The association of pericardial fat with incident coronary heart disease: the Multi-Ethnic Study of Atherosclerosis (MESA)1–3

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ABSTRACT

Background: Pericardial fat (ie, fat around the heart) may have a direct role in the atherosclerotic process in coronary arteries through local release of inflammation-related cytokines. Cross-sectional studies suggest that pericardial fat is positively associated with coronary artery disease independent of total body fat.

Objective: We investigated whether pericardial fat predicts future coronary heart disease events.

Design: We conducted a case-cohort study in 998 individuals, who were randomly selected from 6814 Multi-Ethnic Study of Atherosclerosis (MESA) participants and 147 MESA participants (26 from those 998 individuals) who developed incident coronary heart disease from 2000 to 2005. The volume of pericardial fat was determined from cardiac computed tomography at baseline.

Results: The age range of the subjects was 45–84 y (42% men, 45% white, 10% Asian American, 22% African American, and 23% Hispanic). Pericardial fat was positively correlated with both body mass index (correlation coefficient = 0.45, P < 0.0001) and waist circumference (correlation coefficient = 0.57, P < 0.0001). In unadjusted analyses, pericardial fat (relative hazard per 1-SD increment: 1.33; 95% CI: 1.15, 1.54), but not body mass index (1.00; 0.84, 1.18), was associated with the risk of coronary heart disease. Waist circumference (1.14; 0.97, 1.34; P = 0.1) was marginally associated with the risk of coronary heart disease. The relation between pericardial fat and coronary heart disease remained significant after further adjustment for body mass index and other cardiovascular disease risk factors (1.26; 1.01, 1.59). The relation did not differ by sex.


INTRODUCTION

Fat distribution is associated with the development of coronary heart disease independent of the amount of fat (1). Among the regional fat depots, there is reason to believe that pericardial fat (ie, fat around the heart) may play a direct role in the atherosclerotic process in coronary arteries through local release of inflammation-related cytokines (2, 3). Data from cross-sectional studies suggest that pericardial fat is positively associated with coronary artery disease independent of total body fat (4, 5), and we previously showed a direct cross-sectional association between pericardial fat and the presence of calcified coronary plaque in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort participants (6). However, it is unknown whether pericardial fat predicts the risk of future coronary heart disease events. Using longitudinal data from MESA, we tested the hypothesis that pericardial fat would predict the risk of coronary heart disease independent of body mass index.

SUBJECTS AND METHODS

Study population

MESA is a community-based prospective cohort study designed primarily to investigate prevalence, correlates, and progression of subclinical cardiovascular disease (7). A total of 6814 whites, blacks, Hispanics, and Asian Americans aged 45–84 y were recruited from Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; New York, NY; and St Paul, MN. Individuals with physician-diagnosed cardiovascular disease or any related procedures at baseline were not eligible. The baseline examination and 3 follow-up examinations were conducted at intervals of 18 to 24 mo from 2000 to 2007. By 6 January 2005, a total of 165 MESA participants had developed incident coronary heart disease. MESA participants underwent a computed tomography (CT) scan for the assessment of calcified coronary plaque at baseline, when information on demographic variables, anthropometric measures, and lipid and lipoprotein levels were collected. 

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pometric measures, and other cardiovascular factors was also collected. We measured the volume of pericardial fat using the existing cardiac CT scans at baseline in a random sample of 1000 MESA participants and in MESA participants who developed incident coronary heart disease. After 20 individuals who were missing cardiac CT scans were excluding, the study population consisted of 998 individuals (the MESA 1000 sample) from the random sample of 1000 MESA participants and 147 MESA participants (26 from those 998 individuals) who developed incident coronary heart disease. The study was approved by institutional review boards of participating institutions. All participants gave informed consent.

