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Pericardial adipose tissue and coronary artery calcification in The Multi-Ethnic Study of Atherosclerosis (MESA)

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Abstract

We examined the relationship of pericardial adipose tissue (PAT) with coronary artery calcification in MESA, a large cohort in which associations by race/ethnicity can be compared. The baseline cohort comprised 6,814 Caucasian (38%), African American (28%), Chinese American (12%) and Hispanic (22%) adults aged 45–84, without known clinical cardiovascular disease. Cardiac CT was used to measure PAT (cm^3) and calcification (Agatston score). We examined cross-sectional associations of PAT with the presence (score>0) and severity (continuous score if >0) of calcification using prevalence ratio (PR) (n=6,672) and linear regression (n=3,362), respectively. Main models were adjusted for age, age^2, gender, race/ethnicity, field site, smoking, physical activity, alcohol and education. PAT volume (adjusted for age, height, weight and site) was greatest in Chinese males, while Black males had less PAT than all but Black females. PAT was associated with presence [PR per standard deviation (SD): 1.06 (95% CI: 1.04, 1.08)] and severity [difference in log Agatston score per SD: 0.15 (0.09, 0.21)] of calcification, but neither association varied by race/ethnicity. Adjustment for generalized adiposity attenuated but did not eliminate the associations. With further adjustment for traditional risk factors and inflammatory markers, only the association with severity remained statistically significant [PR: 1.02 (1.00, 1.04), difference: 0.10 (0.03, 0.17)]. Heterogeneity by sex was observed for presence of calcification (PR in men: 1.04; in women: 1.08; p for

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Disclosures

None.

interaction<0.0001). Pericardial adipose tissue was associated with the presence and severity of coronary artery calcification in this cohort, but despite differences in PAT volumes and calcification across race/ethnic groups, neither association varied by race/ethnicity.

Keywords

Coronary artery calcification; pericardial fat; subclinical atherosclerosis risk factors; obesity; epidemiology

Introduction

Excess fat deposition within and around tissues and organs may directly impair the functions of those tissues and organs (1) and may therefore be more pathogenic than fat depots in other locations. Both abdominal visceral fat (2) and pericardial fat (visceral fat around the heart) (3, 4) have a higher release of free fatty acids and inflammatory cytokines than subcutaneous fat. Because of its location, pericardial adipose tissue may constitute an especially harmful fat depot. Recent research has shown that pericardial and epicardial adipose depots are indeed associated with cardiovascular disease risk factors (5) and outcomes (6, 7), and these associations appear to persist after adjustment for other adiposity measures such as BMI and waist circumference (8–10). However, most of the studies on pericardial adipose tissue done to date have been in small populations (11–13), often with indications for imaging (5, 14, 15). The few larger studies have not addressed differences across racial-ethnic groups (7, 16). Our group's preliminary analysis (17) in a subset of the Multi-Ethnic Study of Atherosclerosis (MESA) cohort demonstrated the cross-sectional association of pericardial fat with calcified coronary plaque, an indicator of subclinical atherosclerosis (18) that predicts the risk of future coronary heart disease events (19) beyond that predicted by the Framingham Risk Score (20). This work expands that analysis to the entire cohort and allows us to compare associations across racial/ethnic groups. The latter comparisons are of particular interest because studies of coronary calcification in MESA (21) and other populations (22, 23) have shown lower prevalence and severity in Blacks than in Whites, even after adjustment for sociodemographic variables and CVD risk factors.

A further limitation to many existing studies of pericardial and epicardial adipose tissues is the use of echocardiography (5, 8, 15), which produces only a two-dimensional measure of thickness. Computed tomography (CT) scans, which are available in MESA, permit a three-dimensional assessment of volume. Our group developed an efficient method to measure the volume of pericardial adipose tissue using cardiac CT scans (24) and has developed and validated a simpler method for use in a larger cohort such as MESA (17).

Methods and Procedures

Study population

The Multi-Ethnic Study of Atherosclerosis is a prospective study of sub-clinical markers of cardiovascular disease in a cohort of 6,814 African American, Caucasian, Asian (largely Chinese) and Hispanic adults aged 45–84 years and free of known cardiovascular disease at

baseline (2000–2002) (25). Participants were from six communities in the United States: Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; New York, NY; and St. Paul, MN. The MESA study was approved by the Institutional Review Board (IRB) at each field center. Participants gave written informed consent.

