Title

Relationship of pericardial fat with lipoprotein distribution: The Multi-Ethnic study of atherosclerosis

Journal

Atherosclerosis, 241(2)

ISSN

0021-9150

Authors

Ong, Kwok-Leung
Ding, Jingzhong
McClelland, Robyn L
et al.

Publication Date

2015-08-01

DOI

10.1016/j.atherosclerosis.2015.06.027

Peer reviewed

HHS Public Access

Author manuscript

Atherosclerosis. Author manuscript; available in PMC 2016 August 01.

Published in final edited form as:

Atherosclerosis. 2015 August ; 241(2): 664–670. doi:10.1016/j.atherosclerosis.2015.06.027.

Relationship of pericardial fat with lipoprotein distribution: The Multi-Ethnic Study of Atherosclerosis

Kwok-Leung Ong[a], **Jingzhong Ding**[b], **Robyn L. McClelland**[c], **Bernard M.Y. Cheung**[d], **Michael H. Criqui**[e], **Philip J. Barter**[a,f], **Kerry-Anne Rye**[a,f], and **Matthew A. Allison**[e]

[a]Centre for Vascular Research, University of New South Wales, Sydney, NSW, Australia

[b]Sticht Center on Aging, Wake Forest University School of Medicine, Winston-Salem, NC, United States

[c]Department of Biostatistics, University of Washington, Seattle, WA, United States

[d]Department of Medicine, University of Hong Kong, Hong Kong, China

[e]Department of Family and Preventive Medicine, University of California San Diego, La Jolla, CA, United States

[f]Faculty of Medicine, University of Sydney, Sydney, NSW, Australia

Abstract

Objective—Pericardial fat and lipoprotein abnormalities contribute to increased risk of cardiovascular disease (CVD). We investigated the relationship between pericardial fat volume and lipoprotein distribution, and whether the association of pericardial fat volume with subclinical atherosclerosis and incident CVD events differs according to lipoprotein distribution.

Methods—We analyzed data from 5407 participants from the Multi-Ethnic Study of Atherosclerosis who had measurements of pericardial fat volume, lipoprotein distribution, carotid intima-media thickness (IMT), and coronary artery calcium (CAC). All participants were free of clinically apparent CVD at baseline. Incident CVD was defined as any adjudicated CVD event.

Results—After adjusting for demographic factors, traditional risk factors, and biomarkers of inflammation and hemostasis, a larger pericardial fat volume was associated with higher large VLDL particle (VLDL-P) concentration and small HDL particle (HDL-P) concentration, and smaller HDL-P size (regression coefficients=0.585 nmol/L, 0.366 μmol/L, and −0.025 nm per SD increase in pericardial fat volume respectively, all $P<0.05$). The association of pericardial fat volume with large VLDL-P concentration and HDL-P size, but not small HDL-P concentration, remained significant after further adjusting for each other as well as LDL cholesterol, HDL

Address correspondence to: Dr Kwok-Leung Ong, Centre for Vascular Research, University of New South Wales, Sydney, NSW 2052, Australia. Tel: +61-2-93852532; fax: +61-2-93851797; oklws@yahoo.com.hk.

Disclosures

The authors declare no conflict of interest.

cholesterol, and triglycerides. The relationship of pericardial fat volume with incident CVD events, carotid IMT, and prevalence and severity of CAC did not differ by quartiles of large VLDL-P concentration, small HDL-P concentration, or HDL-P size (*P* for interaction>0.05).

Conclusion—Pericardial fat is associated with atherogenic lipoprotein abnormalities. However, its relationship with subclinical atherosclerosis and incident CVD events does not differ according to lipoprotein distribution.

Keywords

cardiovascular disease; lipids; lipoproteins; pericardial fat; subclinical atherosclerosis

1. Introduction

An excess of ectopic fat deposition, such as in the pericardium, is often found in obese subjects [1]. As pericardial fat is anatomically close to the myocardium, it may contribute to cardiovascular disease (CVD) events by paracrine pathways, with adipokines secreted from pericardial fat acting to promote local vascular inflammation and progression of atherosclerosis [2,3]. Immunohistological studies have identified an association of the extent of inflammation in pericardial adipose tissue with the presence of coronary artery disease [4]. Epidemiological studies have also revealed the association of pericardial fat with CVD events [5-7]. In this regard, recent studies suggest pericardial adipose tissues may contribute to the presence of coronary plaque [8], as well as coronary artery calcification independent of body fat composition, anthropometric measures and traditional cardiovascular risk factors [9,10]. Pericardial fat is also associated with carotid stiffness [11] and atrial fibrillation [12].

Lipoprotein particle subclass and size may affect CVD risk independently of overall cholesterol levels [13-15]. Adipocytokines, such as interleukin-6 (IL-6), that are secreted by pericardial adipose tissue, may lead to insulin resistance [16], which is known to be associated with alterations in lipoprotein particle size and subclass concentrations [17,18]. Therefore, we hypothesized that atherogenic lipoprotein abnormalities may modify the association of pericardial fat with cardiovascular risk and tested this using data from the Multi-Ethnic Study of Atherosclerosis (MESA). Additionally, we investigated whether the relationship of pericardial fat volume with subclinical atherosclerosis (as assessed by coronary artery calcium [CAC] and carotid intima-media thickness [IMT]) and incident cardiovascular events differ by lipoprotein distribution.

2. Methods

2.1. Participants

The MESA study is a longitudinal cohort of 6814 men and women of four major racial/ethnic groups, Caucasian, African American, Hispanic American, and Chinese American [19]. All participants aged 45-84 years of age were free of clinically apparent CVD at baseline [19]. They were recruited from six United States communities between July 2000 and August 2002. Participants were followed up in person at four clinic visits over a 10-year period. Venous blood samples were collected after a 12-hour fast, then shipped to the MESA central laboratory for lipid and glucose measurement. The study was approved by the

institutional review boards at all participating centers and informed written consent was obtained from all participants. The study was performed in compliance with the principles of the Declaration of Helsinki. Details of the study objectives, design, and protocol have been described previously [19].