Assessment of incident coronary heart disease

A telephone interviewer contacted each participant to inquire about all interim hospital admissions, cardiovascular outpatient diagnoses and procedures, and deaths. Additional medical encounters were occasionally identified through follow-up examinations, participant call-ins, medical record abstractions, or obituaries. To verify self-reported diagnoses, copies of all death certificates and medical records were requested for all hospitalizations and selected outpatient cardiovascular diagnoses and procedures. Information was also obtained through next of kin interviews for out of hospital cardiovascular deaths. We were successful in getting hospital records for an estimated 98% of hospitalized cardiovascular events and some information on 95% of outpatient diagnostic encounters. Trained personnel abstracted any hospital records suggesting possible cardiovascular events. They recorded symptoms, history and biomarkers, digitally copied echocardiograms (ECGs), catheterization reports, outpatient records, and other relevant diagnostic and procedure reports. Cardiologists or cardiovascular physician-epidemiologists reviewed cardiovascular events. The review committee adjudicated disagreements. Coronary heart disease events were defined as myocardial infarction, resuscitated cardiac arrest, angina, or fatal coronary heart disease. Myocardial infarction required either abnormal cardiac biomarkers (≥2 times the upper limits of normal) regardless of pain or biomarker findings, evolving Q waves regardless of pain or biomarker findings, or a combination of chest pain and ST evolution or new left bundle branch block and biomarker concentrations 1–2 times the upper limits of normal. Reviewers classified resuscitated cardiac arrest when a patient successfully recovered from a full cardiac arrest through cardiopulmonary resuscitation (including cardioversion). In addition to symptoms of typical chest pain or atypical symptoms, angina required one or more criteria, including coronary artery bypass graft surgery or other revascularization procedure, ≥70% obstruction on coronary angiography, or evidence of ischemia by stress tests or by testing ECG. In addition to the absence of a known nonatherosclerotic or noncardiac cause of death, fatal coronary heart disease required a documented myocardial infarction within the previous 28 d, chest pain within 72 h before death, or a history of coronary heart disease.

Pericardial fat

Cardiac CT scans were performed either with an ECG-triggered (at 80% of the RR interval) electron-beam scanner (Chicago, Los Angeles, and New York field centers; Imatron C-150; GE Imatron, Milwaukee, WI) or with prospectively ECG-triggered scan acquisition at 50% of the RR 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 Country, and St Paul field centers; Lightspeed (GE Medical Systems, Milwaukee, WI) or Volume Zoom (Siemens, Erlangen, Germany)] (8, 9). Three experienced CT analysts measured pericardial fat volume on the previously obtained images of the heart. For pericardial fat volume, slices within 15 mm above and 30 mm below the superior extent of the left main coronary artery were included. 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. Volume analysis software (GE Health Care, Waukesha, WI) was used to discern fat from other tissues with a threshold of −190 to −30 Hounsfield units. The volume was the sum of all voxels containing fat. Our measure of pericardial fat volume was highly correlated with total volume of pericardial fat volume (10) in a random subset of 10 Diabetes Heart Study participants (correlation coefficient = 0.93, P < 0.0001). A random sample of 80 MESA participants was selected and their CT scans were reread. The intraclass correlation coefficients of intrareader and interreader reliability were 0.99 and 0.89, respectively, for pericardial fat.

Pericardial fat includes both epicardial (located within the pericardium) and paracardial fat (located superficial to the pericardium) (11). We measured epicardial fat in a random sample of 159 MESA participants. The Spearman correlation coefficient between pericardial and epicardial fat was 0.92 (P < 0.0001). To distinguish epicardial fat from paracardial fat, one must identify the pericardium. However, it is difficult to visualize the pericardium, especially in lean individuals (12). Therefore, we chose to measure pericardial fat rather than epicardial fat.

Anthropometric measures

Weight was measured with a Detecto Platform Balance Scale (Detecto, Webb City, MO) to the nearest 0.5 kg. Height was measured with a stadiometer (Accu-Hite Measure Device with level bubble; Seca, Hamburg, Germany) to the nearest 0.1 cm. Waist circumference (at the umbilicus) was measured to the nearest 0.1 cm with a steel measuring tape with standard 4-oz (113.4-g) tension (Gulick II 150 cm anthropometric tape; Sammons Preston, Chicago, IL). Body mass index was defined as weight in kilograms divided by the square of height in meters.

