaneous adipose tissue has been demonstrated by microarray hybridization (24). We extend this finding by demonstrating a correlation between systemic inflammation and pericardial and intrathoracic fat volume. Human pericardial and intrathoracic adipose tissue had dense inflammatory cell infiltrates when compared to subcutaneous adipose tissue using hematoxylin and eosin staining and immunohistochemistry, suggesting that these fat depots may play a more central role than subcutaneous fat in the inflammatory process (24,25). MCP-1 from pericardial adipocytes likely plays a role in chemotaxis of the inflammatory cells, as has been shown in vitro (25).

Previous human studies on pericardial (24,26-30) and intrathoracic (25,31) fat used tissue samples procured during cardiovascular surgery to measure mRNA (24,26,29-31) and protein (24,25,27,28) concentrations of multiple markers. Compared with subcutaneous fat, pericardial and intrathoracic fat demonstrated higher concentrations of MCP-1 (24) and other inflammatory markers (24,26,29); lower concentrations of plasminogen activator inhibitor-1 (26); and conflicting results for interleukin-6 (24,26,27) and tumor necrosis factor-alpha (24,26,27). Compared to controls without, those patients with coronary artery disease had higher concentrations of interleukin-6 and tumor necrosis factor-alpha expressed in their pericardial tissue (27). These studies, despite being limited by selected and small samples (range 4 to 46 participants) with limited covariate adjustment, had the advantage of using human adipose tissue samples to examine biomarker expression (24-31). Our study differed in that we measured systemic, as opposed to local, inflammatory marker concentrations. As local adipose tissue expression of inflammatory markers may not correlate with systemic marker concentrations (24), further research is warranted to elucidate the relations between local inflammation demonstrated by previous studies, and systemic inflammation demonstrated by our study. Another important distinction is that the other studies measured inflammation in adipose tissue procured at advanced stages of disease (i.e., at time of heart surgery), whereas our study examined inflammation and adipose tissue in a community-based sample. As our study was observational and roughly cross-sectional, we cannot exclude the possibility that the association was secondary to residual confounding.

Pathophysiological mechanisms

The most likely explanation for our findings is that pericardial and intrathoracic fat may be extensions of abdominal visceral fat or generalized adiposity – both of which are associated with systemic inflammation and oxidative stress (3,4,32). Both pericardial and intrathoracic fat are visceral fat depots, and pericardial fat shares a common embryonic origin with abdominal visceral fat (8). Pericardial and intrathoracic fat volumes correlate closely with abdominal visceral fat volume as well as generalized adiposity (represented by BMI) (10). The interrelations among these fat depots likely explain why adjustments for BMI, waist circumference, and abdominal visceral fat attenuated our principal finding that multiple markers correlate with the fat depot volumes. The large increase in model R^2 attributable to the markers (from 0.046 to 0.244 for pericardial fat, and from 0.034 to 0.425 for intrathoracic fat) in our multivariable models would likely have been more modest if BMI, waist circumference, and abdominal visceral fat were included as covariates before adding the markers to the model. But calculating model R^2 was not the principal objective – the

models were ordered as such to determine whether pericardial and intrathoracic fat volumes reveal information beyond that of the other body fat measurements. Our finding that CRP and isoprostane concentrations are higher across increasing tertiles of intrathoracic and abdominal visceral fat does not prove a causal relation between the fat depot and systemic inflammation and oxidative stress. Such a relation would be remarkable considering the relatively small size of the fat depot – the mean intrathoracic fat volume was roughly one-twentieth the size of the mean abdominal visceral fat depot.

Isoprostanes are produced by non-enzymatic, free radical peroxidation of arachidonic acid. They are markers of oxidative stress, active mediators of vasomotor and platelet activity, and are significant correlates of multiple cardiovascular disease processes (33). CRP is the most extensively researched inflammatory marker, and is a robust clinical biomarker with several speculated inflammatory and atherogenic roles (34). Interleukin-6 is the primary stimulus for hepatic CRP production; it also stimulates MCP-1 secretion by macrophages, and amplifies the inflammation cascade (34). Systemic concentrations of interleukin-6, CRP, and isoprostanes are associated with cardiovascular disease as well as metabolic disorders including obesity (3,21,35-37). We have previously demonstrated that these markers correlate with abdominal visceral adiposity (4), and now extend that finding to show correlations with thoracic visceral adiposity.

Limitations and strengths

Our cross-sectional study cannot determine causal relations between the markers and fat depots. The study sample is mostly white, of European descent, so results may not generalize to other ethnicities. In the time lapse between procurement of the inflammatory marker samples (1998 to 2001) and MDCT scan performance (2002 and 2005) interim disease processes, lifestyle changes, and/or aging may have affected both fat volumes and marker concentrations, thereby altering correlations. The order of our hierarchical models obfuscated the true contribution of markers to the fat volumes (represented by model R^2), likely due to close relations among the fat depots and general adiposity measurements (10). The statistical power of the present study was modest given the magnitude of the associations and multiple testing. Systemic inflammatory marker concentrations may not correlate with pericardial and intrathoracic adipose tissue marker concentrations (25,38). Similarly, whereas our findings may have pathophysiological implications by highlighting the association between inflammation and pericardial and intrathoracic fat, the clinical implications are uncertain. Urinary isoprostanes were measured by enzyme-linked immunosorbent assay (ELISA), not gas chromatography/mass spectrometry; there is a strong correlation between the two measurements (39), nonetheless, and ELISA would bias results towards the null hypothesis. Microbial infections – which increase inflammatory marker concentrations – were not among the exclusion criteria, but would likely result in minor misclassification, and were unlikely to explain our positive findings. The strengths of the present study include its large, community-based sample, routine ascertainment of potential confounders, precise technique of fat volume quantification, and availability of a large inflammatory biomarker panel.

