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Determinants of intrathoracic adipose tissue volume and associations with cardiovascular disease risk factors in Amish

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Abstract

Objective—Hypothesizing that intrathoracic fat might exert local effects on the coronary vasculature, we assessed the association of intrathoracic fat volume and its two subcomponents with coronary artery calcification (CAC) in 909 relatively healthy Amish adults.

Design and Methods—Intrathoracic fat, which is comprised of fat between the surface of the heart and the visceral epicardium (epicardial fat) and fat around the heart but outside of the fibrous pericardium (pericardial fat), was measured from electron beam CT scans. We examined the association between intrathoracic fat volume and cardiovascular disease risk factors in multivariate regression model.

Results—Fat volume in the epicardial and pericardial compartments were highly correlated with each other and with body mass index. Neither CAC extent nor CAC presence (Agatston score>0) was associated with increased intrathoracic fat volume in sex-stratified models adjusting for age ($p>0.10$). Intrathoracic fat volume was significantly correlated with higher systolic/diastolic blood pressure, pulse pressure, fasting glucose, insulin, triglyceride and lower high-density lipoprotein cholesterol in sex-stratified models adjusting for age ($p<0.05$). However, associations were attenuated after further adjustment for body mass index.

Conclusions—These data do not provide support for a significant role for intrathoracic fat in the development of CAC.

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Keywords

Ectopic fat; Intrathoracic fat; Epicardial fat; Obesity; Coronary artery calcification; Cardiovascular diseases

Introduction

Obesity is associated with numerous cardiovascular and metabolic risk factors and predicts the development of cardiovascular disease and diabetes. It is widely appreciated that cardiometabolic risk is influenced not only by the absolute quantity of adipose tissue accumulation but also by where it is distributed. For example, fat tissue in the abdominal visceral compartments may pose particular risk for metabolic diseases because these tissues actively secrete adipocytokines and inflammatory factors and are in close proximity to the abdominal internal organs [1-6]

Intrathoracic adipose tissue is an extra-abdominal visceral fat depot located around the heart in the thoracic cavity. Similar to abdominal fat, intrathoracic fat also expresses and secretes high concentrations of proinflammatory adipokines [6-11]. Intrathoracic fat consists of two compartments: epicardial fat (within the pericardial sac) and pericardial fat (outside the pericardial sac). Because there is no separating fascia between epicardial fat and the myocardium, some have hypothesized that intrathoracic fat, and more specifically, epicardial fat, might exert local paracrine effects on the cardiac vasculature that influences the development of coronary artery disease [7, 11-21].

In recent years the volume of intrathoracic fat has been associated with both prevalent [13] and incident [21] cardiovascular disease (CVD). Moreover, evidence for a local effect of intrathoracic fat on the coronary vasculature was suggested by the Framingham Heart Study, which showed that coronary artery calcification (CAC) was independently associated with epicardial fat volume, after adjustment for body mass index and visceral adipose tissue [20]. In observational studies of smaller samples of individuals, intrathoracic fat has also been associated with other subclinical measures of atherosclerosis, including severity of angiographic coronary disease and carotid artery wall thickness [22]. In summary, studies have suggested that intrathoracic fat could have a local effect to the anatomical structures by the virtue of proximity and such hypothesis has been supported by epidemiological evidences showing independent effect of intrathoracic fat on top of other obesity measurements.

Establishing that intrathoracic fat predicts cardiovascular outcomes or atherosclerosis independently of overall body mass index has important implications not only because it could provide further insights into mechanisms through which obesity promotes cardiometabolic risk, but also because it would offer ways to more precisely identify individuals at higher cardiometabolic risk and could invite discussion about new approaches for prevention. With this in mind, we sought to replicate the previously reported association between intrathoracic fat and coronary artery calcification [20] in a different population characterized by a rural lifestyle and low prescription medication usage, and to determine if the association would be independent of overall adiposity. We sought further to assess the

associations of intrathoracic fat, as well as epicardial fat and pericardial fat, with a panel of cardiovascular and metabolic risk factors. .

Methods

Study population

This report is based on our ongoing epidemiologic and genetic studies of adults from the Old Order Amish (OOA) community in Lancaster County, Pennsylvania [23-25]. Subjects included in this substudy were relatively healthy individuals who volunteered to participate in a study of cardiovascular health, including assessment of coronary artery calcification, between the years of 2002 and 2008. Participants included many sets of related individuals, and indeed all OOA in Lancaster County are more than third degree cousins by virtue of their social insularity.