Other covariates

Standard questionnaires were used to collect information on demographics, cigarette smoking, alcohol drinking, physical activity, education, and medication use. Pack-years of smoking was the average number of packs of cigarettes smoked per day times the number of years of smoking. Alcohol drinking was categorized into never, former, and current. Physical activity was calculated on the basis of duration and intensity of the total intentional exercises, including moderate walking exercise,
moderate dance, vigorous team/dual sports, moderate individual activities, and moderate and vigorous conditioning. Education was categorized into less than high school, complete high school or some college, and college degree or higher. Blood pressure was measured in the right arm of the participant after 5 min in a sitting position with a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, FL). The second and third of 3 readings were averaged to obtain the blood pressure levels. Total and HDL cholesterol were measured in EDTA-treated plasma on a Roche COBAS FARA centrifugal analyzer (Roche Diagnostics, Indianapolis, IN). C-reactive protein was measured by using the BNII nephelometer (Dade Behring Inc, Deerfield, IL). Glucose concentrations were measured by rate reflectance spectrophotometry by using a thin-film adaptation of the glucose oxidase method on the Vitros analyzer (Johnson & Johnson Clinical Diagnostics Inc, Rochester, NY).

Statistical analysis
Cardiovascular characteristics were compared between those with and without incident coronary heart disease by using analysis of variance for continuous variables and chi-square test for categorical variables. Pearson correlation coefficients between pericardial fat and other fat measures were calculated. We estimated the survival function in the MESA 1000 sample. Participants were categorized into quartiles according to pericardial fat. The curves of cumulative incidence of coronary heart disease for each quartile of pericardial fat were compared by using the log-rank test. The follow-up period was from the baseline to the first onset of coronary heart disease, loss to follow-up, death, or 6 January 2005, whichever occurred first. We next used a case-cohort study design to estimate the relative risk of coronary heart disease in the MESA 1000 sample and in MESA participants who developed incident coronary heart disease. We determined the hazard ratios of incident coronary heart disease for each 1-SD increment in pericardial fat, body mass index, and waist circumference using Cox proportional hazard models. The hazard ratios and their 95% CIs were calculated using the exact pseudolikelihood estimator with the robust variance (the sandwich variance estimator) to account for the case-cohort study design (13). We also examined the association between pericardial fat and coronary heart disease after adjusting for other cardiovascular factors. The models were adjusted for body mass index to control for body size. SAS version 9.00 (SAS Institute Inc, Cary, NC) was used for the analysis.

RESULTS
At baseline, individuals with incident coronary heart disease (Table 1) were older and were more likely to be male than were those without incident coronary heart disease; in addition, they had a greater average pack-years of smoking and systolic blood pressure, had a lower concentration of HDL cholesterol, had a higher concentration of fasting glucose, and were more likely to use antihypertensive, lipid-lowering, and diabetes medication. There were no marked differences in ethnicity, physical activity, education, total cholesterol, and C-reactive protein between those with and without incident coronary heart disease. The average volume of pericardial fat and waist circumference was greater in those with incident coronary heart disease, but no differences were found in body mass index. Pericardial fat was positively correlated with both body mass index (correlation coefficient = 0.45, \( P < 0.0001 \)) and waist circumference (correlation coefficient = 0.57, \( P < 0.0001 \)).

In the MESA 1000 sample, cumulative incidence of coronary heart disease was plotted for quartiles of pericardial fat (Figure 1). Individuals in the highest quartile of pericardial fat had the greatest risk of coronary heart disease.

The results of the case-cohort study are shown in Table 2. In the unadjusted analysis, a 1-SD increment in pericardial fat was associated with a 33% greater risk of developing incident coronary heart disease. There seemed to be an association with waist circumference, although the lower 95% CI barely included the null hypothesis. On the other hand, no association was observed between body mass index and incident coronary heart disease. After demographic factors and body mass index were adjusted for, the association between pericardial fat and coronary heart disease was attenuated, but remained statistically significant; further adjustment for other cardiovascular disease risk factors, including lipids and C-reactive protein concentrations, slightly reduced the relative risk. In the fully adjusted model, the excess risk of coronary heart disease for a 1-SD increment in pericardial fat was equivalent to that for a 0.62-mmol/L (24-mg/dL) increment in total cholesterol, a 20-mm Hg increment in systolic blood pressure, or an 18-pack-years increment in cigarette smoking. The interaction term between pericardial fat and sex was not found to be statistically significant (\( P = 0.5 \)). Although the point estimate was slightly higher for women, it did not achieve conventional statistical significance in men (relative hazard: 1.33; 95% CI: 1.00, 1.76) and in women (relative hazard: 1.64; 95% CI: 0.93, 2.92), possibly because of a small number of incident coronary heart disease events in women (100 events in men compared with 47 events in women). After waist circumference was added to the fully adjusted model, the association between pericardial fat and coronary heart disease was marginally significant (relative hazard: 1.24; 95% CI: 0.99, 1.57). Finally, we compared quartiles of pericardial fat with the lowest quartile regarding the risk of coronary heart disease; except for the second quartile, the risk of coronary heart disease increased with higher quartiles of pericardial fat (Figure 2). Participants in the highest quartile had more than double the risk of coronary heart disease than did those in the lowest quartile.

