UCLA
UCLA Previously Published Works

Title
Pericardial Fat and the Risk of Heart Failure

Permalink
https://escholarship.org/uc/item/46p4s35n

Journal
Journal of the American College of Cardiology, 77(21)

ISSN
0735-1097

Authors
Kenchaiah, Satish
Ding, Jingzhong
Carr, J Jeffrey
et al.

Publication Date
2021-06-01

DOI
10.1016/j.jacc.2021.04.003

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

Pericardial Fat and the Risk of Heart Failure
BRIEF TITLE: Kenchaiah et al. Pericardial Fat and Heart Failure

Satish Kenchaiah, MD, MPH,[a,b] Jingzhong Ding, PhD,[c] J Jeffrey Carr, MD, MSCE,[d] Matthew Allison, MD, MPH,[e] Mathew J Budoff,[f] MD, Russell P Tracy, PhD,[g] Gregory L Burke, MD, MS,[h] Robyn L McClelland, PhD,[i] Andrew E Arai, MD,[b] David A Bluemke, MD, PhD[j]
From [a]Cardiovascular Institute, Mount Sinai Hospital, Icahn School of Medicine at Mount Sinai, New York, New York (S.K.); [b]Laboratory for Advanced Cardiovascular Imaging, National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland (S.K., A.E.A.); [c]Department of Gerontology and Geriatric Medicine (J.D.), Wake Forest University Health Science, Winston-Salem, North Carolina; [d]Department of Radiology and Radiological Sciences, Vanderbilt University Medical Center, Nashville, Tennessee (J.J.C.); [e]Department of Family Medicine and Public Health, University of California San Diego, La Jolla, California (M.A.); [f]Division of Cardiology, Lundquist Institute at Harbor-UCLA Medical Center, Torrance, California (M.J.B); [g]Department of Pathology and Laboratory Medicine, Larner College of Medicine, University of Vermont, Colchester, Vermont (R.P.T.); [h]Department of Public Health Sciences, Wake Forest University Health Science, Winston-Salem, North Carolina (G.L.B.); [i]Department of Biostatistics, University of Washington, Seattle, Washington (R.L.M); [j]Department of Radiology, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin (D.A.B).

SOURCES OF FUNDING: Supported by contracts 75N92020D00001, HHSN268201500003I, N01-HC-95159, 75N92020D00005, N01-HC-95160, 75N92020D00002, N01-HC-95161, 75N92020D00003, N01-HC-95162, 75N92020D00006, N01-HC-95163, 75N92020D00004, N01-HC-95164, 75N92020D00007, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168 and N01-HC-95169 from the National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH), and by grants UL1-TR-000040, UL1-TR-001079, and UL1-TR-001420 from the National Center for Advancing Translational Sciences (NCATS). Dr. Kenchaiah was partly supported by the intramural research program of the NHLBI, NIH, grant number Z99 HL999999. The funding agencies had no role in the design of the study; collection, management, and interpretation of the data; preparation of the manuscript; or decision to submit the manuscript for publication. The views expressed in this manuscript are those of the authors and do not necessarily represent the official views of the NHLBI, the NIH, or the U.S. Department of Health and Human Services.

DISCLOSURES: None Relevant To This Manuscript.

ADDRESS FOR CORRESPONDENCE: Dr. Satish Kenchaiah, Cardiovascular Institute, Mount Sinai Hospital, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1030, New York, NY 10029-6574. Email: satish.kenchaiah@mountsinai.org.
Telephone number: 646-889-4654, Fax number: 212-731-7328
Twitter: @SatishKenchaiah
Tweet: Elevated pericardial fat increases the risk of heart failure, particularly heart failure with preserved ejection fraction, in both women and men.

ACKNOWLEDGEMENT: We thank all the other investigators, staff, and participants of the Multi-Ethnic Study of Atherosclerosis (MESA) study for their valuable contributions. All participants provided written informed consent for the overall study. Dr. Kenchaiah had unrestricted access to the data, performed statistical analysis, wrote the first and subsequent drafts of the manuscript, obtained critical inputs from all co-authors, and vouches for the completeness and accuracy of the data and analyses.