Measurements

Coronary artery calcification—Calcified coronary plaque was determined with either an electrocardiogram-triggered (at 80% of the R-R interval) electron-beam CT scanner (Chicago, Los Angeles, and New York field centers; Imatron C-150, Imatron, Tokyo, Japan) or with prospectively electrocardiogram-triggered scan acquisition at 50% of the R-R interval with a multidetector system that acquired 4 simultaneous 2.5-mm slices for each cardiac cycle in a sequential or axial scan mode (Baltimore, Forsyth County, and St. Paul field centers; LightSpeed, General Electric, Waukesha, WI or Volume Zoom, Siemens, Erlangen, Germany). Additional details have been published previously (26). Experienced and trained technologists scanned the heart of each participant two times and transmitted the scans over the internet to the CT Reading Center (Harbor-UCLA Research and Education Institute in Torrance, CA). A cardiologist read all scans in a masked fashion. The Agatston score (27), averaged from the two scans, was used to quantify the amount of calcified coronary plaque. The re-read agreement for the Agatston score was excellent (intraclass correlation coefficient, 0.99) (26). For the presence of calcified coronary plaque (Agatston score>0), agreement between duplicate scans ($\kappa = 0.92$) (28) and re-read agreement ($\kappa =$ 0.93 and 0.90, for intra- and inter-observer, respectively) (21) were also high.

Pericardial adipose tissue—Two experienced CT readers, blinded to the measure of calcified coronary plaque, measured pericardial adipose tissue volume. Pericardial fat was measured according to a sampling protocol developed by our group (17). The superior extent of the left main coronary artery was identified in a cross-sectional scan. Slices within 15 mm above this slice and 30 mm below this slice were included. The anterior border of the volume was defined by the chest wall and the posterior border by the aorta and the bronchus. Volume Analysis software (GE Healthcare, Waukesha, WI) was used to discern fat from the remaining portions of the heart with a threshold of −190 to −30 Hounsfield units. The volume was the sum of all voxels containing pericardial adipose tissue. The sampling protocol was highly correlated (Pearson correlation coefficient: 0.93; $P < 0.0001$) (17) with the “gold standard” method (24), which measures the entire pericardial adipose tissue volume encasing the heart. The intraclass correlation coefficients for intra-reader and inter-reader reliability for the new method were very high (0.999 and 0.997, respectively) (17).

Anthropometrics—Weight was measured with a Detecto Platform Balance Scale (Detecto, Webb City, MO) to the nearest 0.5 kg. Height was measured with an Accu-Hite Measure Device stadiometer with level bubble (Seca, Hamburg, Germany) to the nearest 0.1 cm. Body mass index (BMI) was defined as weight in kilograms divided by the square of height in meters. Waist circumference (at the umbilicus) was measured to the nearest 0.1 cm using a steel measuring tape with standard 4 oz tension (Gulick II, 150-cm anthropometric tape).

Covariates—Questionnaires were used to collect information on demographics, smoking status, alcohol use, physical activity, education, medical history, and medication use. Cigarette smoking status was classified as current, former and never. Alcohol use was defined as current, former and never. Physical activity was based on MET-minutes of intentional physical activity per week, and was classified as low (<300), moderate (300–<1500) and high (>=1500). Education was defined as less than high school, finished high school or finished college. Blood pressure was measured in the right arm of the participant after 5 min in a sitting position using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, FL). The second and third of three readings were averaged to obtain the blood pressure levels. Total cholesterol, high-density lipoprotein cholesterol and triglyceride levels were measured in EDTA-treated plasma on a Roche COBAS FARA centrifugal analyzer (Roche Diagnostics, Indianapolis, IN). C-reactive protein was measured using the BNII nephelometer (Dade Behring, Deerfield, IL). Interleukin-6 was measured by ultra-sensitive ELISA (Quantikine HS Human IL-6 Immunoassay; R&D Systems, Minneapolis, MN). Triglycerides, C-reactive protein and interleukin-6 were log transformed due to non-normality. Glucose levels were measured by rate-reflectance spectrophotometry using thin film adaptation of the glucose oxidase method on the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Rochester, NY), and diabetes was defined as self-reported diabetes, non-fasting glucose $\geqslant$ 11.1 mmol/L (200 mg/dl), fasting glucose $\geqslant$ 7.0 mmol/L (126 mg/dl) or use of hypoglycemic medication (29). Lipid medications and antihypertensive medications were coded yes/no based on medications taken during the last two weeks that were brought to the examination.

Statistical analysis

Sample means and standard deviations (SDs) were computed for the continuous characteristics and proportions were calculated for discrete characteristics by pericardial adipose tissue quartiles. *P*-values for these unadjusted associations were calculated using analysis of variance (ANOVA) for continuous variables and overall chi-square tests for categorical variables. Adjusted means for pericardial fat volume and for prevalence and severity of calcification by race and gender were calculated using SAS LSMEANS.

Pericardial adipose tissue was the main exposure variable. For the presence of coronary artery calcification (Agatston score>0) outcome, we used prevalence ratio regression (log link) with robust confidence intervals. For severity of calcification (Agatston score among participants with score>0), we log-transformed Agatston score and used linear regression. For comparison, we also examined BMI and waist circumference as exposures in separate models and in combined models with pericardial adipose tissue. Prevalence ratios (PRs) and differences in log Agatston score (beta coefficient) were reported per standard deviation of pericardial adipose tissue (42 cm^3), BMI (5 kg/m^2) and waist circumference (14 cm). Covariates for the main models included demographic characteristics (age, age-squared, race/ethnicity, field site and gender), behavioral factors (smoking, alcohol use, physical activity) and education as a measure of socioeconomic status. We also examined models adjusted for traditional cardiovascular risk factors and inflammatory markers that are believed to mediate the association between general obesity and cardiovascular disease: diabetic status, systolic blood pressure, total and high-density lipoprotein (HDL) cholesterol,

triglycerides, C-reactive protein, interleukin-6, and use of antihypertensive or lipid-lowering medications. For both presence and severity of calcified plaques, we evaluated statistical interactions of pericardial adipose tissue with gender and race/ethnicity.