Clinical implications and future directions

Prior studies have demonstrated that inflammation, oxidative stress, and visceral fat volume predispose to cardiovascular disease. It has not been shown previously that pericardial and intrathoracic fat are correlated with systemic inflammation and oxidative stress. Our study – although not demonstrating a causal relation – suggests that inflammation and oxidative stress may be associated with pericardial and intrathoracic fat. The proximity of these fat depots to cardiovascular structures may have implications for cardiovascular disease.

Further research is warranted to determine the pathophysiological mechanisms and temporal relations underlying their association.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

BMI	Body Mass Index
CRP	C-Reactive Protein
MCP-1	Monocyte Chemoattractant Protein-1
MDCT	Multi-Detector Computed Tomography

Figure 1. Mean log-transformed circulating C-reactive protein (CRP) concentrations across tertiles of intrathoracic fat and abdominal visceral adipose tissue. Trend across tertiles of intrathoracic fat were significant within all tertiles of abdominal visceral fat (* $P < 0.05$).

Figure 2.

Mean log-transformed urine isoprostanes concentrations across tertiles of intrathoracic and abdominal visceral adipose tissue. Trend across tertiles of intrathoracic fat were significant within the middle tertile of abdominal visceral fat (* $P < 0.05$).

TABLE 1**Participant Characteristics.**

Number of participants	N=1175
Age, years	59.5±9.1
Women, %	53.5
Current cigarette smoking, %	10.0
Alcohol, % (drinks per week, men ≥14; women ≥7)	15.7
Systolic blood pressure, mm Hg	125±18
Diastolic blood pressure, mm Hg	75±9
Body mass index, kg/m ²	28.2±5.2
Waist circumference, cm	99.3±13.6
Abdominal visceral fat, cm ³	2086±1087
Pericardial fat, cm ³	124±51
Intrathoracic fat, cm ³	114±62
Total/HDL cholesterol, ratio	4.1±1.3
Triglycerides, mg/dL	136±94
Lipid lowering treatment, %	17.5
Aspirin ≥3/week, %	29.2
Current hormone replacement therapy, % women	36.3
Post-menopause, % women	81.9
Diabetes, %	9.2
Cardiovascular disease, %	9.2

Binary characteristics are displayed as %, continuous measures as mean±standard deviation

TABLE 2

Age- and Sex-adjusted Pearson's Correlation Coefficients for Inflammatory Markers and Fat Volumes.

Marker	Pericardial Fat	Intrathoracic Fat
CD40 ligand	-0.05	-0.05
C-reactive protein	0.29 ^a	0.36 ^a
Fibrinogen	0.17 ^a	0.22 ^a
Intercellular adhesion molecule-1	0.11 ^b	0.11 ^b
Interleukin-6	0.20 ^a	0.22 ^a
Lipoprotein-associated phospholipase A ₂		
Activity	0.0002	0.02
Mass	-0.01	0.01
Monocyte chemoattractant protein-1	0.12 ^a	0.13 ^a
Myeloperoxidase	0.04	0.08 ^c
Osteoprotegerin	-0.004	-0.001
P-selectin	0.10 ^b	0.10 ^b
Tumor necrosis factor receptor 2	0.12 ^a	0.12 ^a
Tumor necrosis factor-alpha ^d	0.05	0.04
Urinary isoprostanes ^d	0.17 ^a	0.23 ^a

^a $P < 0.0001$,^b $P < 0.001$,^c $P < 0.01$ ^d Secondary analyses with smaller sample size (urinary isoprostanes, n=961; tumor necrosis factor-alpha, n=813)

TABLE 3
Multivariable-adjusted Backwards Elimination Linear Regression Models for Relations Between Inflammatory Markers & Fat^a.

Model:	1	2	3	4
	Clinical Covariates Only ^b	Clinical Covariates ^b + Markers	P	+ BMI & WC + Additional Covariates ^c
			P	P
Pericardial Fat				
CRP	---	18.0 (13.7-22.2)	<0.0001	6.1 (1.9-10.3)
Interleukin-6	---	4.3 (0.8-7.7)	0.02	---
MCP-1	---	4.4 (1.1-7.6)	<0.01	3.1 (0.02-6.1)
Model R²	0.046	0.244	0.338	0.351
Intrathoracic Fat				
CRP	---	25.1 (20.5-29.6)	<0.0001	11.9 (7.4-16.3)
Interleukin-6	---	4.0 (0.3-7.6)	0.03	---
MCP-1	---	5.0 (1.6-8.5)	<0.01	3.8 (0.6-7.0)
Model R²	0.034	0.425	0.503	0.509

^aExpressed as change in fat volume (cm³ (95% CI)) per inter-quartile increase in log inflammatory marker concentration.

^bAdjusted for age, sex, current smoking, heavy alcohol use, aspirin use, menopausal status and hormone replacement therapy.

^cAdjusted for blood pressure, lipid treatment, total cholesterol/HDL, triglycerides, diabetes mellitus, and cardiovascular disease.