Among 6814 participants at baseline, data on pericardial fat volume were available on 6788 participants, of whom 6760 had their lipoprotein profile measured by nuclear magnetic resonance (NMR) spectroscopy. As lipid-lowering medications can affect lipid and lipoprotein concentrations, 1112 participants taking any lipid-lowering medication (statins, fibrates, niacin, and/or bile-acid sequestrants), or with missing data on lipid-lowering medications, were excluded from this study. After further excluding participants with triglycerides >400 mg/dL (n=64), and missing data on carotid IMT (common and/or internal carotid IMT), CAC, or incident CVD events (n=177), a total of 5407 participants were included in the analysis.

2.2. Lipid and lipoprotein measurement

High-density lipoprotein (HDL) cholesterol was measured using the cholesterol oxidase method (Roche Diagnostics, Indianapolis, IN) after precipitation of non-HDL cholesterol with magnesium/dextran sulphate. Triglyceride levels were measured using a glycerol-blanked enzymatic method with the Triglyceride GB reagent (Roche Diagnostics) on the Roche COBAS FARA centrifugal analyzer. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula in plasma samples having a triglyceride value <400 mg/dL [20]. Lipoprotein particle subclasses and concentrations were measured at LipoScience, Inc. (Raleigh, North Carolina) by NMR spectroscopy using the LipoProfile-3 algorithm as described previously [15,21,22]. Particle concentrations of lipoprotein subclasses of different sizes were measured using the amplitudes of their lipid methyl group NMR signals. Lipoprotein particle diameters were classified as HDL (7.3-14 nm), LDL (18-23 nm) and very-low-density lipoprotein (VLDL) (>29 nm), with HDL subclassified as small HDL (7.3-8.2 nm), medium HDL (8.2-9.4 nm) and large HDL (9.4-14 nm); LDL were subclassified as small LDL (18-20.5 nm) and large LDL (20.5-23 nm). Intermediate-density lipoprotein (IDL) were 23-29 nm, and VLDL were subclassified as small VLDL (29-35 nm), medium VLDL (35-60 nm) and large VLDL (>60 nm). The mean particle sizes were the weighted average of the related subclasses.

2.3. CAC and carotid IMT

Detailed procedures for the measurement of CAC have been described previously [23]. Briefly, all the MESA participants underwent computed tomography (CT) scans of the chest for CAC using either an electron-beam CT scanner at 3 field centers. A multidetector row helical CT scanner was used at the other 3 field centers. Participants were scanned twice at the same visit at one of the field centers, and these scans were read independently at a centralized reading center using a standard protocol. The results of the two scans were averaged to provide a more accurate estimate of the amount of calcium present than a single scan. Calcification was identified as a plaque of ≥1 mm^2 with a density of ≥130 Hounsfield units (HU) and quantified using the previously described Agatston scoring method [24].

Carotid IMT assessment was performed using high-resolution B-mode ultrasound as previously described for the Cardiovascular Health Study [25]. The Logiq 700 ultrasound device (General Electric Medical Systems, Waukesha, Wisconsin) was used to record images of the left and right carotid arteries at all centers. A single longitudinal lateral view of each common carotid artery (CCA) and 3 longitudinal views in different imaging planes of each internal carotid artery (ICA) were obtained. The maximal IMT of the internal and common carotid sites was then measured as the mean of the maximum IMT of the near and far walls of the right and left sides at the ultrasound reading center as described previously [26,27].

2.4. Pericardial fat measurement

The CT scans used to ascertain the presence and extent of CAC were analyzed for pericardial fat volume as described previously [5,11]. Briefly, the CT slices within 15 mm above and 30 mm below the superior extent of the left main coronary artery were analyzed by three experienced CT analysts. This region of the heart was selected because it includes the pericardial fat located around the proximal coronary arteries (left main coronary, left anterior descending, right coronary, and circumflex arteries). The anterior border of the volume was defined by the chest wall and the posterior border by the aorta and the bronchus. Pericardial fat volume was defined as the sum of all voxels containing fat based on volume analysis software (GE HealthCare, Waukesha, WI), which could discern fat from other tissues with a threshold of -190 to -30 Hounsfield units.

2.5. CVD event ascertainment

CVD end-points included myocardial infarction, resuscitated cardiac arrest, definite angina, probable angina associated with coronary revascularization, stroke, stroke death, coronary heart disease death, other atherosclerotic death, and other CVD death. At intervals of 9-12 months, a trained telephone interviewer contacted each participant to inquire about all interim hospital admissions, cardiovascular outpatient diagnoses and procedures, and deaths. Some additional medical encounters were identified occasionally through follow-up visits, participant call-ins, medical record abstractions, or obituaries. Copies of all death certificates and medical records for all hospitalizations, and selected outpatient cardiovascular diagnoses and procedures were also requested to verify self-reported diagnoses. Out of hospital cardiovascular deaths were also identified through next of kin interviews. Follow-up started from the baseline examination until death, loss to follow-up, or 31 December 2011, whichever came first, with a mean follow-up period of 9.5 years.

2.6. Other variables of interest

Information on age, race/ethnicity, education, smoking, alcohol use, physical activity, and total gross family income were obtained using standardized questionnaires. Education level was defined as less than high school, high school, and more than high school. Cigarette smoking was defined as never, former, and current. Medication use was determined by questionnaire. Additionally, the participant was asked to bring to the clinic containers for all medications used during the two weeks prior to the visit. The interviewer then recorded the name of each medication, the prescribed dose, and frequency of administration from the containers. Participants wore light clothing and no shoes when measuring height and weight.

