Epicardial fat volume is related to atherosclerotic calcification in multiple vessel beds

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Aim
To investigate relationships between epicardial fat volume and atherosclerosis in multiple major vessel beds.

Methods and results
From the population-based Rotterdam Study, 2298 participants underwent computed tomography examinations to quantify epicardial fat volume and atherosclerotic calcification volume in the coronary arteries, aortic arch, and extracranial and intracranial internal carotid arteries. Using linear regression modelling, we investigated relationships of epicardial fat volume with atherosclerotic calcification volume in each vessel bed, adjusting for conventional cardiovascular risk factors (waist circumference, systolic and diastolic blood pressure, total and high-density lipoprotein cholesterol, smoking, diabetes, and usage of blood pressure-lowering and lipid-lowering medication). To test whether associations of epicardial fat with calcification per vessel bed were independent of calcification elsewhere, we created a model in which all vessel beds were entered together. We found that a larger epicardial fat volume was associated with larger calcification volumes in the coronary arteries, aortic arch, and extracranial carotid arteries in both sexes. After adjustment for cardiovascular risk factors, larger epicardial fat volume was related to coronary and extracranial carotid artery calcification volume in males only [difference in calcification volume per SD increase in epicardial fat volume: 0.12 (95% confidence interval, CI: 0.04; 0.19) and 0.14 (95% CI: 0.06; 0.22)]. These associations remained unchanged after entering all vessel beds into one model.

Conclusion
Larger volumes of epicardial fat are associated with larger amounts of coronary and extracranial carotid artery atherosclerosis in males, independent of cardiovascular risk factors. This could imply that epicardial fat also exerts a systemic effect on atherosclerosis development. Future longitudinal research is warranted to further disentangle these relationships with a specific focus on sex differences.

Keywords
epicardial fat • atherosclerosis • imaging • CT • epidemiology

Introduction
Epicardial fat is defined as the adipose tissue located between the outer wall of the myocardium and the visceral layer of pericardium.¹,² Several studies have shown associations between larger amounts of epicardial fat and the occurrence of cardiovascular disease.³–⁷ Anatomically, epicardial fat is directly surrounding the adventitia of the coronary arteries, without the interposition of a fascial layer.⁸,⁹ Without this physical border, local secretion of pro-atherogenic factors by epicardial fat might directly contribute to development of atherosclerosis and subsequent clinical coronary events.⁵,⁸,⁹ However, given this close relationship to the vascular system, epicardial fat might also exert a systemic effect on the development of atherosclerosis located in other vessel beds.

Conventional cardiovascular risk factors are associated with both the amount of epicardial fat⁵,⁷ and the amount of atherosclerosis across vessel beds.¹⁰–¹² It is therefore important to investigate whether any association between epicardial fat and atherosclerosis is present independent of conventional cardiovascular risk factors. Disentangling the role of epicardial fat in the aetiology of atherosclerosis may eventually serve as a basis for developing therapeutic or preventive strategies for atherosclerosis.
In this study, we set out to investigate the relationship of the epicardial fat volume with atherosclerotic calcification, as proxy of atherosclerosis, in the coronary arteries, aortic arch, extracranial carotid arteries, and intracranial carotid arteries, in a large sample of participants from the population-based Rotterdam Study.

Methods

Setting
This study is based on the population-based Rotterdam Study, which is an ongoing cohort study that started in 1990, with follow-up every 3–4 years. From 2003 until 2006, all participants who completed a regular visit at the research centre were invited to undergo multidetector computed tomography (MDCT) of the coronary arteries, aortic arch, extracranial carotid arteries, and intracranial carotid arteries. In total, 2524 participants were scanned. The Rotterdam Study has been approved by the medical ethics committee according to the Population Study Act Rotterdam Study, executed by the Ministry of Health, Welfare and Sports of the Netherlands. A written informed consent was obtained from all participants.