Intrathoracic fat volume measurement

Non-contrast electron beam computed tomography (EBCT) scans were obtained on an Imatron scanner (Imatron Inc., San Francisco, CA) in 3-mm thick contiguous slices with pixel size of 0.7813*0.7813 mm. The scans cover the full length of the heart from the great vessels to the apex of the heart. Scans were initially obtained for measurement of coronary artery calcification (see below), but were re-analyzed for this substudy for assessment of intrathoracic fat volume.

In this paper, epicardial adipose tissue is defined as adipose tissue between the surface of the heart and the visceral epicardium (within the intrathoracic sac). Pericardial adipose tissue is defined as pericardial adipose tissue around the heart but outside of the fibrous pericardium. Intrathoracic adipose tissue refers to the combination of the epicardial (within the pericardial sac) and pericardial adipose tissue (in the thorax but outside of pericardial sac) from the right pulmonary artery to the diaphragm and the anterior chest wall to the vertebral column. Manual segmentation of the epicardial and pericardial adipose tissue was performed by drawing regions-of-interest (ROIs) on every selected slice from the lower boundary of right pulmonary artery as it crosses the mid-sagittal plane to diaphragm. A threshold of -190 to -30 Hounsfield units was applied to identify adipose tissue voxels. Volumes (cm^3) of intrathoracic, epicardial, and pericardial adipose tissue were measured without knowledge of the participant's coronary calcification score. Sample images showing the ROIs are shown in Figure 1 for the upper (Fig 1a), middle (Fig 1b), and lower (Fig 1c) heart.

Both inter-observer and intra-observer reproducibility of the fat volume measurement were evaluated. Two observers (authors X.L. and I.Z.) reviewed and measured epicardial and pericardial fat volume on 12 representative scans using the manual segmentation protocol described above. The correlation in measurements between the two observers was 0.93 ($p<0.001$) and in no case did we find a between-observer difference more than 10%. X.L. also evaluated intra-observer reproducibility by re-measuring 100 randomly chosen scans one month after the initial measurement without knowledge of the initial measure. The correlation in repeat measurements of the same scan was 0.97 ($p<0.001$). Using Bland-Altman analysis, we observed high agreement between the two observers for both

intrathoracic (9.7 cm^3; 95% CI 1.1 to 18.4) and epicardial (−0.4 cm^3; 95% CI −4.2 to 3.3) fat volume. Moreover, differences between the two observers reading the same scan were relatively constant across the range of intrathoracic and epicardial fat volume (data not shown). There was very high intra-observer agreement between measurements for both intrathoracic (mean difference = 6.5cm^3, 95% CI: 1.6 to 11.3) and epicardial (−4.6 cm^3; 95% CI: −7.7 to −1.4) fat volume. Similarly high measures of inter- and intra-observer agreement were found for epicardial and pericardial fat volume measurements.

Cardiovascular disease risk factor measurement

All participants underwent a detailed clinical examination at the Amish Research Clinic in Strasburg (PA) that included assessment of CVD risk factors and a medical history interview. Examinations were conducted after an overnight fast. Height and weight were measured with a stadiometer and calibrated scale with shoes removed and in light clothing. Systolic (first phase) blood pressure (BP) and diastolic (fifth phase) BP were obtained in duplicate with a standard sphygmomanometer with the subject sitting for at least 5 minutes. Pulse pressure was defined as the difference between the systolic and diastolic BPs. Blood samples were obtained for determination of fasting glucose and lipid levels. Total and percent body fat were estimated by DXA (Hologic 4500W). Glucose concentrations were assayed with a Beckman glucose analyzer using the glucose oxidase method. Lipid concentrations were assayed by Quest Diagnostics (Baltimore, MD). Low-density lipoprotein cholesterol levels were calculated using the Friedewald equation.