Body mass index (BMI) was measured as the weight in kilograms divided by height in meters squared. A standard flexible tape measure was used to measure hip and waist circumferences. Resting blood pressure was measured three times in a seated position with a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon). The average of the last two BP readings was used in the analysis. Hypertension was defined as blood pressure ≥140/90 mm Hg or use of anti-hypertensive medications. Diabetes was defined as fasting glucose ≥126 mg/dl or use of glucose-lowering medications. Physical activity was measured as the total number of hours of moderate and vigorous activities per week, multiplied by metabolic equivalent level as described previously [28]. Insulin resistance was estimated using the homeostasis model assessment index (HOMA2-IR), according to the updated computer model as described previously [29]. C-reactive protein (CRP), fibrinogen, IL-6, factor VIII, D-dimer, and plasmin-antiplasmin complex (PAP) were measured as described previously [30,31].

2.7. Statistical analysis

Data analysis was performed using SPSS 22 (IBM, Armonk, NY) or STATA 13.0 (StataCorp, College Station, TX). Data were presented as mean (SD) or percentage (number). Data were checked for normality by skewness and kurtosis. For variables with a skewed distribution, data were presented as median (interquartile range) and nature log (ln)-transformed before analysis. Multivariable linear regression model was used to investigate the cross-sectional association of different characteristics with pericardial fat volume after adjusting for age, sex, and race/ethnicity. Variables with a significant trend ($P<0.1$) were used as covariates in subsequent regression analysis.

Multivariable linear regression was performed to investigate the association of pericardial fat volume with lipoprotein particle concentrations and sizes, and carotid IMT with adjustment for confounding factors. Multivariable linear regression assumptions were evaluated by checking the normality and variance of residuals, and no substantial deviation was found in the fully adjusted models. For carotid IMT, analysis was performed separately for CCA-IMT, ICA-IMT and their mean values. The association of pericardial fat volume with incident CVD events was assessed using Cox proportional hazard regression analysis and hazard ratios (HR) were estimated after adjusting for confounding factors. For the association of pericardial fat volume with CAC, CAC was assessed as a categorical variable (zero score versus non-zero score). As there was a high prevalence of calcification in the cohort, odds ratio from the logistic regression did not approximate the relative risk. Therefore, prevalence ratio (PR) was estimated from the regression model $y = \exp(XT^{T\beta})$ [32]. For the severity of CAC, multivariable linear regression was used to assess the association of pericardial fat volume with natural log (ln)-transformed CAC score among participants with non-zero CAC score.

No multi-collinearity was detected (variance inflation factors < 7.0 in all the analyses). The proportional hazard assumption was checked by using Schoenfeld residuals. *P* for interaction was estimated by including the multiplicative interaction term in the regression models in full sample after adjusting for the main effects of the covariates and the categorical subgroup variable. A two-tailed $P<0.05$ was considered statistically significant.

3.Results

3.1. Participant characteristics

As shown in Table 1, participants with more pericardial fat were more likely to be older, male, Caucasian or Hispanic American, and an ever smoker with higher pack-years of smoking, while also being less likely to be African American and a current alcohol user than those with less pericardial fat. Participants with more pericardial fat had lower education level, gross family income, and physical activity with higher BMI, waist-to-hip ratio, heart rate, and prevalence of diabetes and hypertension. Participants with more pericardial fat also had higher LDL cholesterol, triglycerides, HOMA2-IR, circulating levels of inflammation and hemostasis biomarkers (i.e. CRP, fibrinogen, IL-6, factor VIII, D-dimer, and PAP), but lower HDL cholesterol. Moreover, they had higher IMT, prevalence and severity of CAC, and rate of incident CVD events.

3.2. Association of pericardial fat volume with lipoprotein distribution

As shown in Table 2, with adjustment for age, sex, race/ethnicity, the total very-low-density lipoprotein particle (VLDL-P), intermediate-density lipoprotein particle (IDL-P) and total LDL particle (LDL-P) concentrations increased with pericardial fat volume, but total HDL particle (HDL-P) concentration decreased with pericardial fat volume (all $P<0.001$). Similarly, mean VLDL-P size increased with pericardial fat volume, but mean LDL-P and HDL-P sizes decreased with pericardial fat volume (all $P<0.001$). Among different lipoprotein subclasses, large VLDL-P, medium VLDL-P, small LDL-P and small HDL-P concentrations increased with pericardial fat volume, but large LDL-P, large HDL-P and medium HDL-P concentrations decreased with pericardial fat volume (all $P<0.001$).

In multivariable linear regression analysis, and after adjusting for demographic factors, traditional CVD risk factors (including LDL cholesterol, HDL cholesterol, and triglycerides), and biomarkers of inflammation and hemostasis, a larger pericardial fat volume was significantly associated with higher concentrations of large VLDL-P and small HDL-P, and smaller HDL-P size ($P=0.018$, 0.020, and 0.001 respectively) (model 3, Table 3), but not the concentrations and sizes of other lipoprotein subclasses. The association of pericardial fat volume with large VLDL-P concentration ($P=0.011$) and HDL-P size ($P=0.004$), but not small HDL-P concentration ($P=0.091$), remained significant after further adjusting for each other (model 4, Table 3; adjusted $R^2=0.772$, 0.608, and 0.249 respectively). Similar results were obtained when BMI in the adjustment model was replaced by height and waist-to-hip ratio, although the association of pericardial fat volume with small HDL-P concentration became significant (model 5, Table 3). For large VLDL-P concentration, a significant interaction with race/ethnicity was found, in which its association with pericardial fat volume was significant in Caucasians only (P for interaction=0.022, Table 4). For HDL-P size, its association with pericardial fat volume was significant only in Caucasians with a borderline non-significant P for interaction with race/ethnicity ($P=0.052$).