For the analyses using presence of calcification as the outcome, we excluded participants missing pericardial adipose tissue data (n=32), BMI or waist circumference (n=2), or covariates (n=53), for a total sample of 6,727. For the analyses of severity of calcification, we excluded participants with an Agatston score of 0 (n=3,416) and those missing pericardial adipose tissue data (n=13), BMI or waist circumference (n=1), or covariates (n=22), for a total sample of 3,362. For the models that adjusted for traditional cardiovascular risk factors and markers of inflammation, we further excluded participants missing values of those variables, for total samples of 6,510 for the presence of calcification analysis and 3,247 for severity.

Results

Sample characteristics (unadjusted) are shown in Table 1 by quartiles of pericardial adipose tissue. Participants with higher volumes of pericardial fat were slightly older, with higher BMIs and waist circumferences. They had higher mean systolic blood pressure, triglycerides, C-reactive protein and interleukin-6 levels and lower mean HDL cholesterol. They were more likely to be male, to be taking lipid or blood pressure medications and to be diabetic, and they had higher Agatston scores. Pericardial fat was also associated with education, smoking, drinking and physical activity.

Table 2 shows crude and adjusted mean pericardial adipose tissue volume by race and gender. Adjusted for age, height, weight, and study site, pericardial fat volumes were substantially lower in women than in men and in Blacks than in other race/ethnic groups, regardless of gender. Among women, Chinese had higher levels than Hispanics and Whites. Among men, Chinese, Whites and Hispanics did not differ. Notably, Black men had less pericardial fat than all groups other than Black women.

Table 3 shows associations of both presence (prevalence ratios) and severity (differences in log Agatston score) of coronary calcification per one standard deviation increment in pericardial adipose tissue. Associations with BMI and waist circumference (modeled separately) are also shown for comparison. In unadjusted models (not shown), pericardial adipose tissue was associated with both presence [prevalence ratio (PR) = 1.19 (1.16, 1.21)] and severity [difference in log Agatston score = 0.27 (0.21, 0.33)] of calcification. These associations were attenuated by adjustment for demographic factors (“Basic adjusted model” in Table 3), but were not further attenuated by adjustment for behavioral and sociodemographic factors (“Main models”). Additional adjustment for BMI or waist circumference (“Mutually adjusted models”) further attenuated but did not eliminate the associations. Adjustment for traditional cardiovascular risk factors and inflammatory markers (diabetic status, systolic blood pressure, total and high-density lipoprotein (HDL) cholesterol, triglycerides, use of antihypertensive or lipidlowering medications, C-reactive protein and interleukin-6) also attenuated but did not eliminate the associations. When models were adjusted for BMI plus traditional cardiovascular risk factors and inflammatory

markers, only the association with severity remained statistically significant (although the lower confidence limit of 1.00 for the PR suggests an association, albeit very weak, remains for presence of calcification as well).

Race and gender stratified results (using the Main model) are shown in Table 4. We found no statistically significant heterogeneity by race/ethnicity in the association of pericardial fat with either presence or severity of calcification. Nor were there differences by gender in the association with severity. The prevalence ratio for presence of calcification was larger in women than in men (p for interaction <0.0001), but the absolute differences in prevalence across quartiles of pericardial fat (results not shown) were similar between men and women.

We ran several additional analyses in which we varied the definitions of our outcome and exposure (results not shown). These analyses used main model covariates. We defined presence of calcification using several different cutpoints. Using an Agatston score of 10 or more vs. <10, there was little change in the PR for pericardial fat [1.07 (95% CI: 1.05, 1.09)]. Using 100 or more vs. <100, the PR was 1.11 (1.08, 1.15). Using the ethnic-specific 75^{th} percentile of calcification (49 for Blacks, 66 for Chinese, 61 for Hispanics and 159 for Whites), the overall PR was 1.11 (1.07, 1.14), and, as with the main analysis of >0 vs 0, we found no interaction by race/ethnicity. We also repeated the main model analysis using ethnic-specific standard deviations as the increment in pericardial fat (Whites: 46 cm^3, Chinese: 32 cm^3, Blacks: 35 cm^3, Hispanics: 44 cm^3) and again found no interaction by race/ethnicity [PR for Whites: 1.06 (1.04, 1.09), Chinese: 1.07 (1.01, 1.14), Blacks: 1.06 (1.02, 1.10), Hispanics: 1.04 (1.00, 1.08); *p* for interaction: 0.94].