Coronary artery calcification (CAC) scores were quantified from the EBCT scans using the Agatston method [26]. These scores quantify calcification density and impact area in the proximate coronary arteries and are a measure of subclinical coronary atherosclerosis that is strongly associated with risk for future cardiovascular disease events [27]. CAC scores followed a slightly right skewed distribution with 50% of subjects having a score of 0. We therefore natural log-transformed CAC scores after adding 1 to the raw value. The age- and sex- residuals of the transformed scores were approximately normally distributed. Liver fat was also measured on EBCT scans from two 1.0-cm^2 regions-of-interest as previously described [28]. The attenuation value of spleen in Hounsfield divided by that of liver was log transformed to reflect the content of liver fat.

Statistical analysis

We initially examined the distribution of intrathoracic fat and its two subcomponents, epicardial fat and pericardial fat among different age and gender strata. We next evaluated the correlation between different obesity phenotypes using Pearson correlation coefficient, unadjusted and adjusted for age, sex and BMI. Our primary analysis was designed to test the association of intrathoracic fat volume (as the independent variable) with cardiovascular risk factors and with CAC quantity. We modeled CAC quantity and each cardiovascular risk factor one at a time as dependent variable in separate models using a multiple linear regression framework. We constructed two sets of models for each dependent variable: a base model including intrathoracic fat volume and adjusted only for age; and an obesity-mediated model that adjusted for age and BMI. Regression analyses were conducted in males and females separately.

In order to account for the non-independence of participants due to family correlation, we carried out regression analyses under a variance component framework. The association between intrathoracic fat volume and cardiovascular risk factors/CAC quantity was estimated conditional on the kinship matrix, which was derived from the known genealogical relationships between study participants. Model parameters were estimated by maximum likelihood methods, and the significance of intrathoracic fat parameters was evaluated by likelihood ratio tests that compared the natural log likelihood of a model that included intrathoracic fat in the model with that of a reduced model that excluded this variable. The proportion of the variance explained by the kinship matrix corresponds to the heritability of the outcome variable conditional on exclusion of all other variables in the model (e.g., age and sex). The variance component analyses were conducted using the SOLAR software program [29].

Results

Study population characteristics

Out of 1021 participants with CT scans available, 112 were excluded from analysis because the CT scan did not cover the full length of the heart, leaving a final analysis set of 909 subjects.

Table 1 summarizes the characteristics of the study participants. The mean (± SD) age of study participants was 56.1±12.9 years, and 44.4% were men. Mean (± SD) BMI was 28.1 ± 5.2 kg/m^2; approximately 1/3 of the sample met the WHO criteria for obesity (BMI ≥ 30 kg/m^2) and another 39% met the criteria for overweight (BMI ≥ 25 kg/m^2 and < 30 kg/m^2). Slightly more than half of the study sample had coronary artery calcification present (CAC>0). 8.5% of study subjects reported having had cardiovascular disease (including heart attack, stroke, heart/carotid artery surgery or blocked arteries), 3.0% reported having been previously diagnosed with diabetes, and 17.6% of men self-identified as smokers. No women self-identified as smoker. Mean BMI and percentage body fat were higher in women compared to men, although men had higher mean waist circumference and CAC/AC scores than women.

Intrathoracic, epicardial and pericardial fat volume distribution

The distributions of fat volume of fat volume in all three compartments were slightly right skewed. Epicardial fat volume (91.8 ± 43.0 cm^3) constitutes about half of intrathoracic fat volume (173.0 ± 87.5cm^3) (Table 1). Increased intrathoracic, epicardial and pericardial fat volume were associated with older age and male gender (Table 2), and age and gender remained associated with epicardial and pericardial fat even following adjustment for BMI. Compared with females, males had a significantly lower proportion of fat distributed within the epicardial sac relative to total intrathoracic fat (51% vs. 57%, p<0.001) and this difference was apparent across all age (Table 2) and height groups (results not shown). Height was not significantly associated with epicardial, pericardial, or intrathoracic fat volume.

Correlations among epicardial, pericardial, and intrathoracic fat volume and of these measures with waist circumference, total and percent fat mass are shown in Table 3. After adjustment for age and sex, epicardial and pericardial fat volume remained highly correlated with each other (partial R = 0.67, p<0.001). The adjusted correlations of epicardial and pericardial fat volume with waist circumference, total body fat, and % body fat ranged from 0.54 to 0.61. Liver fat, measured by the attenuation value of spleen in Hounsfield divided by that of liver, was only weakly correlated with all other fat measurements. After further adjustment for BMI, all correlations tended to decrease, suggesting that the correlations of pericardial and epicardial fat with each other and with some of these other traits is influenced in part by overall adiposity. The heritabilities of epicardial, pericardial and intrathoracic fat volume were 0.48 (p<0.001), 0.28 (p<0.001) and 0.34 (p<0.001) respectively.

