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Association of Epicardial Fat With Cardiovascular Risk Factors and Incident Myocardial Infarction in the General Population

The Heinz Nixdorf Recall Study

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Objectives This study sought to determine whether epicardial fat volume predicts coronary events in the general population.

Background Epicardial adipose tissue (EAT) is suggested to promote plaque development in the coronary artery tree.

Methods We quantified EAT volume in participants from the prospective population-based Heinz Nixdorf Recall cohort study free of cardiovascular disease. Incident coronary events were assessed during a follow-up period of 8.0 ± 1.5 years. Multivariable association of EAT with cardiovascular risk factors, coronary artery calcification (CAC), and coronary events was assessed using regression analysis.

Results From the overall 4,093 participants (age 59.4 years, 47% male), 130 subjects developed a fatal or nonfatal coronary event. Incidence of coronary events increased by quartile of EAT (0.9% vs. 4.7% for 1st and 4th quartile, respectively, $p < 0.001$). Doubling of EAT was associated with a 1.5-fold risk of coronary events when adjusting for cardiovascular risk factors (hazard ratio [HR] [95% confidence interval (CI)]: 1.54 [1.09 to 2.19]), which remained unaltered after further adjustment for CAC score (HR [95% CI]: 1.50 [1.07 to 2.11]). For discrimination of subjects with events from those without, we observed a trend for improvement of Harrell's C and explained variance by EAT over traditional cardiovascular risk factors, which, however, did not reach statistical significance (0.720 to 0.730 for risk factors alone and with EAT added, respectively, $p = 0.10$, $R^2 = 2.73\%$ to $R^2 = 2.92\%$, time-dependent integrated discrimination improvement = 0.196%).

Conclusions Epicardial fat is associated with fatal and nonfatal coronary events in the general population independent of traditional cardiovascular risk factors and complements information from cardiac computed tomography above the CAC score. (J Am Coll Cardiol 2013;61:1388–95) © 2013 by the American College of Cardiology Foundation

Epicardial adipose tissue (EAT) is a visceral adipose tissue surrounding the heart and the coronary arteries. Because of its endocrine and paracrine activity, secreting pro-inflammatory and anti-inflammatory cytokines and chemokines, it has been suggested to influence coronary atherosclerosis development (1–5). EAT is associated with cardiovascular risk factors (6,7), coronary atherosclerosis (8–10), and prevalent coronary artery disease (11–13). In addition, a case-control study, drawn from the MESA (Multi-Ethnic Study of Atherosclerosis), suggested a role of increased EAT volume for coronary event manifestation (14). However, to date, large-population–based longitudinal data on the prognostic value of EAT fat for prediction of hard coronary events are lacking.

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Cardiac computed tomography (CT) imaging of the heart is the gold standard for EAT quantification with non-contrast enhanced cardiac CT enabling risk assessment through coronary artery calcification (CAC) quantification

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(15–17). However, because EAT is associated with coronary atherosclerosis, implications of EAT on risk assessment above CAC remains unknown.

Therefore, the aim of the present study was to determine the association of epicardial fat volume with incident fatal and nonfatal coronary events in the population-based cohort of the Heinz Nixdorf Recall study. Furthermore, we aimed to investigate whether or not a potential prognostic value of EAT is independent of CAC.

Methods

Study cohort. The Heinz Nixdorf Recall study is a population-based prospective cohort study, designed to assess the predictive value of novel markers for risk stratification in addition to traditional cardiovascular risk factors. The participants (age 45 to 75 years) were randomly selected from mandatory lists of residence from the 3 adjacent cities of Bochum, Essen, and Mülheim, and enrolled between 2000 and 2003. Details for recruitment and study design have been previously published (15,18). Overall response rate was 56%. For this analysis, we excluded subjects with known coronary artery disease, history of myocardial infarction, or history of open heart surgery (including bypass and valve surgery) at baseline. All participants provided written informed consent, and the study was approved by the institutional ethics committee.

Cardiovascular risk factor assessment. Traditional cardiovascular risk factors were measured at baseline, with details being previously published (19). Waist circumference was measured at the leanest circumference between the costal arch and the iliac crest. Standardized enzymatic methods were used to determine serum total cholesterol level, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol. Diabetes was defined as a history of diabetes, being on medical treatment for diabetes, or having blood glucose levels as previously published (20). Smoking history was classified in current and former smokers, as well as in patients with no history of smoking, assessed by computer-assisted interview (21).

Cardiac CT. As part of the study, subjects underwent cardiac CT for quantification of artery CAC. Electron beam CT scans were performed utilizing a C-100 or C-150 scanner (GE Imatron, South San Francisco, California) without the use of contrast media. Imaging was prospectively triggered at 80% of the RR interval, and contiguous 3-mm-thick slices from the right pulmonary artery to the apex of the heart were obtained at an image acquisition time of 100 ms. CAC was defined as a focus of at least 4 contiguous pixels with a CT density >130 Hounsfield units (HU) and quantified using the Agatston method (22).

Epicardial fat volume quantification. Epicardial fat volume was assessed using a dedicated workstation. The pericardium was manually traced from the right pulmonary artery to the diaphragm to determine a region of interest. Within the region of interest, fat was defined as pixels within a window of −195 to −45 HU and a window center of −120 HU. Overall, only pixels with Hounsfield units equivalent to fat within the pericardial sac were counted as epicardial adipose tissue. Reproducibility was excellent (intraclass correlation coefficient = 0.988, $p < 0.0001$, for interobserver and intraclass correlation coefficient = 0.996, $p < 0.0001$, for intraobserver variability). Details of EAT quantification have been previously described in detail (8). In addition to overall epicardial fat volume, we determined the pericoronary fat area of each of the 3 coronary vessels in a subgroup of participants that received initial revascularization of a single coronary artery for acute treatment of the coronary event. Therefore, the area of the epicardial fat around the coronary artery in the middle of the proximal segment was quantified by manual delineation after 3-dimensional reconstruction of an image perpendicular to the coronary vessel.

Abbreviations and Acronyms

CAC = coronary artery calcification
CHD = coronary heart disease
CI = confidence interval
CT = computed tomography
EAT = epicardial adipose tissue
HDL = high-density lipoprotein
HR = hazard ratio
LDL = low-density lipoprotein

Follow-up and endpoint definition. Primary endpoints were defined as incident coronary events that met predefined study criteria as previously described (18). In brief, questionnaires on the current state of health including questions about current medications, hospital admissions, and outpatient diagnosis of cardiovascular disease were annually sent to the participants. In parallel, all death certificates were regularly screened. Incident cardiovascular morbidity and fatal events were validated by review of hospital records and records of the attending physicians, and classified by an external endpoint committee, blinded to the risk factor status and the CAC score. Myocardial infarction was defined based on symptoms, electrocardiographic signs, and enzymes (levels of creatine kinase, as well as troponin T or I), and necropsy as: 1) nonfatal acute myocardial infarction; and 2) coronary death.

Statistical analysis. Continuous variables are reported as mean ± SD or median (interquartile range). Discrete variables are given in frequency and percent. Distribution of cardiovascular risk factors was assessed per quartiles of EAT. Differences between quartiles of EAT were assessed using trend test (tests for non-zero Spearman correlation). Linear regression analysis was used to investigate the multivariable-adjusted association of EAT with cardiovascular risk factors, including age, sex, waist circumference, systolic blood pressure, hypertensive medication, diabetes, and smoking. Log2(EAT) was used to adjust for right skewness of EAT volume, and regression coefficients were retransformed to demonstrate multiplicative effect sizes on EAT volume related to covariables. Likewise, the association of EAT with CAC was assessed using linear regression