Assessment of epicardial fat and atherosclerosis

Computed tomography acquisition
A 16-slice ($n=785$) or 64-slice ($n=1739$) MDCT-scanner (Somatom Sensation, Siemens, Forchheim, Germany) was used to perform non-enhanced computed tomography (CT) scanning. Using a cardiac scan and a scan that reached from the aortic arch to the intracranial vasculature (1 cm above the sella turcica), the following vessel beds were scanned: the coronary arteries, the aortic arch, extracranial carotid arteries, and intracranial carotid arteries. In total, 2524 participants were scanned. The Rotterdam Study has been approved by the medical ethics committee according to the Population Study Act Rotterdam Study, executed by the Ministry of Health, Welfare and Sports of the Netherlands. A written informed consent was obtained from all participants.

Quantification of epicardial fat
The cardiac scan was used for the quantification of epicardial fat (Figure 1). We used a fully automatic tool for quantification of epicardial fat in millilitres. This quantification method consisted of two steps: (i) whole heart segmentation and (ii) epicardial fat volume quantification. For whole heart segmentation, we used a multi-atlas-based segmentation approach. In this approach, eight manually segmented contrast-enhanced cardiac scans (atlases) were registered (spatially aligned) with every participant’s CT scan. The atlas scans and subject’s scan were initially aligned using an affine transformation, which was followed by a non-rigid registration. After registration, the segmentations of the atlases were mapped onto the subject’s scan to obtain the whole heart segmentation. All registrations were performed using Elastix, a publicly available software package.

Next, we used the obtained whole heart segmentation as a region of interest and a threshold window of $-30$ to $-200$ Hounsfield Units for the quantification of the amount of fat. A connected-component analysis was applied to all adipose tissue voxels using an 18-neighbourhood rule, to remove regions smaller than 10 voxels ($2.8 \text{ mm}^3$) in size, which we considered to be noise.

This fully automatic method was validated by an expert reviewer panel and proved to be as good as manual segmentation.

Quantification of atherosclerotic calcification
Dedicated commercially available software (Syngo CalciumScoring, Siemens, Germany) was used to automatically quantify atherosclerotic calcification in the coronary arteries, the aortic arch, and the extracranial internal carotid arteries. Calcification in the intracranial internal carotid arteries was quantified using a semi-automated method. Calcification volumes were expressed in cubic millimetres.

Assessment of cardiovascular risk factors
Information on cardiovascular risk factors was obtained during a home interview and a visit to the research centre. Waist circumference was measured as a proxy of the amount of visceral adipose tissue. Systolic and diastolic blood pressures were measured twice at the right arm using a random zero sphygmomanometer. The mean of the two measurements was used for the analyses. Fasting blood samples were obtained, and serum total cholesterol and high-density lipoprotein cholesterol were measured using an automatic enzymatic procedure (Hitachi analyser, Roche Diagnostics). Glucose was determined enzymatically by the Hexokinase method. Diabetes was defined as fasting serum glucose levels $\geq 7.0 \text{ mmol/L}$ or non-fasting serum glucose levels $\geq 11.0 \text{ mmol/L}$ and/or the use of anti-diabetic therapy. Participants were categorized based on smoking status into ‘past or current smoker’ or ‘never smoker’. Finally, information on the use of blood pressure-lowering medication and lipid-lowering medication was assessed by interview.

Figure 1 Different degrees of epicardial fat volume. Epicardial fat is identified (red) on approximately the same slice in three different study participants. The epicardial fat volume increases from left to right.
Population characteristics