3.3. Association of pericardial fat volume with incident CVD events and subclinical atherosclerosis

As pericardial fat volume was significantly associated with large VLDL-P concentration, small HDL-P concentration and HDL-P size in model 3 of Table 3, we then investigated whether the association of pericardial fat volume with incident CVD events and subclinical atherosclerosis differed across the quartiles of large VLDL-P concentration and HDL-P size. As shown in online Supplementary Tables S1-S3, the overall association of pericardial fat volume with incident CVD events, carotid IMT, and presence and severity of CAC did not reach statistical significance after adjusting for confounding factors. Similar results were found after further adjustment for large VLDL-P concentration and HDL-P size (data not shown). Moreover, the association of pericardial fat volume with incident CVD events, carotid IMT, and presence and severity of CAC did not differ significantly across quartiles of large VLDL-P concentration, small HDL-P concentration and HDL-P size.

4. Discussion

Pericardial fat and lipoprotein abnormalities have both been suggested as CVD risk factors. However, there are only limited studies on the relationship between pericardial fat and different lipoprotein subclasses. In this study, we found that a larger pericardial fat volume was associated with higher large VLDL-P concentration and smaller HDL-P size. Large VLDL-P concentration and small HDL-P size have been reported to be atherogenic in several studies. In a study of 158 men, large VLDL-P and small HDL-P concentrations were positively associated with severity of coronary artery disease [33]. In another study of 27,673 initially healthy women from the Women's Health Study (WHS), both higher large VLDL-P concentration and smaller HDL-P size were associated with higher risk of incident CVD over a follow-up period of 11 years [34]. In a more recent analysis from WHS, both higher large VLDL-P concentration and smaller HDL-P size were associated with higher risk of hypertension after adjusting for non-lipid risk factors and concentrations or sizes of other lipoprotein subclasses [35]. To the best of our knowledge, there are no studies on the racial/ethnic difference in lipoprotein distribution determined by NMR spectroscopy. In racial/ethnic-specific analysis, the association of pericardial fat volume with large VLDL-P concentration was significant only in Caucasians in both adjustment models with BMI or waist-to-hip ratio + height with significant interaction heterogeneity. A similar, but non-significant, trend was also found for HDL-P size. Further studies are needed to confirm the ethnic difference in association of pericardial fat volume with atherogenic lipoprotein abnormalities in other populations or cohort studies.

Larger pericardial fat volume is associated with higher CVD risk and other CVD risk factors such as obesity, vascular inflammation, atherosclerosis progression, coronary artery calcification, carotid stiffness, and atrial fibrillation [3-12]. However, the association of pericardial fat with CVD events has often been attenuated after adjustment for other CVD risk factors, especially measures of visceral adiposity [31,36]. The mechanism underlying the relationship between pericardial fat and atherogenic lipoprotein abnormalities is unclear, but it may be related to insulin resistance. In this respect, we previously reported that pericardial fat is associated with circulating level of IL-6 [31]. Therefore, an increase in

pericardial fat volume may be associated with increased secretion of pro-inflammatory adipocytokines, such as IL-6 from visceral adipose tissue, which may lead to systemic insulin resistance [1]. Insulin resistance has been shown to be associated with atherogenic lipoprotein abnormalities as determined by NMR spectroscopy, including an increase in large VLDL-P concentration and a decrease in small HDL-P size [17,18]. Despite the significant association of pericardial fat with atherogenic lipoprotein abnormalities, we found that atherogenic lipoprotein abnormalities are unlikely to modify the association of pericardial fat with measures of subclinical atherosclerosis and incident CVD events.

There are several limitations in our study. The major limitation is that the pericardial fat volume in the present study includes both epicardial fat (located within the pericardium) and paracardial fat (located superficial to the pericardium). In fact, in a random sample of 159 MESA participants, epicardial fat was measured and the Spearman correlation coefficient between pericardial and epicardial fat was 0.92 ($P<0.0001$) [5], suggesting that the findings from this study should be mainly contributed by the epicardial fat. The cross-sectional nature of the association between pericardial fat and lipoprotein distribution may also result in selection and temporal bias. Therefore, no causal relationship can be proved in this observational study. Moreover, the regression coefficients for the association of pericardial fat with different lipoprotein subclasses and sizes are small and interpretation should be cautious as the clinical relevance may be minimal. There is also a lack of data on body fat composition and regional fat depots such as abdominal visceral fat, although some studies have suggested that the association of pericardial fat with chronic inflammation and subclinical atherosclerosis is independent of abdominal visceral fat or body fat composition [9,37]. Lipoprotein distribution was measured at the baseline only and the effect of change in the distribution over time may confound the findings in this observational study. Moreover, due to multiple comparison, some of the positive findings may be due to random chance. However, adjustment for multiple comparison was not performed as the different lipoprotein subclasses are closely related to each other.

In conclusion, pericardial fat is associated with higher large VLDL-P concentration and smaller HDL-P size. Further studies are needed to investigate the underlying mechanisms of this relationship.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

KL Ong was supported by a Grant-in-Aid (G 12S 6681) from the National Heart Foundation of Australia, and the Vice-Chancellor's Postdoctoral Fellowship from the University of New South Wales. The MESA study was supported by a grant (5R01-HL-088451 and R01-HL-085323) and contracts N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168 and N01-HC-95169 from the National Heart, Lung, and Blood Institute. The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