ABSTRACT

BACKGROUND Obesity is a well-established risk factor for heart failure (HF). However, implications of pericardial fat on incident HF is unclear.

OBJECTIVE To examine the association between pericardial fat volume (PFV) and newly-diagnosed HF.

METHODS We ascertained PFV using cardiac computed tomography in 6785 participants (3584 women and 3201 men) without preexisting cardiovascular disease from Multi-Ethnic Study of Atherosclerosis. We used Cox proportional hazards regression to evaluate PFV as continuous and dichotomous variable, maximizing J-statistic: *(Sensitivity+Specificity–1)*.

RESULTS In 90,686 person-years (median [interquartile range], 15.7 [11.7–16.5] years), 385 (5.7%, 164 women and 221 men) developed newly-diagnosed HF. PFV was lower in women than men (mean±SD, 69±33 cm^3 vs. 92±47 cm^3, $P<0.001$). In multivariable analyses, every 1-SD (42 cm^3) increase in PFV was associated with higher HF risk in women (hazard ratio [HR] 1.44, 95% confidence interval [CI] 1.21–1.71, $P<0.001$) than men (HR 1.13, 95%CI 1.01–1.27, $P=0.03$) (P-for-interaction=0.01). High PFV (≥ 70cm^3 in women; ≥ 120cm^3 in men) conferred 2-fold greater HF risk in women (HR 2.06, 95%CI 1.48–2.87, $P<0.001$) and 53% higher risk in men (HR 1.53, 95%CI 1.13–2.07, $P=0.006$). In sex-stratified analyses, greater HF risk remained robust with additional adjustment for anthropometric obesity indicators ($P \leq 0.008$), abdominal subcutaneous or visceral fat ($P \leq 0.02$) or biomarkers of inflammation and hemodynamic stress ($P<0.001$) and was similar among whites, Blacks, Hispanics, and Chinese (P-for-interaction=0.24). Elevated PFV predominantly augmented risk of HF with preserved ejection fraction (HFpEF, $P<0.001$) rather than reduced (HFrEF, $P=0.31$).

CONCLUSION In our large, community-based, ethnically-diverse, prospective cohort study, pericardial fat was associated with increased risk of HF, particularly HFpEF, in women and men.

CONDENSED ABSTRACT

In a large, community-based, ethnically-diverse, prospective cohort of 45-to-84-year-old participants free of cardiovascular disease at baseline, amount of pericardial fat was lower in women than men. After adjusting for established risk factors of heart failure, elevated pericardial fat doubled the risk of heart failure in women and conferred about a 50% greater risk in men. This association remained statistically significant even after accounting for anthropometric indicators of obesity, abdominal fat depots, or inflammatory biomarkers and a plasma natriuretic peptide. It was not modified by race/ethnicity. High pericardial fat predominantly augmented risk of heart failure with preserved rather than reduced left ventricular ejection fraction.

KEY WORDS adiposity, heart failure, obesity, pericardial fat

ABBREVIATIONS AND ACRONYMS

BMI = body mass index
CT = computed tomography
HF = heart failure
HFmrEF = heart failure with mid-range ejection fraction
HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction
HFuEF = heart failure with unknown ejection fraction
LVEF = left ventricular ejection fraction
MESA = Multi-Ethnic Study of Atherosclerosis
PFV = pericardial fat volume

Obesity, defined using anthropometric indicators such as body-mass index (BMI) and waist circumference, is an established risk factor for heart failure (HF) (1-5). Epicardial fat, located between myocardium and visceral pericardium, has potential cardioprotective effects and cardiotoxic implications mediated by proinflammatory and profibrotic cytokines through vasocrine and paracrine pathways (6-8) and is associated with coronary atherosclerosis (9). Paracardial mediastinal fat, located external to the parietal pericardium and contiguous with perivascular aortic adipose tissue, is an established location of brown adipose tissue (10) and expresses markers of metabolic activity but it has a less certain physiopathological significance from a cardiac standpoint (6-8). Nonetheless, in epidemiologic studies, the composite of epicardial and paracardial fat, termed as pericardial fat, has been correlated with coronary atherosclerotic plaques (11) and associated with incident myocardial infarction (12). However, the evidence linking pericardial fat depot to the occurrence of HF is limited (13). Therefore, we examined the influence of pericardial fat volume (PFV), noninvasively determined using computed tomography (CT), on HF risk in a large, community-based, ethnically diverse, prospective cohort of women and men.