<table>
<thead>
<tr>
<th>Sample size</th>
<th>2298</th>
</tr>
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<tbody>
<tr>
<td>Women</td>
<td>52.8%</td>
</tr>
<tr>
<td>Age (years)</td>
<td>69.4 (6.6)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>94.2 (11.6)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>146.7 (20.0)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>80.4 (10.7)</td>
</tr>
<tr>
<td>Use of blood pressure-lowering medication</td>
<td>38.5%</td>
</tr>
<tr>
<td>Serum total cholesterol (mmol/L)</td>
<td>5.7 (1.0)</td>
</tr>
<tr>
<td>Serum HDL cholesterol (mmol/L)</td>
<td>1.4 (0.4)</td>
</tr>
<tr>
<td>Use of lipid-lowering medication</td>
<td>22.1%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>12.2%</td>
</tr>
<tr>
<td>Past and current smokers</td>
<td>69.0%</td>
</tr>
<tr>
<td>Epicardial fat volume$^a$ (mL)</td>
<td>101.5 (80.0–129.8)</td>
</tr>
<tr>
<td>Coronary artery calcification volume$^a$ (mm$^3$)</td>
<td>49.5 (1.8–258.4)</td>
</tr>
<tr>
<td>Aortic arch calcification volume$^a$ (mm$^3$)</td>
<td>244.1 (42.8–819.1)</td>
</tr>
<tr>
<td>Extracranial carotid artery calcification volume$^a$ (mm$^3$)</td>
<td>21.4 (0.0–108.2)</td>
</tr>
<tr>
<td>Intracranial carotid artery calcification volume$^a$ (mm$^3$)</td>
<td>40.7 (6.2–135.2)</td>
</tr>
</tbody>
</table>

Values are mean (standard deviation) for continuous variables, percentages for dichotomous variables.

$^a$Median (inter-quartile range).

Results

Table 1 shows the characteristics of the study population. The mean age of the study population was 69.4 ± 6.6 years and 52.8% was female. The median epicardial fat volume in the population was 101.5 mL (inter-quartile range: 80.0–129.8 mL). The mean systolic blood pressure and diastolic blood pressure were 146.7 ± 20.0 and 80.4 ± 10.7 mmHg, and 12.2% of the population had diabetes. The prevalence of coronary calcification was 81.7%; for aortic arch calcification, extracranial carotid artery calcification, and intracranial carotid artery calcification, this was 92.4, 72.8, and 81.5%, respectively.

The distribution of epicardial fat volume in these groups is shown in Supplementary material online, Table S1.

The associations between conventional cardiovascular risk factors and epicardial fat volume are shown in Table 2. We found that all cardiovascular risk factors, except total cholesterol, were significantly associated with larger epicardial fat volume in the age- and sex-adjusted analyses. Yet, in the multivariate model, systolic and diastolic blood pressures and diabetes were no longer statistically significantly related to epicardial fat volume. We found no prominent sex differences for the risk factor profile between males and females.

We found that a larger epicardial fat volume was associated with larger volumes of coronary, aortic, and extracranial carotid artery calcification in both males and females (Table 3, Model 1). Moreover, in males only, epicardial fat volumes were also associated with intracranial carotid artery calcification [difference in calcification volume per SD increase in epicardial fat volume: 0.11 (95% confidence interval, CI: 0.05; 0.17)]. After adjusting for cardiovascular risk factors, this association remained present for coronary artery calcification and extracranial carotid artery calcification in males only [difference in calcification volume per SD increase in epicardial fat volume: 0.12 (95% CI: 0.04; 0.19) and 0.14 (95% CI: 0.06; 0.22), respectively]. This pattern of associations remained unchanged after entering all vessel beds into one model.

Discussion

In this sample of middle-aged and elderly community-dwelling persons, we found that larger epicardial fat volumes are associated with a larger amount of atherosclerotic calcification in the coronary arteries and the extracranial carotid arteries in males, independent of cardiovascular risk factors. In females, these associations are less prominent and only seem to hold for coronary artery calcification.