References

1. Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature. 2006; 444:881–7. [PubMed: 17167477]
2. Mazurek T, Zhang L, Zalewski A, Mannion JD, Diehl JT, Arafat H, et al. Human epicardial adipose tissue is a source of inflammatory mediators. Circulation. 2003; 108:2460–6. [PubMed: 14581396]
3. Lim S, Meigs JB. Ectopic fat and cardiometabolic and vascular risk. Int J Cardiol. 2013; 169:166–76. [PubMed: 24063931]
4. Konishi M, Sugiyama S, Sato Y, Oshima S, Sugamura K, Nozaki T, et al. Pericardial fat inflammation correlates with coronary artery disease. Atherosclerosis. 2010; 213:649–55. [PubMed: 21040916]
5. Ding J, Hsu FC, Harris TB, Liu Y, Kritchevsky SB, Szklo M, 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]
6. Cheng VY, Dey D, Tamarappoo B, Nakazato R, Gransar H, Miranda-Peats R, et al. Pericardial fat burden on ECG-gated noncontrast CT in asymptomatic patients who subsequently experience adverse cardiovascular events. JACC Cardiovasc Imaging. 2010; 3:352–60. [PubMed: 20394896]
7. Mahabadi AA, Massaro JM, Rosito GA, Levy D, Murabito JM, Wolf PA, et al. Association of pericardial fat, intrathoracic fat, and visceral abdominal fat with cardiovascular disease burden: the Framingham Heart Study. Eur Heart J. 2009; 30:850–6. [PubMed: 19136488]
8. Konishi M, Sugiyama S, Sugamura K, Nozaki T, Ohba K, Matsubara J, et al. Association of pericardial fat accumulation rather than abdominal obesity with coronary atherosclerotic plaque formation in patients with suspected coronary artery disease. Atherosclerosis. 2010; 209:573–8. [PubMed: 19892354]
9. Yun CH, Lin TY, Wu YJ, Liu CC, Kuo JY, Yeh HI, et al. Pericardial and thoracic periaortic adipose tissues contribute to systemic inflammation and calcified coronary atherosclerosis independent of body fat composition, anthropometric measures and traditional cardiovascular risks. Eur J Radiol. 2012; 81:749–56. [PubMed: 21334840]
10. Liu J, Fox CS, Hickson D, Sarpong D, Ekunwe L, May WD, et al. Pericardial adipose tissue, atherosclerosis, and cardiovascular disease risk factors: the Jackson heart study. Diabetes Care. 2010; 33:1635–9. [PubMed: 20413524]
11. Brinkley TE, Hsu FC, Carr JJ, Hundley WG, Bluemke DA, Polak JF, et al. Pericardial fat is associated with carotid stiffness in the Multi-Ethnic Study of Atherosclerosis. Nutr Metab Cardiovasc Dis. 2011; 21:332–8. [PubMed: 20153618]
12. Al Chekakie MO, Welles CC, Metoyer R, Ibrahim A, Shapira AR, Cytron J, et al. Pericardial fat is independently associated with human atrial fibrillation. J Am Coll Cardiol. 2010; 56:784–8. [PubMed: 20797492]
13. St-Pierre AC, Cantin B, Dagenais GR, Mauriège P, Bernard PM, Després JP, et al. Low-density lipoprotein subfractions and the long-term risk of ischemic heart disease in men: 13-year follow-up data from the Québec Cardiovascular Study. Arterioscler Thromb Vasc Biol. 2005; 25:553–9. [PubMed: 15618542]
14. Lamarche B, Tchernof A, Moorjani S, Cantin B, Dagenais GR, Lupien PJ, et al. Small, dense low-density lipoprotein particles as a predictor of the risk of ischemic heart disease in men. Prospective results from the Québec Cardiovascular Study. Circulation. 1997; 95:69–75. [PubMed: 8994419]
15. Mackey RH, Greenland P, Goff DC Jr, Lloyd-Jones D, Sibley CT, Mora S. High-density lipoprotein cholesterol and particle concentrations, carotid atherosclerosis, and coronary events: MESA (multi-ethnic study of atherosclerosis). J Am Coll Cardiol. 2012; 60:508–16. [PubMed: 22796256]
16. Kremen J, Dolinkova M, Krajickova J, Blaha J, Anderlova K, Lacinova Z, et al. Increased subcutaneous and epicardial adipose tissue production of proinflammatory cytokines in cardiac surgery patients: possible role in postoperative insulin resistance. J Clin Endocrinol Metab. 2006; 91:4620–7. [PubMed: 16895955]

17. Garvey WT, Kwon S, Zheng D, Shaughnessy S, Wallace P, Hutto A, et al. Effects of insulin resistance and type 2 diabetes on lipoprotein subclass particle size and concentration determined by nuclear magnetic resonance. Diabetes. 2003; 52:453–62. [PubMed: 12540621]
18. Goff DC Jr, D'Agostino RB Jr, Haffner SM, Otvos JD. Insulin resistance and adiposity influence lipoprotein size and subclass concentrations. Results from the Insulin Resistance Atherosclerosis Study. Metabolism. 2005; 54:264–70. [PubMed: 15690322]
19. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, et al. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol. 2002; 156:871–81. [PubMed: 12397006]
20. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972; 18:499–502. [PubMed: 4337382]
21. Mora S, Szklo M, Otvos JD, Greenland P, Psaty BM, Goff DC Jr, et al. LDL particle subclasses, LDL particle size, and carotid atherosclerosis in the Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis. 2007; 192:211–7. [PubMed: 16765964]
22. de Boer IH, Astor BC, Kramer H, Palmas W, Rudser K, Seliger SL, et al. Mild elevations of urine albumin excretion are associated with atherogenic lipoprotein abnormalities in the Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis. 2008; 197:407–14. [PubMed: 17681346]
23. Carr JJ, Nelson JC, Wong ND, McNitt-Gray M, Arad Y, Jacobs DR Jr, 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]
24. 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; 15:827–32. [PubMed: 2407762]
25. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotidartery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med. 1999; 340:14–22. [PubMed: 9878640]
26. Folsom AR, Kronmal RA, Detrano RC, O'Leary DH, Bild DE, Bluemke DA, et al. Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). Arch Intern Med. 2008; 168:1333–9. [PubMed: 18574091]
27. Soliman EZ, Ding J, Hsu FC, Carr JJ, Polak JF, Goff DC Jr. Association between carotid intima-media thickness and pericardial fat in the Multi-Ethnic Study of Atherosclerosis (MESA). J Stroke Cerebrovasc Dis. 2010; 19:58–65. [PubMed: 20123228]
28. Bertoni AG, Whitt-Glover MC, Chung H, Le KY, Barr RG, Mahesh M, et al. The association between physical activity and subclinical atherosclerosis: the Multi-Ethnic Study of Atherosclerosis. Am J Epidemiol. 2009; 169:444–54. [PubMed: 19075250]
29. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care. 2004; 27:1487–95. [PubMed: 15161807]
30. Veeranna V, Zalawadiya SK, Niraj A, Kumar A, Ference B, Afonso L. Association of novel biomarkers with future cardiovascular events is influenced by ethnicity: results from a multi-ethnic cohort. Int J Cardiol. 2013; 166:487–93. [PubMed: 22240756]
31. Ong KL, Ding J, McClelland RL, Cheung BM, Criqui MH, Barter PJ, et al. Relationship of pericardial fat with biomarkers of inflammation and hemostasis, and cardiovascular disease: The Multi-Ethnic Study of Atherosclerosis. Atherosclerosis. 2015; 239:386–92. [PubMed: 25682037]
32. Allison MA, Budoff MJ, Nasir K, Wong ND, Detrano R, Kronmal R, et al. Ethnic-specific risks for atherosclerotic calcification of the thoracic and abdominal aorta (from the Multi-Ethnic Study of Atherosclerosis). Am J Cardiol. 2009; 104:812–7. [PubMed: 19733716]
33. Freedman DS, Otvos JD, Jeyarajah EJ, Barboriak JJ, Anderson AJ, Walker JA. Relation of lipoprotein subclasses as measured by proton nuclear magnetic resonance spectroscopy to coronary artery disease. Arterioscler Thromb Vasc Biol. 1998; 18:1046–53. [PubMed: 9672064]