Association between intrathoracic fat volume and cardiovascular disease risk factors

Before performing regression analysis stratified by sex group, we first examined the association of coronary calcification score with intrathoracic fat volume in all participants. Neither coronary calcification score (log transformed after adding 1) nor coronary calcification presence (defined by coronary calcification score>0) was associated with increased intrathoracic fat tissue volume after adjusting for age, sex, age*sex interaction term and family structure. We further explored the association in men and women separately, adjusting for age and family structure. In men, each standard deviation (88 cm^3) increase of intrathoracic fat volume was associated with a 0.09 increase in log transformed CAC (p = 0.39) and with a 4% increased odds of having CAC (p=0.83). In women, each standard deviation (88 cm^3) increase of intrathoracic fat volume was associated with a 0.12 increase in log transformed CAC (p = 0.35) and with a 16% decreased odds of having CAC (p=0.50) (Table 4). With further adjustment for BMI, intrathoracic fat volume remained not significantly associated with CAC.

We examined the association between intrathoracic fat volume (independent variable) and other cardiovascular disease risk factors (dependent variable, one at a time) in models adjusted for age, sex and family structure. Intrathoracic fat volume was associated with higher systolic blood pressure, diastolic blood pressure, pulse pressure, fasting glucose, insulin, triglyceride, and lower high-density lipoprotein cholesterol (all p<0.001). However, after adjusting for BMI, the magnitudes of all of these associations diminished and, with the exceptions of fasting glucose and HDL cholesterol and triglycerides, most were no longer statistically significant. Table 4 shows the estimated changes of various cardiovascular risk factors with each standard deviation increase of intrathoracic fat volume, in males and females separately. After adjustment for age and BMI, intrathoracic fat volume remained significantly associated with increased triglyceride levels in both sexes, and with increased fasting glucose and decreased HDL cholesterol levels in males. However, none of the associations between cardiometabolic risk factors and intrathoracic fat differed significantly by sex.

Findings were similar for pericardial fat volume and epicardial fat volume; that is, both were significantly associated with multiple cardiovascular disease risk factors in age and sex

adjusted models, but the magnitude of associations diminished greatly with additional adjustment for BMI for most risk factors. The only exception is, unlike epicardial fat volume, increased pericardial fat volume remained significantly associated with higher insulin and fasting glucose, lower HDL and higher triglyceride levels even after adjusting for BMI. Neither epicardial nor pericardial fat volume was associated with coronary calcification score in age and sex adjusted models.

Discussion

Associations between intrathoracic fat and cardiovascular risk have been reported previously in both clinical-based [7, 15, 30] and large population [16, 20, 21, 31] studies; however, the mechanisms underlying this association have not been established. Intrathoracic fat could influence cardiometabolic risk either systemically, through secretion of adipokines and inflammatory factors into the circulation that interact with multiple targets, including coronary vasculature, or through local (non-systemic) pathways in which secreted adipokines interact directly with proximal anatomic structures. Firm data supporting either hypothesis, or indeed supporting the importance of intrathoracic fat accumulation in the pathology of CAC are lacking.

In the Amish we observed no association between quantity of intrathoracic fat and cardiometabolic risk, and the correlation of intrathoracic fat with CAC was small and did not achieve statistical significance even before adjustment for BMI. Our results thus stand in contrast to those obtained from the Framingham Heart Study, for which intrathoracic fat remained significantly associated with presence of CAC even after adjustment for visceral fat volume ($p=0.02$), and marginally associated after adjustment for visceral fat volume, BMI and waist circumference ($p=0.08$) [20]. Moreover, in the Framingham Study, intrathoracic fat was correlated with dyslipidemia, hypertension, impaired fasting glucose, and metabolic syndrome when adjusted for BMI, but not when adjusted for abdominal visceral fat volume, suggesting that at least some of the correlation between intrathoracic fat and cardiometabolic risk factors may be confounded by the quantity of abdominal visceral fat. In a clinic-based sample of 113 subjects, Sironi et al. observed that visceral, but not epicardial, fat was associated with coronary disease risk based on the 10-year Framingham Heart Study prediction score, although extra-pericardial (but not epicardial) fat was independently associated with triglycerides and blood pressure [32].