Strengths of this study include the population-based setting and the image-based quantification of both epicardial fat and atherosclerosis. Although the majority of previous studies performed measurements of epicardial fat using ultrasound, CT is superior in detecting and quantifying the amount of epicardial fat accurately.\textsuperscript{6,22} Moreover, we were the first to develop and apply a fully automatic method to quantify epicardial fat volume on non-enhanced CT-scans.\textsuperscript{23} In agreement with others, we found that most conventional cardiovascular risk factors are associated with the amount of epicardial fat.\textsuperscript{6,7} Also our finding that systolic and diastolic blood pressures were not associated with epicardial fat volume has been shown before from a population-based perspective.\textsuperscript{6}
In our study, we applied the definition as proposed by Iacobellis et al. interchangeably used, which may hamper the comparison of results. Several potential limitations of our study should also be addressed. First, the definition of epicardial fat which is used in the literature is a matter of debate. Especially, pericardial fat and epicardial fat are interchangeably used, which may hamper the comparison of results. In our study, we applied the definition as proposed by Iacobellis et al. Secondly, we were not able to measure the complete atherosclerotic plaque with non-enhanced CT. Nonetheless, there is strong evidence from autopsy studies that CT-based calcification quantification provides a sensitive and reliable marker of the total underlying atherosclerotic burden. Finally, we did not have information on renal function as a possible confounder of the relationship between epicardial fat volume and atherosclerosis. We found a strong association between the amount of epicardial fat and larger volumes of coronary artery calcification, which was independent of conventional cardiovascular risk factors. This relationship was stronger in males than in females, but tests for effect modification by sex were non-significant. The relationship between epicardial fat volume and the amount of coronary artery calcification has been extensively demonstrated previously and has been postulated to be due to the production of inflammatory factors by epicardial fat, directly influencing the formation of atherosclerotic plaques in the coronary arteries.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Cardiovascular risk factors and epicardial fat volume</th>
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<tbody>
<tr>
<td><strong>Difference in epicardial fat volume</strong></td>
<td><strong>Regression coefficients (95% CI)</strong></td>
</tr>
<tr>
<td><strong>Model 1</strong></td>
<td><strong>P</strong></td>
</tr>
<tr>
<td>Age, 10 years</td>
<td>0.07 (0.05; 0.09)</td>
</tr>
<tr>
<td>Sex, male</td>
<td>0.30 (0.27; 0.32)</td>
</tr>
<tr>
<td>Waist circumference, 10 cm</td>
<td>0.20 (0.20; 0.21)</td>
</tr>
<tr>
<td>Systolic blood pressure, 10 mmHg</td>
<td>0.02 (0.01; 0.02)</td>
</tr>
<tr>
<td>Diastolic blood pressure, 10 mmHg</td>
<td>0.02 (0.01; 0.04)</td>
</tr>
<tr>
<td>Use of blood pressure-lowering medication</td>
<td>0.02 (0.01; 0.03)</td>
</tr>
<tr>
<td>Serum total cholesterol, 10 mmol/L</td>
<td>−0.11 (−0.26; 0.03)</td>
</tr>
<tr>
<td>Serum HDL cholesterol, 10 mmol/L</td>
<td>−2.37 (−2.73; −2.02)</td>
</tr>
<tr>
<td>Use of lipid-lowering medication</td>
<td>0.12 (0.09; 0.15)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.16 (0.12; 0.20)</td>
</tr>
<tr>
<td>Past and current smokers</td>
<td>0.09 (0.06; 0.13)</td>
</tr>
</tbody>
</table>

Model 1: Adjusted for age and sex; Model 2: Additionally adjusted for waist circumference, systolic blood pressure, diastolic blood pressure, use of blood pressure-lowering medication, serum total cholesterol, serum HDL cholesterol, use of lipid-lowering medication, diabetes, and smoking status.

HDL: high-density lipoprotein.

*ln(epicardial fat volume in mL).

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Epicardial fat volume and atherosclerotic calcification in multiple vessel beds</th>
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</thead>
<tbody>
<tr>
<td><strong>Epicardial fat volume</strong></td>
<td><strong>Coronary artery calcification</strong></td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td><strong>Model 1, per SD increase</strong></td>
</tr>
<tr>
<td>Model 1, per SD increase</td>
<td>0.18 (0.11; 0.22)</td>
</tr>
<tr>
<td>Model 2, per SD increase</td>
<td>0.12 (0.04; 0.19)</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td><strong>Model 1, per SD increase</strong></td>
</tr>
<tr>
<td>Model 1, per SD increase</td>
<td>0.14 (0.08; 0.20)</td>
</tr>
<tr>
<td>Model 2, per SD increase</td>
<td>0.06 (−0.01; 0.14)</td>
</tr>
</tbody>
</table>

Values represent differences in standardized calcification volumes [ln(calcification volume in mm^3 + 1 mm^3)] with 95% confidence intervals in each vessel bed, per standard deviation (SD) increase in epicardial fat volume.