34. Mora S, Otvos JD, Rifai N, Rosenson RS, Buring JE, Ridker PM. Lipoprotein particle profiles by nuclear magnetic resonance compared with standard lipids and apolipoproteins in predicting incident cardiovascular disease in women. Circulation. 2009; 119:931–9. [PubMed: 19204302]

35. Paynter NP, Sesso HD, Conen D, Otvos JD, Mora S. Lipoprotein subclass abnormalities and incident hypertension in initially healthy women. Clin Chem. 2011; 57:1178–87. [PubMed: 21700954]

36. Fitzgibbons TP, Czech MP. Epicardial and perivascular adipose tissues and their influence on cardiovascular disease: basic mechanisms and clinical associations. J Am Heart Assoc. 2014; 3:e000582. [PubMed: 24595191]

37. Tadros TM, Massaro JM, Rosito GA, Hoffmann U, Vasan RS, Larson MG, et al. Pericardial fat volume correlates with inflammatory markers: the Framingham Heart Study. Obesity (Silver Spring). 2010; 18:1039–45. [PubMed: 19875999]

Highlights

- Pericardial fat may be related to atherogenic lipoprotein abnormalities.
- We analysed data from the Multi-Ethnic Study of Atherosclerosis.
- Pericardial fat was associated with higher level of VLDL-P and smaller HDL-P.
- Lipoprotein profile does not modify association of pericardial fat with CVD risk.

Table 1

Clinical characteristics of participants according to pericardial fat volume

Characteristics	n	Pericardial fat volume, cm^3				*P* for trend
		Quartile 1 (≤47.7)	Quartile 2 (47.8-68.5)	Quartile 3 (68.6-96.3)	Quartile 4 (≥96.4)	
n	5407	1351	1352	1354	1350	-
Age, years	5407	57.8 (9.9)	60.8 (10.1)	63.2 (10.3)	64.1 (9.9)	<0.001
Women, %	2859	67.9 (917)	61.0 (825)	50.4 (683)	32.1 (434)	<0.001
Race/ethnicity, %						
Caucasian	2050	36.9 (499)	33.6 (454)	36.1 (489)	45.0 (608)	<0.001
African American	1479	37.7 (509)	30.0 (406)	25.0 (338)	16.7 (226)	
Hispanic American	1213	14.9 (201)	20.6 (278)	25.1 (340)	29.2 (394)	
Chinese American	665	10.5 (142)	15.8 (214)	13.8 (187)	9.0 (122)	
Education, %						
<High school	967	11.4 (154)	16.0 (216)	22.3 (301)	22.0 (296)	<0.001
High school	2218	38.2 (514)	41.9 (565)	41.7 (564)	42.8 (575)	
>High school	2204	50.3 (677)	42.1 (569)	36.0 (486)	35.1 (472)	
Smoking, %						
Never	2726	55.7 (750)	53.9 (727)	50.4 (681)	42.3 (568)	<0.001
Former	1935	29.9 (403)	33.2 (448)	36.2 (489)	44.3 (595)	
Current	729	14.3 (193)	13.0 (175)	13.4 (181)	13.4 (180)	
Pack-years of smoking	5327	7.0 (13.2)	9.3 (19.3)	11.9 (21.4)	15.8 (25.3)	<0.001
Current alcohol use, %	5368	58.0 (778)	55.5 (747)	51.7 (693)	57.8 (774)	0.012
Total gross family income						
<$30 000	1924	31.0 (403)	35.7 (463)	41.2 (539)	40.1 (519)	<0.001
$30 000-$74 999	2088	39.9 (519)	42.0 (545)	40.1 (525)	38.6 (499)	
≥$75 000	1187	29.1 (378)	22.3 (289)	18.7 (244)	21.3 (276)	
Physical activity, MET-hours/weeks	5393	105 (96)	103 (112)	94 (96)	91 (99)	0.004
BMI, kg/m^2	5407	25.0 (4.5)	27.0 (4.8)	28.9 (5.2)	31.4 (5.2)	<0.001
Waist-to-hip ratio	5406	0.86 (0.08)	0.91 (0.07)	0.94 (0.06)	0.98 (0.06)	<0.001
Heart rate, beats per minute	5374	61.6 (8.9)	62.5 (9.7)	63.2 (9.5)	64.4 (9.8)	<0.001
Diabetes, %	5403	5.0 (68)	8.3 (112)	11.8 (160)	16.4 (221)	<0.001
Hypertension, %	5407	29.5 (398)	39.5 (534)	43.9 (595)	51.4 (694)	<0.001
LDL cholesterol, mg/dL	5404	115 (31)	122 (31)	121 (32.0)	120 (31)	0.006
HDL cholesterol, mg/dL	5404	58.7 (16.8)	52.7 (14.7)	49.0 (12.8)	45.1 (11.7)	<0.001
Triglycerides, mg/dL	5407	99 (55)	119 (58)	129 (64)	149 (71)	<0.001
HOMA2-IR[a]	5394	0.7 (0.5-0.9)	0.8 (0.6-1.1)	1.0 (0.7-1.4)	1.3 (0.9-1.8)	<0.001
CRP, mg/L[a]	5380	1.3 (0.5-2.9)	1.7 (0.8-4.1)	2.2 (1.0-4.7)	2.7 (1.3-5.0)	<0.001
Fibrinogen, mg/dL	5379	328 (71)	341 (71)	348 (73)	356 (75)	<0.001
IL-6, pg/mL[a]	5286	0.9 (0.6-1.5)	1.1 (0.7-1.7)	1.3 (0.8-1.9)	1.5 (1.0-2.4)	<0.001