Discussion

Consistent with other studies (7, 12, 13, 16, 30–32), including a substudy of MESA data by our group (17), we found that pericardial adipose tissue was associated with both the presence and severity of coronary calcification in this cohort. These associations persisted when adjusted for BMI or waist circumference. The magnitude of the associations was small, but associations of calcification with both BMI and waist – well established risk factors for CVD – were also weak in this population, which was free of clinical CVD at baseline.

The inflammatory action of adipocytokines is thought to be one mechanism by which excess adipose tissue contributes to cardiovascular disease (33, 34). Pericardial adipose tissue, like visceral adipose tissue, produces more inflammatory cytokines than subcutaneous fat (3, 4). This inflammatory activity, combined with pericardial fat's proximity to the coronary arteries, may explain our and others' findings that pericardial adipose tissue may be more important than generalized adiposity as a predictor of some cardiovascular outcomes. The associations observed in our main model were attenuated when additionally adjusted for CVD risk factors, including inflammatory markers.

Our study found substantial differences in the volume of pericardial fat by race/ethnicity. Notably, blacks in MESA had substantially less pericardial fat than the other groups despite having higher BMIs. Divers et al compared European Americans to African Americans in

the African American Diabetes Heart Study and found between-group differences like those shown here, with blacks having less pericardial fat despite having higher BMIs (overall pericardial fat volumes were higher than in MESA) (35). A study of 150 echocardiography patients also found that blacks had substantially less pericardial fat than whites, and blacks have been shown to have less visceral adipose tissue than Whites in other studies (36, 37). Other racial/ethnic groups also differ in the distribution of body fat (38, 39).

Despite these marked differences by race/ethnicity in pericardial fat volume and well-established differences by race in calcification (21–23), our study found no difference in the association of pericardial fat with calcification across race/ethnic groups. In the Divers analysis (n=1,136) an association between pericardial adipose tissue and coronary calcified plaque was observed in African Americans, but not in European Americans (35), but the finding of no association in Whites is inconsistent with other analyses (10, 31) in a variety of samples (7, 16), including our own. Racial differences have been observed in the association of other body size variables with atherosclerotic disease, including the association of BMI with coronary heart disease in other large cohorts (40). However, in the MESA cohort, Bild et al found the association of BMI with CAC was similar across the 4 race/ethnic groups, though it was only significant in whites (21).

The consistency of the association between pericardial fat and calcification across race/ethnic groups suggests that the mechanism for the association may not differ by race. More information from other populations would be helpful, but unless future studies find substantially larger associations between pericardial fat and coronary calcification than those observed in MESA, it is unlikely that a finding of between-group differences, even if statistically significant, would have important clinical applications.

Statistically significant heterogeneity by sex was observed for the prevalence ratios, though, as noted, the absolute difference in prevalence associated with pericardial fat was similar between men and women. The observed heterogeneity may therefore not be very meaningful. Indeed, for our severity analysis, in which a difference measure was used, no interactions were found. In the Framingham cohort, Rosito *et al* found no sex interaction in the association of pericardial fat with coronary calcification despite significant heterogeneity for associations of pericardial fat with most of the other CVD risk factors they examined (7).

The pericardial fat-calcification associations seen here were independent of BMI and waist, which suggests that pericardial fat may be a more specific risk factor than generalized obesity in the pathogenesis of CVD. There has been little research on interventions targeting pericardial adipose tissue, but pericardial fat has been shown to decrease with weight loss, and changes in left ventricular mass with weight loss may be more associated with changes in pericardial adipose tissue than with changes in body mass or waist circumference (11).

This study had several strengths. Pericardial adipose tissue was assessed by multi-slice CT, allowing the use of a volumetric measure. The large diverse cohort allowed comparison across race/ethnic groups. We used prevalence ratios, which are more appropriate than odds ratios when the outcome (presence of calcification in this case) has a high prevalence. Our prevalence ratios were, as expected, smaller in magnitude than the odds ratios reported in

similar analyses, so we repeated our analyses using logistic regression for comparison and obtained odds ratios similar to those seen in other studies. The relatively weak associations found here could also be influenced by the use of pericardial adipose tissue, comprising both the epicardial adipose tissue (within the pericardium, and therefore in direct contact with the coronary vessels) and the paracardial adipose tissue (outside the pericardium). The epicardial tissue may be more important in any causal mechanism, but is more difficult to measure due to the difficulty in accurately defining the pericardium. This could be considered a limitation of the present study. The principal limitation of this research was its cross-sectional nature. Cross-sectional analyses can suffer from survival bias and prevent examination of temporality. Studies using longitudinal data may find larger associations. A major limitation of this analysis is the inability to compare pericardial fat to visceral adipose tissue. It is likely that adjustment for visceral fat would attenuate the associations more than did BMI or waist circumference, but the visceral fat data are not yet available in MESA.

We used standard deviations as the units for our variables to facilitate comparison of pericardial fat to BMI and waist. Such a comparison may not translate to other populations in which the standard deviations of these variables may differ substantially from this cohort. However, in the present analysis, the difference in log Agatston score was much larger for pericardial fat (0.12 per SD) than for BMI or waist (0.05 and 0.06, respectively, in the mutually adjusted models). It is unlikely that the standard deviations in other populations would differ from the MESA population by enough to eliminate or reverse this finding.