Model 1: Adjusted for age; Model 2: Additionally adjusted for waist circumference, systolic blood pressure, diastolic blood pressure, use of blood pressure-lowering medication, serum total cholesterol, serum HDL cholesterol, use of lipid-lowering medication, diabetes, and smoking status.

*P < 0.05 for interaction by sex.
Interestingly, in males we also found associations between epicardial fat with atherosclerosis in the extracranial and intracranial carotid arteries, of which the first was even independent of cardiovascular risk factors. Although data on this subject are scarce, it was demonstrated that epicardial fat is related to carotid artery atherosclerosis, as measured with carotid ultrasound (intima-media thickness). In these studies, there was no reporting on sex differences. A possible explanation for the distinct differences we found between males and females for the association of epicardial fat and extracranial carotid artery atherosclerosis might lie in plaque composition. Recent evidence suggests that epicardial fat might be more prominently associated with non-calcified plaque components.

Against this background, it is very interesting that for the carotid arteries clear differences in the pattern of plaque composition have been described between the sexes. More specifically, carotid plaques in males tend to contain more non-calcified plaque components such as lipid, intraplaque haemorrhage, or necrotic components, which thus might drive the associations we found.

In line with this, it is likely that we found the relationships of epicardial fat with aortic arch atherosclerosis to be much weaker, because specifically at this location plaques tend to be more calcified and consist of less non-calcified plaque. This also directly points to that there could be slight differences in the location-specific pathophysiology of atherosclerosis. Evidence for such differences comes from findings that although atherosclerosis occurs systematically throughout the arterial system, correlations between atherosclerosis across different vessel beds are only moderate. Moreover, it has been shown that specific risk factors of atherosclerosis contribute differentially to atherosclerosis in different locations. Specifically for the associations with epicardial fat, it might thus be that the formation of atherosclerosis in certain vessels is influenced more by the changes induced by epicardial fat than atherosclerotic changes in other vessel beds and warrants further investigation.

In summary, we found that epicardial fat volume is associated with atherosclerosis at various locations, and that there are distinct sex differences for these associations. Our finding suggests that at least in males, epicardial fat seems to exert a systemic effect on the formation of atherosclerosis in other vessel beds. A possible mechanism underlying this association may be the increased levels of adipocytokines (e.g. resistin, adiponectin). These increased levels of inflammatory factors known to be excreted by epicardial fat possibly also influence the development of atherosclerosis at other locations. Yet, longitudinal research is needed to further disentangle the complex role of epicardial fat in the development of atherosclerosis in multiple locations, with a strong focus on sex differences.

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The dedication, commitment, and contribution of inhabitants, general practitioners, and pharmacists of the Ommoord district to the Rotterdam Study are gratefully acknowledged.

Conflict of interest: None declared.

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Supplementary data

Supplementary data are available at European Heart Journal – Cardiovascular Imaging online.

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**IMAGE FOCUS**

**Migrated venous stent causing severe heart failure: a multimodality imaging approach**

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A 52-year-old male with hypertension and two previous kidney transplants had unscheduled return due to reduced urinary output, lower extremity oedema, ascites, and shortness of breath. During last year, the patient has been followed for recurrent focal segmental glomerulosclerosis complicated with catheter-related superior vena cava obstruction. He underwent successful stenting of the right internal jugular vein (see Supplementary data online, Figure S1).

Laboratory work-up confirmed progressive advanced kidney dysfunction. There was a new incomplete right bundle branch block (Panel A). Previous ECG in Supplementary data online, Figure S2. Chest X-ray demonstrated mild cardiac enlargement (Panel B). Transthoracic echocardiogram revealed the presence of two large metallic mesh tubular structures extending from the right atrium (RA) into the right ventricle across the tricuspid valve (Panels C and D; see Supplementary data online, Videos S1–S3). This resulted in severe tricuspid regurgitation with a triangular-shaped Doppler signal consistent with rapid rise in RA pressure (Panel E). CT confirmed embolization of the previously placed internal jugular vein stent (Panel F) and the patient underwent endovascular retrieval (Panels G and H).

Supplementary data are available at European Heart Journal — Cardiovascular Imaging online.