Characteristics	n	Pericardial fat volume, cm^3				*P* for trend
		Quartile 1 (≤47.7)	Quartile 2 (47.8-68.5)	Quartile 3 (68.6-96.3)	Quartile 4 (≥96.4)	
Factor VIII, %	5378	96.7 (37.2)	95.9 (35.4)	99.7 (37.6)	101.6 (39.1)	<0.001
D-dimer, μg/mL[a]	5381	0.20 (0.10-0.32)	0.20 (0.13-0.35)	0.23 (0.13-0.42)	0.23 (0.13-0.39)	<0.001
PAP, nM[a]	5270	4.7 (3.8-5.9)	4.4 (3.5-5.8)	4.3 (3.4-5.5)	4.1 (3.2-5.3)	<0.001
IMT, mm						
CCA	5407	0.80 (0.18)	0.85 (0.19)	0.88 (0.19)	0.91 (0.19)	<0.001
ICA	5407	0.92 (0.47)	1.00 (0.56)	1.05 (0.57)	1.17 (0.67)	<0.001
Mean	5407	0.86 (0.29)	0.92 (0.33)	0.97 (0.34)	1.04 (0.38)	<0.001
CAC						
Presence, % (n)	5407	31.4 (424)	41.2 (557)	52.2 (707)	61.7 (833)	<0.001
Score[a,b]	2521	52 (13-192)	64 (18-218)	80 (22-269)	115 (26-365)	<0.001
Incident CVD events, %	5407	5.0 (68)	6.8 (92)	9.4 (127)	13.3 (180)	<0.001

MET, metabolic equivalent.

Data are expressed as mean (SD), percent (n), or median (interquartile range). *P* for trend was estimated from multivariable linear regression model with continuous pericardial fat volume as the dependent variable after adjusting for age, sex, and race/ethnicity.

[a] *P* values were estimated using ln-transformed data.

[b] Data were estimated among subjects with the indicated calcium score or the sum score >0.

Table 2

Lipoprotein particle concentrations and sizes according to the quartile of pericardial fat volume

Characteristics	n	Pericardial fat volume, cm^3				*P* for trend
		Quartile 1 (<47.7)	Quartile 2 (47.8-68.5)	Quartile 3 (68.6-96.3)	Quartile 4 (>96.4)	
Lipoprotein particle concentration						
VLDL-P, nmol/L						
Total	5407	55.7 (33.5)	66.1 (35.1)	70.0 (35.4)	73.9 (33.9)	<0.001
Large	5407	2.5 (3.9)	3.8 (4.6)	4.8 (5.4)	6.9 (6.4)	<0.001
Medium	5407	21.4 (19.1)	27.7 (21.6)	30.1 (21.3)	33.0 (21.9)	<0.001
Small	5407	31.8 (19.9)	34.7 (19.6)	35.1 (19.7)	34.1 (18.8)	0.45
IDL-P, nmol/L	5407	116 (93)	133 (97)	136 (100)	132 (96)	<0.001
LDL-P, nmol/L						
Total	5407	1031 (295)	1139 (311)	1155 (316)	1191 (318)	<0.001
Large	5407	682 (236)	640 (245)	585 (253)	524 (252)	<0.001
Small	5407	349 (336)	499 (376)	570 (365)	667 (372)	<0.001
HDL-P, μmol/L						
Total	5407	35.4 (7.0)	34.4 (6.8)	33.3 (6.3)	32.2 (6.1)	<0.001
Large	5407	7.9 (3.9)	6.4 (3.5)	5.6 (3.0)	4.6 (2.6)	<0.001
Medium	5407	14.9 (7.4)	14.2 (7.2)	12.9 (6.4)	11.8 (5.9)	<0.001
Small	5407	12.6 (5.6)	13.8 (5.6)	14.9 (5.5)	15.8 (5.1)	<0.001
Lipoprotein particle size, nm						
VLDL-P	5015	45.5 (6.8)	47.2 (7.2)	48.4 (7.4)	51.2 (8.4)	<0.001
LDL-P	5405	21.0 (0.5)	20.8 (0.5)	20.7 (0.5)	20.6 (0.5)	<0.001
HDL-P	5407	9.5 (0.5)	9.3 (0.4)	9.2 (0.4)	9.1 (0.4)	<0.001

Data are expressed as mean (SD). *P* for trend was estimated from multivariable linear regression model with continuous pericardial fat volume as the dependent variable after adjusting for age, sex, and race/ethnicity.