Pericardial fat may be a more specific risk factor than generalized obesity. Results from this study suggest that it may also be a consistent risk factor across racial/ethnic groups.

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Reference List

1. Montani JP, Carroll JF, Dwyer TM, Antic V, Yang Z, Dulloo AG. Ectopic fat storage in heart, blood vessels and kidneys in the pathogenesis of cardiovascular diseases. Int J Obes Relat Metab Disord. 2004; 28(Suppl 4):S58–S65. [PubMed: 15592488]
2. Bjorntorp P. Metabolic implications of body fat distribution. Diabetes Care. 1991; 14:1132–1143. [PubMed: 1773700]
3. Marchington JM, Mattacks CA, Pond CM. Adipose tissue in the mammalian heart and pericardium: structure, foetal development and biochemical properties. Comp Biochem Physiol B. 1989; 94:225–232. [PubMed: 2591189]
4. Mazurek T, Zhang L, Zalewski A, et al. Human epicardial adipose tissue is a source of inflammatory mediators. Circulation. 2003; 108:2460–2466. [PubMed: 14581396]
5. Iacobellis G, Willens HJ, Barbaro G, Sharma AM. Threshold values of high-risk echocardiographic epicardial fat thickness. Obesity (Silver Spring). 2008; 16:887–892. [PubMed: 18379565]
6. Ahn SG, Lim HS, Joe DY, et al. Relationship of epicardial adipose tissue by echocardiography to coronary artery disease. Heart. 2008; 94:e7. [PubMed: 17923467]

7. Rosito GA, Massaro JM, Hoffmann U, et al. Pericardial fat, visceral abdominal fat, cardiovascular disease risk factors, and vascular calcification in a community-based sample: the Framingham Heart Study. Circulation. 2008; 117:605–613. [PubMed: 18212276]
8. Jeong JW, Jeong MH, Yun KH, et al. Echocardiographic epicardial fat thickness and coronary artery disease. Circ J. 2007; 71:536–539. [PubMed: 17384455]
9. Ding J, Hsu FC, Harris TB, et al. The association of pericardial fat with incident coronary heart disease: the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Clin Nutr. 2009; 90:499–504. [PubMed: 19571212]
10. Alexopoulos N, McLean DS, Janik M, Arepalli CD, Stillman AE, Raggi P. Epicardial adipose tissue and coronary artery plaque characteristics. Atherosclerosis. 2010; 210:150–154. [PubMed: 20031133]
11. Iacobellis G, Singh N, Wharton S, Sharma AM. Substantial changes in epicardial fat thickness after weight loss in severely obese subjects. Obesity (Silver Spring). 2008; 16:1693–1697. [PubMed: 18451775]
12. Sarin S, Wenger C, Marwaha A, et al. Clinical significance of epicardial fat measured using cardiac multislice computed tomography. Am J Cardiol. 2008; 102:767–771. [PubMed: 18774004]
13. Wang CP, Hsu HL, Hung WC, et al. Increased epicardial adipose tissue (EAT) volume in type 2 diabetes mellitus and association with metabolic syndrome and severity of coronary atherosclerosis. Clin Endocrinol (Oxf). 2009; 70:876–882. [PubMed: 18778397]
14. Gorter PM, de Vos AM, van der Graaf Y, et al. Relation of epicardial and pericoronary fat to coronary atherosclerosis and coronary artery calcium in patients undergoing coronary angiography. Am J Cardiol. 2008; 102:380–385. [PubMed: 18678291]
15. Chaowalit N, Somers VK, Pellikka PA, Rihal CS, Lopez-Jimenez F. Subepicardial adipose tissue and the presence and severity of coronary artery disease. Atherosclerosis. 2006; 186:354–359. [PubMed: 16183065]
16. de Vos AM, Prokop M, Roos CJ, et al. Peri-coronary epicardial adipose tissue is related to cardiovascular risk factors and coronary artery calcification in post-menopausal women. Eur Heart J. 2008; 29:777–783. [PubMed: 18156138]
17. Ding J, Kritchevsky SB, Harris TB, et al. The association of pericardial fat with calcified coronary plaque. Obesity (Silver Spring). 2008; 16:1914–1919. [PubMed: 18535554]
18. Rumberger JA, Simons DB, Fitzpatrick LA, Sheedy PF, Schwartz RS. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study. Circulation. 1995; 92:2157–2162. [PubMed: 7554196]
19. Brown ER, Kronmal RA, Bluemke DA, et al. Coronary calcium coverage score: determination, correlates, and predictive accuracy in the Multi-Ethnic Study of Atherosclerosis. Radiology. 2008; 247:669–675. [PubMed: 18413889]
20. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA. 2004; 291:210–215. [PubMed: 14722147]
21. Bild DE, Detrano R, Peterson D, et al. Ethnic differences in coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation. 2005; 111:1313–1320. [PubMed: 15769774]
22. Budoff MJ, Yang TP, Shavelle RM, Lamont DH, Brundage BH. Ethnic differences in coronary atherosclerosis. J Am Coll Cardiol. 2002; 39:408–412. [PubMed: 11823077]
23. Lee TC, O'Malley PG, Feuerstein I, Taylor AJ. The prevalence and severity of coronary artery calcification on coronary artery computed tomography in black and white subjects. J Am Coll Cardiol. 2003; 41:39–44. [PubMed: 12570942]
24. Wheeler GL, Shi R, Beck SR, et al. Pericardial and visceral adipose tissues measured volumetrically with computed tomography are highly associated in type 2 diabetic families. Invest Radiol. 2005; 40:97–101. [PubMed: 15654254]
25. Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol. 2002; 156:871–881. [PubMed: 12397006]
26. Carr JJ, Nelson JC, Wong ND, et al. Calcified coronary artery plaque measurement with cardiac CT in population-based studies: standardized protocol of Multi-Ethnic Study of Atherosclerosis