An intriguing observation from our study is that the quantity of intrathoracic fat appears to be much lower in the Amish despite comparable levels of BMI (mean BMI=28.2±5.1 kg/m^2 vs. 28.1±5.2 kg/m^2 in Framingham and Amish, respectively). Specifically, mean epicardial and pericardial fat volumes were 92±43 cm^3 and 81±51 cm^3 in the Amish compared to 124 ±50 cm^3 and 92±43 cm^3 in Framingham. Although it is possible that these differences are artifactual and arise from differences in measurement procedures, the protocols used by Framingham and the Amish were very similar. A second possibility is that these differences may be attributable to the much higher physical activity levels present in the Amish given prior reports that aerobic exercise can promote decreases in visceral and intrathoracic fat [33]. One might speculate that higher physical activity levels might also lead to lower BMI in the Amish sample. However our data in a limited number of Amish participants did not

support this hypothesis. In a subsample of 306 Amish subjects in whom we had also measured physical activity levels by accelerometer, we did indeed observe higher physical activity levels to be inversely correlated with quantity of intrathoracic fat ($p < 0.001$), but this correlation was diminished and was longer statistically significant upon further adjustment for BMI. We are not aware of any dietary factors that might explain the differences in intrathoracic fat volume between Amish and Framingham based on our analysis of food frequency questionnaires collected from the Amish. We hypothesize these differences could be attributed in part to other unmeasured lifestyle or genetic factors.

Why intrathoracic fat should be correlated with presence of CAC in Framingham but not in the Amish is not clear, but it may be related to the low volume of intrathoracic fat observed in the Amish. There might be a “threshold effect” whereby larger volumes of intrathoracic fat reflect more metabolically active fat, and/or that only when intrathoracic fat becomes dysfunctional does it become associated with cardiometabolic risk. It is possible that the intrathoracic fat accumulation is still not high enough in this relatively healthy Amish population and the intrathoracic depot is not yet dysfunctional. In addition, the volume of intrathoracic fat was highly correlated with volume of visceral fat ($r = 0.76$) in the Framingham Heart Study[20] and perhaps some of the adverse effects attributable to intrathoracic fat were related to residual confounding due to the high correlation with visceral fat. We did not have measurement of abdominal visceral fat in the Amish. If the correlation between a low quantity of intrathoracic and abdominal visceral fat was low in this population, this might weaken any associations between intrathoracic fat and cardiometabolic risk due to residual associations with visceral fat.

The major strengths of our study include the relative homogeneity of this rural dwelling population in terms of socioeconomic status and lifestyle, as well as the thorough assessment of intrathoracic fat volume and cardiometabolic risk factors. Very few of the associations we observed with intrathoracic fat withstood adjustment for overall adiposity, as measured by BMI. The residual associations of intrathoracic fat with triglycerides, fasting glucose, and HDL could reflect a strong correlation between intrathoracic fat and total visceral fat that cannot be fully adjusted for by BMI. Unfortunately, our ability to pursue this hypothesis further was limited because we did not have a direct measure of abdominal visceral adiposity. Using waist circumference as an indirect measurement of abdominal visceral adiposity, we did observe that the association of these variables with intrathoracic fat was even more attenuated with adjustment for waist circumference, with none of above associations remaining statistically significant.

Conclusion

In conclusion, our analyses provide no evidence for an association of intrathoracic fat with CAC, although failure to detect an association does not necessarily exclude the possibility that intrathoracic fat volume might exert a direct local effect of intrathoracic fat on coronary atherosclerosis as suggested by others. However, consistent with some other reports, we did observe associations of increased intrathoracic fat volume with multiple cardiovascular risk factors, although with a few exceptions these associations were not independent of BMI. These latter results are consistent with multiple interpretations including that intrathoracic

fat may be a marker for a more global deposition of abdominal visceral fat that affects metabolic risk systemically via its effects on a range of metabolic risk factors