Table 3

Associations of pericardial fat volume with different lipoprotein particle concentrations and sizes

Biomarkers	Model 1	Model 2	Model 3	Model 4	Model 5
Lipoprotein particle concentration					
VLDL-P, nmol/L					
Total	4.1 (3.1, 5.1)‡	2.9 (1.6, 4.15)‡	0.16 (−0.72, 1.05)	-	-
Large	1.5 (1.3, 1.6)‡	0.59 (0.39, 0.78)‡	0.12 (0.02, 0.23)*	0.13 (0.03, 0.24)*	0.20 (0.11, 0.30)‡
Medium	2.5 (1.8, 3.1)‡	1.3 (0.5, 2.1)‡	−0.35 (−0.89, 0.18)	–	–
Small	0.17 (−0.41, 0.75)	0.94 (0.20, 1.69)*	0.39 (−0.30, 1.09)	–	–
IDL-P, nmol/L	5.6 (2.7, 8.5)‡	2.5 (−1.2, 6.2)	−2.2 (−5.2, 0.9)	–	–
LDL-P, nmol/L					
Total	42.6 (33.3, 51.9)‡	9.3 (−0.3, 21.1)	−0.66 (−8.59, 7.28)	–	–
Large	−40.2 (−47.4, −33.0)‡	−9.4 (−18.5, −0.23)*	−1.2 (−7.8, 5.4)	-	-
Small	82.8 (72.3, 93.4)‡	18.6 (5.6, 31.7)†	0.5 (−9.0, 10.0)	-	-
HDL-P, μmol/L					
Total	−0.56 (−0.73, −0.38)‡	0.04 (−0.18, 0.26)	0.04 (−0.12, 0.21)	-	-
Large	−0.83 (−0.93, −0.74)‡	−0.12 (−0.23, −0.01)*	−0.05 (−0.10, 0.01)	-	-
Medium	−0.79 (−0.98, −0.60)‡	−0.21 (−0.45, 0.03)	−0.15 (−0.37, 0.07)	-	-
Small	1.1 (0.9, 1.2)‡	0. 37 (0.16, 0.57)‡	0.23 (0.04, 0.43)*	0.17 (−0.03, 0.36)	0.20 (0.01, 0.38)*
Lipoprotein particle size, nm					
VLDL-P	2.1 (1.8, 2.3)‡	0.51 (0.24, 0.79)‡	0.12 (−0.09, 0.32)	-	-
LDL-P	−0.11 (−0.13, −0.10)‡	−0.03 (−0.05, −0.02)‡	−0.01 (−0.02, 0.01)	-	-
HDL-P	−0.11 (−0.13, −0.10)‡	−0.03 (−0.04, −0.01)†	−0.02 (−0.03, −0.01)†	−0.02 (−0.03, −0.01)†	−0.02 (−0.03, −0.01)†

Data are expressed as regression coefficient (95% CI) in terms of per SD 41.7 cm^3 increase in pericardial fat volume.

Model 1: Adjusted for age, sex, race/ethnicity, education, smoking, pack-years of smoking, current alcohol use, total gross family income, and physical activity.

Model 2: Further adjusted for BMI, heart rate, diabetes, hypertension, HOMA2-IR (ln-transformed), CRP (ln-transformed), fibrinogen, IL-6 (ln-transformed), factor VIII, D-dimer (ln-transformed), and PAP (ln-transformed).

Model 3: Further adjusted for LDL cholesterol, HDL cholesterol, and triglycerides.

Model 4: Further adjusted for large VLDL-P concentration, small HDL-P concentration, and HDL-P size, where appropriate.

Model 5: Same as model 4, except that BMI was replaced by waist-to-hip ratio and height in the model.

*$P<0.05$,

†$P<0.01$,

‡$P<0.001$.

Table 4

Racial/ethnic-specific associations of pericardial fat volume with large VLDL-P concentration and HDL-P size

Biomarkers	Caucasian (n=2050)	African American (n=1479)	Hispanic American (n=1213)	Chinese American (n=665)	*P* for interaction
Large VLDL-P, nmol/L					
Model 1	0.22 (0.05, 0.38)†	0.10 (−0.08, 0.28)	−0.09 (−0.30, 0.13)	0.21 (−0.22, 0.64)	0.022
Model 2	0.22 (0.07, 0.38)†	0.19 (0.01, 0.36)*	0.07 (−0.13, 0.27)	0.34 (−0.06, 0.74)	0.024
HDL-P size, nm					
Model 1	−0.02 (−0.03, 0.00)*	−0.02 (−0.05, 0.00)	−0.01 (−0.03, 0.01)	−0.01 (−0.05, 0.04)	0.052
Model 2	−0.02 (−0.04, −0.01)†	−0.02 (−0.05, 0.01)	−0.01 (−0.03, 0.01)	−0.02 (−0.06, 0.02)	0.070

Data are expressed as regression coefficient (95% CI) in terms of per SD 41.7 cm^3 increase in pericardial fat volume.

Model 1: Adjusted for age, sex, race/ethnicity, education, smoking, pack-years of smoking, current alcohol use, total gross family income, physical activity, BMI, heart rate, diabetes, hypertension, HOMA2-IR (ln-transformed), LDL cholesterol, HDL cholesterol, triglycerides, CRP (ln-transformed), fibrinogen, IL-6 (ln-transformed), factor VIII, D-dimer (ln-transformed), PAP (ln-transformed), large VLDL-P concentration, small HDL-P concentration, and HDL-P size.

Model 2: Same as model 1, except that BMI was replaced by waist-to-hip ratio and height in the model.

‡ $P<0.001$.

* $P<0.05$,

† $P<0.01$,