(MESA) and Coronary Artery Risk Development in Young Adults (CARDIA) study. Radiology. 2005; 234:35–43. [PubMed: 15618373]

27. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol. 1990; 15:827–832. [PubMed: 2407762]
28. Detrano RC, Anderson M, Nelson J, et al. Coronary calcium measurements: effect of CT scanner type and calcium measure on rescan reproducibility--MESA study. Radiology. 2005; 236:477–484. [PubMed: 15972340]
29. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care. 2003; 26(Suppl 1):S5–S20. [PubMed: 12502614]
30. Djaberi R, Schuijf JD, van Werkhoven JM, Nucifora G, Jukema JW, Bax JJ. Relation of epicardial adipose tissue to coronary atherosclerosis. Am J Cardiol. 2008; 102:1602–1607. [PubMed: 19064012]
31. Dey D, Wong ND, Tamarappoo B, et al. Computer-aided non-contrast CT-based quantification of pericardial and thoracic fat and their associations with coronary calcium and Metabolic Syndrome. Atherosclerosis. 2010; 209:136–141. [PubMed: 19748623]
32. Liu J, Fox CS, Hickson D, et al. Pericardial adipose tissue, atherosclerosis, and cardiovascular disease risk factors: the Jackson heart study. Diabetes Care. 2010; 33:1635–1639. [PubMed: 20413524]
33. Knudson JD, Dick GM, Tune JD. Adipokines and coronary vasomotor dysfunction. Exp Biol Med (Maywood). 2007; 232:727–736. [PubMed: 17526764]
34. Ross R. Atherosclerosis--an inflammatory disease. N Engl J Med. 1999; 340:115–126. [PubMed: 9887164]
35. Divers J, Wagenknecht LE, Bowden DW, et al. Ethnic differences in the relationship between pericardial adipose tissue and coronary artery calcified plaque: African-American-diabetes heart study. J Clin Endocrinol Metab. 2010; 95:5382–5389. [PubMed: 20810573]
36. Conway JM, Yanovski SZ, Avila NA, Hubbard VS. Visceral adipose tissue differences in black and white women. Am J Clin Nutr. 1995; 61:765–771. [PubMed: 7702017]
37. Hill JO, Sidney S, Lewis CE, Tolan K, Scherzinger AL, Stamm ER. Racial differences in amounts of visceral adipose tissue in young adults: the CARDIA (Coronary Artery Risk Development in Young Adults) study. Am J Clin Nutr. 1999; 69:381–387. [PubMed: 10075320]
38. Deurenberg P, Deurenberg-Yap M, Guricci S. Asians are different from Caucasians and from each other in their body mass index/body fat per cent relationship. Obes Rev. 2002; 3:141–146. [PubMed: 12164465]
39. Wang J, Thornton JC, Russell M, Burastero S, Heymsfield S, Pierson RN Jr. Asians have lower body mass index (BMI) but higher percent body fat than do whites: comparisons of anthropometric measurements. Am J Clin Nutr. 1994; 60:23–28. [PubMed: 8017333]
40. Abell JE, Egan BM, Wilson PW, Lipsitz S, Woolson RF, Lackland DT. Differences in cardiovascular disease mortality associated with body mass between Black and White persons. Am J Public Health. 2008; 98:63–66. [PubMed: 18048799]

Table 1

Means (standard deviations) and prevalences of sample characteristics by quartiles of pericardial adipose tissue