DISCUSSION
In the present study, increased pericardial fat was associated with a higher risk of developing incident coronary heart disease in community-based adults without a history of cardiovascular disease, even after body mass index and other cardiovascular disease risk factors were adjusted for. However, the association between waist circumference and coronary heart disease was only marginally significant, and body mass index was not associated with coronary heart disease.

Our data support the idea that pericardial fat is a better predictor of incident coronary heart disease than are more general measures of adiposity (eg, body mass index or waist circumference). In a study of 251 Japanese male patients, pericardial fat, but not body mass index, was associated with the presence and severity of coronary artery disease determined by...
coronary angiogram (5). Since then, 2 more studies reported a positive association between pericardial fat and coronary artery disease (4, 14), but another study found no association (15). The results from these studies could, however, be biased because the study participants were limited to clinic patients referred for diagnostic coronary angiography. Two recent community-based studies further showed that pericardial fat was positively associated with calcified coronary plaque determined by CT (16, 17), consistent with our earlier report from a subsample of the MESA cohort (6). The present study extends these findings by relating pericardial fat to incident coronary heart disease in community-based adults without a history of cardiovascular disease. Consistent with a previous MESA report (18), we found no association between body mass index and incident coronary heart disease. Although numerous studies have shown that body mass index is associated with incident coronary heart disease, some studies did not find this association (19, 20). Furthermore, abdominal visceral fat, but neither body mass index nor waist circumference, was associated with incident coronary heart disease in a study of Japanese-American men (21). An examination of the heterogeneity of regional fat depots may further our understanding of the link between obesity and coronary heart disease.

The mechanism underlying the strong relation between pericardial fat and coronary heart disease may be due to its proximity to coronary arteries and release of inflammation-related cytokines. A large amount of pericardial fat is distributed around the adventitia of the coronary arteries. Fat tissue, in addition to its energy storage function, also interacts with other

### TABLE 1
Baseline characteristics in the Multi-Ethnic Study of Atherosclerosis (MESA) 1000 sample and the MESA participants who developed incident coronary heart disease: 2000–2005

<table>
<thead>
<tr>
<th>Incident coronary heart disease</th>
<th>No (n = 972)</th>
<th>Yes (n = 147)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>59 ± 10^7</td>
<td>68 ± 9</td>
<td>&lt;0.0001</td>
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<tr>
<td>Male (%)</td>
<td>43</td>
<td>70</td>
<td>&lt;0.0001</td>
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<tr>
<td>Ethnicity (%)</td>
<td></td>
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<tr>
<td>White</td>
<td>46</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>10</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>21</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>23</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Pack-years of smoking</td>
<td>11 ± 21</td>
<td>21 ± 31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Alcohol drinking (%)</td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Never</td>
<td>20</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>21</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>59</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Physical activity (MET-min/wk)</td>
<td>1553 ± 2370</td>
<td>1281 ± 1564</td>
<td>0.06</td>
</tr>
<tr>
<td>Education (%)</td>
<td></td>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td>Less than high school,</td>
<td>17</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Complete high school or some college</td>
<td>46</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>College degree or higher</td>
<td>37</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>124 ± 21</td>
<td>135 ± 23</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.02 ± 0.9</td>
<td>5.15 ± 1.1</td>
<td>0.2</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.32 ± 0.4</td>
<td>1.22 ± 0.4</td>
<td>0.002</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>5.61 ± 1.6</td>
<td>6.38 ± 2.7</td>
<td>0.0003</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>4.1 ± 7</td>
<td>3.5 ± 5</td>
<td>0.3</td>
</tr>
<tr>
<td>Any antihypertensive medication (%)</td>
<td>34</td>
<td>54</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Any lipid-lowering medication (%)</td>
<td>13</td>
<td>28</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Any diabetes medication (%)</td>
<td>9</td>
<td>22</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28 ± 6</td>
<td>27 ± 5</td>
<td>0.6</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>98 ± 15</td>
<td>102 ± 12</td>
<td>0.01</td>
</tr>
<tr>
<td>Pericardial fat (cm³)</td>
<td>79 ± 42</td>
<td>100 ± 51</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

