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RESEARCH LETTER
Cardiovascular Disease

Epicardial fat volume and the risk of cardiometabolic diseases among women and men from the general population

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Epicardial fat is the visceral fat depot located between the visceral pericardium and the myocardium.[1] Increasing evidence points towards a link between larger amounts of epicardial fat and the development of cardiometabolic disorders.[2–4] The contribution of epicardial fat to an unfavourable cardiometabolic risk profile might be due to its endocrine and paracrine effect and its proximity to the heart and the coronary arteries.[5]

Clinical imaging, histological, and several autopsy studies indicate that epicardial fat mass is increased with generalized increases in body fat.[6] Mainly among obese individuals, a strong correlation between the amount of epicardial fat and abdominal visceral adiposity has been reported.[7] While obesity might lead to an increase in visceral adipose tissue deposition in the epicardium, epicardial fat itself could be an important independent contributor to the increased risk for cardiometabolic diseases among obese individuals.[7] Moreover, as fat deposits differentially in women and men,[8] the impact of epicardial fat on cardiometabolic risk might differ between sexes. Hence, we studied the associations of epicardial fat volume (EFV) with incident events of various cardiometabolic outcomes including type 2 diabetes mellitus (T2DM), coronary heart disease (CHD), and stroke among women and men from the large prospective population-based Rotterdam Study.[9,10] We further evaluated the impact of obesity on these associations.

Between 2003 and 2006, 2524 participants from the Rotterdam Study underwent cardiac CT to quantify EFV. Using the cardiac scan, EFV was quantified in millilitres with a fully automatic in-house developed image-analysis tool. This method is capable of segmenting the pericardium and quantifying epicardial fat on non-enhanced cardiac CT. From 2524 participants with available EFV data, 208 were excluded due to image artefacts or segmentation errors or missing data, resulting in a total of 2316 participants (1211 women and 1105 men) included in the current analyses. First, we used Cox proportional hazard models to investigate sex-specific associations between EFV and incident T2DM, CHD, and stroke. Measurements of EFV were used first as a continuous variable per standard deviation (SD). We then created sex-specific EFV tertiles, considering the first tertile as the reference in all analyses. Associations were adjusted for age and traditional cardiometabolic risk factors. To test whether the association of EFV with CHD was modified by the presence of severe

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Table 1 Association of epicardial fat volume with cardio-metabolic diseases among women and men

	Women (*N* = 1211)			Men (*N* = 1105)		
Analyses in the total population of women and men	**HR (95% CI)**			**HR (95% CI)**		
	Continuous	**EFV-tertile 2**	**EFV-tertile 3**	**Continuous**	**EFV-tertile 2**	**EFV-tertile 3**
Type 2 diabetes[a]	**1.45 (1.09, 1.93)**	1.77 (0.86, 3.63)	**2.01 (1.00, 4.20)**	1.12 (0.87, 1.46)	0.86 (0.49, 1.49)	1.20 (0.66, 2.16)
Coronary heart disease[b]	1.22 (0.85, 1.75)	1.47 (0.64, 3.39)	1.51 (0.62, 3.68)	1.30 (0.99, 1.68)	1.27 (0.71, 2.29)	**1.93 (1.05, 3.54)**
Ischaemic stroke[c]	1.02 (0.72, 1.43)	0.82 (0.40, 1.72)	0.92 (0.41, 2.03)	1.04 (0.73, 1.47)	1.02 (0.47, 2.20)	1.27 (0.57, 2.83)

	18.5 < BMI < 30	**BMI ≥ 30**	**18.5 < BMI < 30**	**BMI ≥ 30**
BMI-stratified analyses	**Women**		**Men**	
	HR (95% CI)		**HR (95% CI)**	
Type 2 diabetes[a]	**1.46 (1.04, 2.07)**	**1.89 (1.25, 2.86)**	**1.33 (1.02, 1.74)**	0.84 (0.51, 1.38)
Coronary heart disease[b]	1.02 (0.69, 1.51)	1.73 (0.84, 3.53)	1.26 (0.98, 1.61)	1.51 (0.80, 2.87)
Ischaemic stroke[c]	0.81 (0.58, 1.15)	**2.88 (1.18, 7.05)**	1.04 (0.73, 1.49)	1.95 (0.85, 4.50)