	Pericardial adipose tissue quartiles				
	0–49 cm^3 (N=1,726)	**50–69 cm^3 (N=1,572)**	**70–99 cm^3 (N=1,749)**	**≥100 cm^3 (N=1,680)**	**P-value**
Race/ethnicity, %					<0.001
Caucasian	36	34	37	47	
Chinese	10	15	14	8	
Black	38	30	25	16	
Hispanic	15	21	24	28	
Female, %	68	60	51	33	<0.001
Age (years)	59 (10)	62 (10)	64 (10)	65 (10)	<0.001
Age groups, %					<0.001
44–54	43	30	22	18	
55–64	26	29	29	27	
65–74	22	28	32	36	
75–84	9	13	17	19	
Education, %					<0.001
Less than high school	12	17	21	22	
Finished high school	45	47	47	47	
Finished college	43	36	32	31	
Smoking, %					<0.001
Current	14	14	13	12	
Former	31	33	37	45	
Never	56	53	50	43	
Intentional Physical Activity, %					<0.001
Low (0–299 MET-mins/wk)	25	27	31	36	
Moderate (300–1499 MET-mins/wk)	36	39	38	37	
High (≥1500 MET-mins/wk)	39	35	31	27	
Alcohol use, %					<0.001
Current drinker	58	55	51	58	

	Pericardial adipose tissue quartiles				
	0–49 cm^3 (N=1,726)	**50–69 cm^3 (N=1,572)**	**70–99 cm^3 (N=1,749)**	**≥100 cm^3 (N=1,680)**	**P-value**
Former heavy drinker	4	5	6	8	
Former light drinker	17	19	20	18	
Never drinker	21	22	23	16	
Systolic Blood Pressure (mmHg)	121 (21)	126 (22)	128 (21)	131 (20)	<0.001
HDL Cholesterol (mmol/l)	1.5 (0.4)	1.4 (0.4)	1.3 (0.3)	1.2 (0.3)	<0.001
Triglycerides (mmol/l)	1.2 (0.7)	1.4 (0.9)	1.6 (1.1)	1.8 (1.1)	<0.001
Taking lipid-lowering medication, %	11	15	18	21	<0.001
Taking antihypertensive medication, %	26	33	42	47	<0.001
Diabetic, %	7	11	15	20	<0.001
C-reactive protein (nmol/l)	28 (49)	34 (58)	40 (58)	42 (56)	<0.001
Interleukin-6 (pg/ml)	1.2 (1)	1.4 (1)	1.6 (1)	1.9 (1)	<0.001
Pericardial adipose tissue (cm^3)	38 (8)	60 (6)	83 (8)	137 (37)	<0.001
Body Mass Index (kg/m^2)	25 (4)	27 (5)	29 (5)	32 (5)	<0.001
Waist (cm)	88 (12)	95 (12)	101 (12)	109 (13)	<0.001
Agatston score (positives only)	214 (428)	263 (543)	283 (571)	365 (600)	<0.001
Presence of coronary calcification (Agatston score > 0), %	34	45	54	66	<0.001

HDL indicates high-density lipoprotein. P-values are from analysis of variance (ANOVA) (continuous variables), indicating whether the means are different, or overall chi-square tests (categorical variables), indicating whether the cell percents are different than expected.

Table 2

Pericardial adipose tissue by race and gender

	Both genders		Women		Men	
	N	**Mean/% (95% CI)**	**N**	**Mean/% (95% CI)**	**N**	**Mean/% (95% CI)**
Crude pericardial adipose tissue (cm^3)						
All	6,727	80 (79, 81)	3,558	69 (68, 70)	3,169	92 (90, 93)
White	2,586	85 (83, 87)	1,346	70 (68, 72)	1,240	101 (99, 104)
Chinese	792	74 (72, 76)	408	70 (67, 72)	384	78 (75, 82)
Black	1,862	67 (66, 69)	1,033	61 (59, 63)	829	75 (73, 78)
Hispanic	1,487	88 (86, 91)	771	76 (74, 79)	716	101 (98, 105)
Adjusted* pericardial adipose tissue (cm^3)						
All	6,727	80 (79, 81)	3,558	72 (71, 74)	3,169	92 (91, 93)
White	2,586	85 (84, 87)	1,346	74 (73, 76)	1,240	97 (95, 100)
Chinese	792	94 (91, 97)	408	91 (88, 95)	384	97 (94, 100)
Black	1,862	60 (58, 61)	1,033	51 (49, 53)	829	69 (67, 72)
Hispanic	1,487	87 (85, 89)	771	75 (73, 78)	716	100 (97, 102)

*Adjusted for age, height, weight and study site, and for race or gender where not stratified.

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Table 3

Association of pericardial adipose tissue with the presence and severity of coronary artery calcification