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1. MET, metabolic equivalent tasks.
2. ANOVA for continuous variables and chi-square test for categorical variables.
3. Mean ± SD (all such values).

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**FIGURE 1.** Cumulative incidence of coronary heart disease by quartiles of pericardial fat in the Multi-Ethnic Study of Atherosclerosis (MESA) 1000 sample, 2000–2005 (log-rank test for an overall difference between the quartiles: P = 0.01).
tissues and organs through endocrine and paracrine activities. Compared with subcutaneous fat, pericardial fat has a higher rate of secreting inflammatory cytokines, such as monocyte chemo-tactic protein 1, interleukin-6, and tumor necrosis factor-α (22). The presence of inflammatory mediators in the tissues surrounding coronary arteries induces the influx of inflammatory cells into the arterial wall (23). Moreover, results from both human and animal studies suggest that atherosclerotic lesions are absent in the segments of coronary arteries lacking pericardial fat (24, 25). In addition, it has been observed that pericardial fat has a higher expression of adiponectin, an antiinflammatory cytokine, in individuals with normal coronary arteries than in patients with severe coronary artery disease (26).

The strength of the present study was in its prospective study design, community-based study participants without a history of cardiovascular disease, and rigorous ascertainment of coronary heart disease events. A shortcoming of the present analysis was the lack of measures of other regional fat depots. Pericardial fat is closely correlated with abdominal visceral fat (10), which may be a predictor of incident coronary heart disease independent of total body fat (21, 27). Therefore, the relative importance of these depots could not be determined. However, Taguchi et al (5) found that the association of pericardial fat with coronary artery disease determined by coronary angiogram was independent of abdominal visceral fat, but that abdominal visceral fat was not associated with coronary artery disease after adjustment for pericardial fat (5). A report from the Framingham Heart Study also showed that pericardial fat was associated with calcified coronary plaque measured by CT after abdominal visceral fat was controlled for (17). Thus, the association between pericardial fat and incident coronary heart disease observed in our study may have been independent of abdominal visceral fat.

In summary, we showed for the first time that increased pericardial fat predicts a higher risk of future coronary heart disease in community-based middle-aged and older adults without a history of cardiovascular disease. Future studies should examine whether pericardial fat is the primary fat depot regarding the risk of developing coronary heart disease, after other regional fat depots are controlled for. If the hypothesis is confirmed, pericardial fat may serve as a more specific and sensitive marker of coronary heart disease risk than other fat measures. Routine CT scans are still not feasible for mass screenings. However, the echocardiographic measurement of pericardial fat has potential for coronary heart disease risk stratification (28). Ultimately, with a better understanding of the determinants of pericardial fat accumulation and the underlying mechanisms of the link between pericardial fat and coronary heart disease, new therapeutic targets may be identified in the prevention of coronary heart disease, the leading cause of death in the United States.

We thank the other investigators, the staff, and the participants of MESA for their valuable contributions and especially the CT Reading Center personnel at both Harbor UCLA and Wake Forest University School of Medicine for their hard work on this project. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

The authors’ responsibilities were as follows—JD, JJC, and SBK: responsible for the conception, design, and conduct of the study and for the data interpretation; and F-CH, TBH, YL, MS, PO, MAE, KKL, MHC, MA, and DAB: responsible for the conduct of the study and the data interpretation. None of the authors had any conflicts of interest.

REFERENCES