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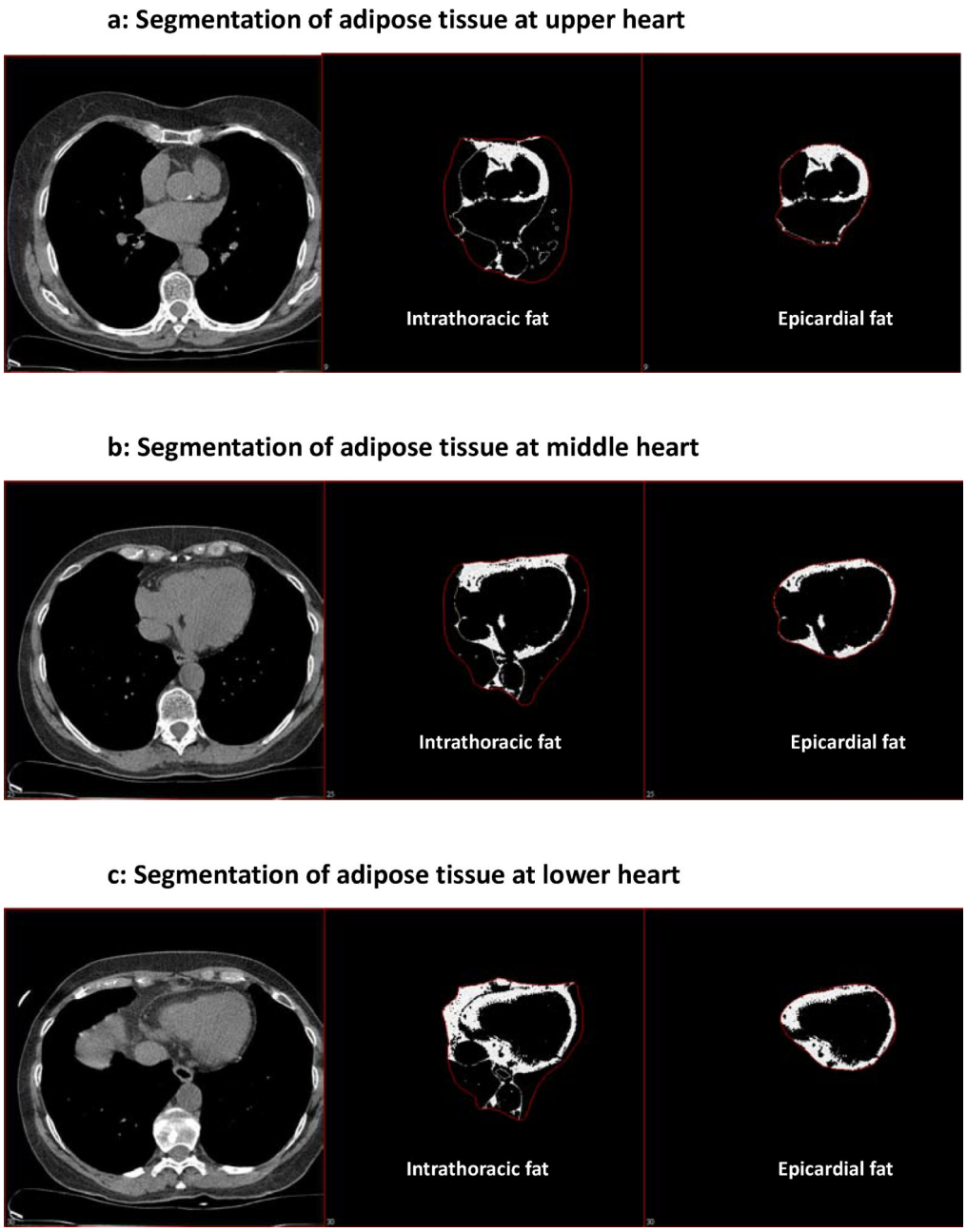

Figure 1.
Segmentation of adipose tissue at upper heart

Table 1

Characteristics of included study participants (N=909)