	Presence	*p*-value	Severity	*p*-value
	Prevalence ratio (95% CI) (N=6,727)		**Difference in log Agatston score (β) (95% CI) (N=3,362)**	
Basic adjusted models[a]				
Pericardial adipose tissue (42 cm^3)	**1.06** (1.04, 1.08)	<.0001	**0.15** (0.09, 0.20)	<.0001
BMI (5 kg/m^2)	**1.07** (1.05, 1.09)	<.0001	**0.11** (0.05, 0.17)	0.0002
Waist circumference (14 cm)	**1.07** (1.05, 1.10)	<.0001	**0.13** (0.07, 0.19)	<.0001
Main models[b]				
Pericardial adipose tissue (42 cm^3)	**1.06** (1.04, 1.08)	<.0001	**0.15** (0.09, 0.21)	<.0001
BMI (5 kg/m^2)	**1.08** (1.05, 1.10)	<.0001	**0.12** (0.06, 0.18)	<.0001
Waist circumference (14 cm)	**1.07** (1.05, 1.10)	<.0001	**0.13** (0.07, 0.20)	<.0001
Mutually adjusted[c] (PAT and BMI)				
Pericardial adipose tissue (42 cm^3)	**1.03** (1.01, 1.05)	0.0017	**0.12** (0.06, 0.19)	0.0004
BMI (5 kg/m^2)	**1.06** (1.03, 1.08)	<.0001	0.05 (−0.02, 0.12)	0.1587
Mutually adjusted[c] (PAT and waist)				
Pericardial adipose tissue (42 cm^3)	**1.03** (1.01, 1.05)	0.0008	**0.12** (0.05, 0.19)	0.0007
Waist circumference (14 cm)	**1.05** (1.03, 1.08)	<.0001	0.06 (−0.01, 0.14)	0.0908
Main models adjusted for CVD risk factors[d]				
Pericardial adipose tissue (42 cm^3)	**1.03** (1.01, 1.05)	0.0013	**0.11** (0.05, 0.17)	0.0007
BMI (5 kg/m^2)	**1.04** (1.02, 1.06)	0.0008	**0.07** (0.01, 0.14)	0.0340
Waist circumference (14 cm)	**1.04** (1.02, 1.06)	0.0011	**0.08** (0.01, 0.15)	0.0327
Mutually adjusted[c] (PAT and BMI) main model adjusted for CVD risk factors[d]				
Pericardial adipose tissue (42 cm^3)	1.02 (1.00, 1.04)	0.1039	**0.10** (0.03, 0.17)]	0.0068
BMI (5 kg/m^2)	**1.03** (1.00, 1.06)	0.0265	0.02 (−0.05, 0.10)	0.5470
Mutually adjusted[c] (PAT and waist) main model adjusted for CVD risk factors[d]				
Pericardial adipose tissue (42 cm^3)	1.02 (1.00, 1.04)	0.0886	**0.10** (0.03, 0.17)	0.0070
Waist circumference (14 cm)	**1.03** (1.00, 1.06)	0.0251	0.02 (−0.05, 0.10)	0.5389

Estimates are per standard deviation (in the full cohort) increment: 42 cm^3 of pericardial adipose tissue, 5 kg/m^2 of body mass index and 14 cm of waist circumference. PAT indicates pericardial adipose tissue; BMI, body mass index; CI, confidence interval. PAT, BMI and waist are modeled separately except in 'mutually adjusted' models. Boldface indicates that the 95% CI does not include the null.

[a] Adjusted for study site, age, age squared, gender and race/ethnicity.

[b] Further adjusted for smoking, physical activity, alcohol and education.

[c] Mutually adjusted models contain pericardial adipose tissue and either BMI or waist circumference in the same model and are adjusted for study site, age, age squared, gender, race/ethnicity, smoking, physical activity, alcohol and education.

[d] Main models plus CVD risk factors are additionally adjusted for systolic blood pressure, total and HDL cholesterol, triglycerides, lipid-lowering medications, antihypertensive medications and diabetic status, interleukin-6 and C-reactive protein. These models have a reduced N compared to

the main models due to missing CVD risk factor observations for some participants: N=6,510 for presence of CAC and N=3,247 for difference in Agatston score. We checked main models in these subsamples; estimates did not change.

Table 4

Association of pericardial adipose tissue with the presence and severity of coronary artery calcification by race and gender

	Presence			Severity		
Stratification variable	**N**	**Prevalence ratio (95% CI)**	***p*-value**	**N**	**Difference in log Agatston score (β) (95% CI)**	***p*-value**
Race/ethnicity						
Caucasians	2,586	**1.06** (1.04, 1.08)	<.0001	1,473	**0.13** (0.05, 0.21)	0.0016
Chinese Americans	792	**1.10** (1.02, 1.18)	0.0168	399	0.16 (−0.04, 0.37)	0.1142
African Americans	1,862	**1.07** (1.03, 1.12)	0.0019	813	**0.21** (0.08, 0.35)	0.0018
Hispanics	1,487	1.04 (1.00, 1.08)	0.0590	677	0.08 (−0.04, 0.21)	0.1886
p for interaction		0.84			0.55	
Gender						
Women	3,558	**1.08** (1.04, 1.13)	<.0001	1,421	0.10 (−0.01, 0.21)	0.0632
Men	3,169	**1.04** (1.03, 1.06)	<.0001	1,941	**0.16** (0.09, 0.22)	<.0001
p for interaction		<0.0001			0.47	

Estimates are per 42 cm^3 increment (one standard deviation in the full cohort) in pericardial adipose tissue. Models are adjusted for study site, age, age squared, gender, race/ethnicity, smoking, physical activity, alcohol and education (main model from Table 3). CI indicates confidence interval. Boldface indicates that the 95% CI does not include the null.