EFV-tertile 1 is the reference. EFV tertiles were <78.11, 78.11–101.46, and >101.46 for women and <104.33, 104.33–139.96, and >139.96 for men. Bold indicates significant results at $P \leq 0.05$. Hazard ratios were adjusted for age, BMI, hypertension, smoking, total and high-density lipoprotein (HDL) cholesterol levels, lipid-lowering medications, prevalent cardiovascular disease,[a] prevalent diabetes,[b,c] and prevalent atrial fibrillation.[c] The included participants for the analyses of each outcome slightly differed, based on the exclusion of individuals with that prevalent condition at baseline. For the analyses of type 2 diabetes mellitus, 1064 women and 951 men were included. For coronary heart disease analyses, we included 1180 women and 1022 men. For ischaemic stroke, 1173 women and 1053 men were included in the analyses. Incident rates (per 1000 person-years) were 11.97 and 16.26 for type 2 diabetes mellitus, 4.24 and 10.88 for coronary heart disease, and 4.35 and 5.45 for stroke for women and men, respectively.
BMI, body mass index; CI, confidence interval; HR, hazard ratio.

coronary calcification, we stratified the analyses based on coronary artery calcification (CAC) scores of 400. We further stratified the analyses based on obesity status (body mass index ≥30 kg/m^2).

The mean (±SD) age was 68.9 (±6.7) years in women and 69.0 (±6.5) years in men. The median (inter-quartile range) for EFV was 90.1 (71.8–110.1) in women and 121.2 (95.9–152.3) in men. During a follow-up period of up to 12 years, 188 (8.1%) participants developed T2DM, 149 (6.4%) suffered from CHD, and 102 (5.4%) suffered an ischaemic stroke. Larger EFV was significantly associated with an increased risk of incident T2DM among women {multivariable adjusted hazard ratio per 1 SD Ln-transformed EFV [95% confidence interval: 1.45 (1.09, 1.93)]} and with incident ischaemic stroke among obese women [2.88 (1.18, 7.05)]. The association between EFV and T2DM diminished after taking into account serum fasting glucose and insulin. Among men, the third EFV tertile was associated with incident CHD, compared to the first tertile [1.93 (1.05, 3.54)] (*Table 1*).

We have previously reported that larger EFV was cross-sectionally associated with a larger burden of CAC in men.[2] In the current analyses, the association between EFV and CHD diminished after taking into account the baseline CAC burden among both women and men. When we stratified the analysis based on the CAC burden, the association of EFV and CHD remained statistically significant only among men with a CAC burden of <400, consisting of 66.2% of the male population in our study.

Although CHD and stroke share common risk factors, differences exist in the magnitude or direction of associations of risk factors with CHD and stroke. In our study, no association between EFV and ischaemic stroke was found among women and men from the general population. The only significant association was between EFV and stroke in obese women.

It has been shown that body fat is independently associated with future cardiovascular events.[11] Compared to non-obese women, the associations of EFV with cardiometabolic outcomes were overall larger among obese women. This might support the hypothesis that epicardial fat might be linked with cardiometabolic events through mechanisms such as obesity. It has been suggested that EFV could be a general marker of a decline in overall health status or compromised immune function. Epicardial fat, which in healthy conditions produces cytokines that nourish the heart, may mediate deleterious effects of obesity and inflammation on the myocardium, representing an important target for therapeutic interventions. This underscores the importance of focusing on simple and effective interventions such as weight loss or other lifestyle changes, particularly among high-risk individuals.[12]

In summary, EFV was independently associated with increased risk for T2DM among women and for CHD among men. Our findings indicate that obesity is associated with a greater impact of epicardial fat on the risk of cardiometabolic disorders, particularly among women.

Data Availability

Rotterdam Study data can be made available to interested researchers upon request. Requests can be directed to data manager Frank J.A. van Rooij (f.vanrooij@erasmusmc.nl) or visit the following website for more information http://www.ergo-onderzoek.nl/wp/contact. We are unable to place data in a public repository due to legal and ethical

restraints. Sharing of individual participant data was not included in the informed consent of the study, and there is potential risk of revealing participants' identities as it is not possible to completely anonymize the data.

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Conflict of interest: The authors have no conflict of interest.

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