	Male, n=404	Female, n=505	P value	All, n=909
Age, years	56.5±13.3	55.8±12.6	0.445	56.1±12.9
BMI, kg/m^2	27.1±4.0	29.0±5.8	<0.001	28.1±5.2
Waist circumference, cm	95.9±10.7	89.2±11.1	<0.001	92.2±11.4
Percentage body fat, % [a]	21.7±6.7	36.3±6.6	<0.001	29.7±9.9
Liver fat, log (spleen/liver)[a]	−0.23±0.15	−0.23±0.17	0.738	−0.23±0.16
Coronary calcification score	329.6±689.1	112.8±364.3	<0.001	209.0±543.8
Calcification:>0	245(60.6%)	227(44.9%)	<0.001	472 (51.9%)
SBP, mm Hg	118.9±14.6	118.4±17.9	0.653	118.6±16.5
DBP, mm Hg	72.4±9.1	69.9±8.8	<0.001	71.0±9.0
Pulse pressure, mm Hg	46.5±10.9	48.5±13.1	0.013	47.6±12.2
Fasting glucose, mg/dL[a]	92.5±17.2	90.9±14.2	0.157	91.6±15.6
Insulin, mcU/mL	11.3±6.2	12.5±6.6	0.007	12.0±6.5
Total cholesterol, mg/dL	209.2±39.2	220.4±44.8	<0.001	215.4±42.7
HDL, mg/dL	52.1±13.3	60.0±15.6	<0.001	56.5±15.1
LDL, mg/dL	139.4±36.1	141.4±41.4	0.433	140.6±39.1
Triglycerides, mg/dL	87.4±52.5	95.6±62.4	0.031	92.0±58.3
Epicardial fat, cm^3	96.6±47.2	88.0±38.9	<0.001	91.8±43.0
Pericardial fat, cm^3	98.6±61.8	67.3±34.8	<0.001	81.2±51.1
Intrathoracic fat, cm^3	195.2±103.3	155.3±67.3	<0.001	173.0±87.5

Notes:

Continuous variables are shown as mean ± standard deviation; categorical variables are shown as count (percentage).

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein. Liver fat, log transformed spleen CT attenuation/liver CT attenuation ratio, higher value indicates increased fat in liver.

[a] 56 male and 82 female participants were not measured for liver fat; 44 males and 61 females were not measured for fasting glucose; 135 males and 180 females were not measured for percentage body fat. We have almost (total number of missing value<10) or complete measurements on all other collected variables.

Table 2

Mean (± SD) fat volume (cm^3) in the epicardial, pericardial, and intrathoracic compartments by age and sex

	Epicardial (cm^3)		Pericardial (cm^3)		Intrathoracic (cm^3)	
	Male	**Female**	**Male**	**Female**	**Male**	**Female**
All	96.6±47.2	88.0±38.9	98.6±61.8	67.3±34.8	195.2±103.3	155.3±67.3
Age						
29-45yrs	69.9±29.6	61.3±23.5	58.1±31.3	44.5±22.1	128.1±56.5	105.7±41.1
46-55yrs	90.0±42.7	85.3±30.4	89.9±47.8	66.9±29.5	180.0±86.1	152.2±52.6
56-65yrs	102.6±40.6	96.3±36.8	109.7±52.3	79.3±36.7	212.3±86.3	175.6±66.9
66-93yrs	126.0±54.5	110.6±44.6	139.8±75.9	79.6±36.7	265.9±121.3	190.2±72.5

Note:

Age groups defined by quartiles of the whole sample. Number of males/females in 29-45 yrs, 46-55 yrs, 56-65 yrs and 66-93yrs subgroups are: 113/130, 88/127, 101/135 and 102/113 respectively.

$P < 0.05$ for sex difference (M > F) in epicardial, pericardial, and intrathoracic fat within each age subgroup.

Table 3

Pearson partial correlation coefficients (r) between different obesity measurements adjusted for age and sex (with coefficients adjusted for age, sex and BMI in parentheses)

	Epicardial	Pericardial	Intrathoracic	WC	Total Fat	% Fat Mass	Liver fat
Epicardial	1.0	0.67[a] (0.53[a])	0.90[a](0.86[a])	0.57[a](0.29[a])	0.56[a](0.28[a])	0.54[a](0.27[a])	0.21[a](0.07,p=0.027)
Pericardial		1.0	0.93[a](0.89[a])	0.61[a](0.30[a])	0.61[a](0.29[a])	0.60[a](0.32[a])	0.23[a](0.10,p=0.008)
Intrathoracic			1.0	0.64[a](0.34[a])	0.64[a](0.33[a])	0.63[a](0.34[a])	0.24[a](0.10,p=0.005)
WC				1.0	0.87[a](0.36[a])	0.77[a](0.27[a])	0.27[a](0.04,p=0.241)
Total Fat					1.0	0.92[a](0.81[a])	0.23[a](−0.05,p=0.283)
% Fat Mass						1.0	0.14[a](−0.12,p=0.007)
Liver fat							1.0

Note:

Abbreviations: BMI, body mass index; WC, waist circumference; Liver fat, log transformed spleen CT attenuation/liver CT attenuation ratio, higher value indicating increased fat in liver.

[a] p value ≤ 0.001

Table 4

Changes in cardiovascular disease risk factors per standard deviation increase in intrathoracic fat volume (per 88 cm^3 increase), stratified by sex

	adjusted for age		adjusted for age and BMI	
	Per SD increase of intrathoracic fat	**P value[a]**	**Per SD increase of intrathoracic fat**	**P value[a]**
Male				
Presence of CAC[b] (OR)	1.04(0.72 to 1.51)	0.829	1.24(0.76 to 2.02)	0.386
Log(CAC score)	0.09(−0.11 to 0.29)	0.389	0.10(−0.18 to 0.37)	0.477
SBP, mm Hg	3.29(1.99 to 4.60)	<0.001	0.21(−1.47 to 1.89)	0.803
DBP, mm Hg	1.94(1.07 to 2.79)	<0.001	−0.33(−1.43 to 0.77)	0.557
Pulse Pressure, mm Hg	1.37(0.43 to 2.31)	0.005	0.60(−0.65 to 1.86)	0.346
Fasting Glucose, mg/dL	4.32(2.60 to 6.05)	<0.001	2.51(0.21 to 4.80)	0.033
Insulin, mcU/mL	2.31(1.74 to 2.88)	<0.001	0.62(−0.11 to 1.34)	0.095
Cholesterol, mg/dL	−2.45(−6.18 to 1.28)	0.200	2.17(−2.79 to 7.13)	0.391
HDL, mg/dL	−4.51(−5.67 to −3.35)	<0.001	−1.85(−3.36 to −0.33)	0.017
LDL, mg/dL	−1.33(−4.78 to 2.12)	0.450	2.09(−2.46 to 6.66)	0.368
Triglyceride, mg/dL	16.63(11.98 to 21.30)	<0.001	8.79(2.65 to 14.94)	0.005
Female				
Presence of CAC[b] (OR)	0.84(0.50 to 1.39)	0.496	1.13(0.58 to 2.21)	0.722
Log(CAC score)	0.12(−0.13 to 0.38)	0.348	0.07(−0.25 to 0.40)	0.660
SBP, mm Hg	5.61(3.56 to 7.66)	<0.001	0.11(−2.36 to 2.59)	0.928
DBP, mm Hg	2.51(1.40 to 3.62)	<0.001	−0.43(−1.77 to 0.91)	0.524
Pulse Pressure, mm Hg	3.06(1.59 to 4.54)	<0.001	0.54(−1.29 to 2.37)	0.566
Fasting Glucose, mg/dL	4.27(2.41 to 6.12)	<0.001	1.65(−0.66 to 3.96)	0.164
Insulin, mcU/mL	3.09(2.26 to 3.92)	<0.001	0.84(−0.15 to 1.83)	0.098
Cholesterol, mg/dL	1.75(−3.61 to 7.11)	0.523	−0.61(−7.40 to 6.20)	0.862
HDL, mg/dL	−5.81(−7.73 to −3.90)	<0.001	−2.23(−4.60 to 0.15)	0.067
LDL, mg/dL	2.43(−2.54 to 7.40)	0.338	−0.98(−7.27 to 5.31)	0.760
Triglyceride, mg/dL	25.70(18.37 to 33.04)	<0.001	12.65(3.47 to 21.82)	0.007

Note:

Coefficient estimates of intrathoracic fat volume were multiplied by SD of intrathoracic fat volume (88 cm^3) to estimate the change in risk factors per SD change of intrathoracic fat volume.

Abbreviations: OR, odds ratio; SD, standard deviation; CAC, coronary artery calcification;; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density Lipoprotein.

[a] all p values are also adjusted for family structure (see methods)

[b] presence of CAC is defined as having CAC score>0.