METHODS

STUDY SAMPLE. The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective study of 6814 participants (53% women and 47% men) from four different ethnic groups (38% White, 28% African-American, 22% Hispanic, and 12% Chinese-American) aged 45 to 84 years and without clinical cardiovascular disease (no history of angina, nitroglycerin intake, myocardial infarction, stroke, transient ischemic attack, HF, current atrial fibrillation, or cardiovascular procedures such as angioplasty, coronary artery bypass graft surgery, valve replacement,

pacemaker or defibrillator implantation, or any other surgery of the heart or blood vessels) at baseline who were recruited between July 2000 and August 2002 from six communities in the United States (Baltimore City and Baltimore County, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; Northern Manhattan and the Bronx, New York; and St. Paul, Minnesota) (14). After excluding 3 participants who did not undergo cardiac CT at baseline and 26 participants with suboptimal image quality for PFV measurement, 6785 participants (3584 women and 3201 men) were eligible. Additional 29 participants (0.4% of eligible participants) were excluded due to missing information on newly-diagnosed HF during follow-up. The MESA steering committee approved the research proposal and the Mount Sinai Institutional Review Board determined the study as Not Human Subjects Research because de-identified datasets were used for analyses.

EXPOSURE. We performed cardiac CT scans in axial scan mode using an electron-beam CT scanner (General Electric's Imatron C-150 at Chicago, Los Angeles, and New York field centers) with electrocardiogram-triggered at 80% of the RR interval, exposure time of 100 ms, fixed peak voltage of 130 kVp, fixed tube current of 630mA, and nominal section thickness of 3.0 mm; or a multidetector CT system (General Electric's LightSpeed QXi or Plus or Siemens' Volume Zoom at Baltimore, Forsyth County, and St. Paul field centers) with prospective ECG-triggered at 50% of the RR interval, exposure time of 250-300 ms, fixed peak voltage of 120 kVp and acquired 4 concurrent 2.5-mm slices per cardiac cycle (12,15,16). Three experienced CT analysts measured PFV around the proximal coronary arteries (left main, left anterior descending, left circumflex, and right coronary arteries) on tomographic slices within 15 mm above and 30 mm below the superior extent of left main coronary artery with anterior border of

the volume defined by the chest wall and posterior border by aorta and bronchus (16). We used General Electric's volume analysis software in Advantage Workstation for Diagnostic Imaging to manually draw the outer contour of pericardial fat and specified a density range of –190 to –30 Hounsfield units to isolate adipose tissue (**Supplemental Figure S1, Panel A**) (11). We calculated PFV as sum of all voxels containing fat. Our measurement of PFV around proximal coronary arteries was highly reproducible; intraclass correlation coefficient was 0.99 for intra-reader reliability and 0.89 for inter-reader reliability in a random sample of 80 MESA participants (16).

COVARIATES. We used standard questionnaires to collect information on demographic variables, medical history and medication use performed physical examination, and obtained blood samples to measure biomarkers (**Table 1**). Measurement and definition of baseline covariates, abdominal subcutaneous and visceral fat areas at the level of L4/L5 intervertebral disc space in a 30% random sample of MESA participants as part of Abdominal Body Composition ancillary study (**Supplemental Figure S1, Panel B**), and interim myocardial infarction are shown in **Supplemental Table S1**.

OUTCOME. The MESA participants are contacted annually for development of cardiovascular outcomes and death. At least two physicians who were blinded to exposure status independently reviewed medical records to ascertain HF diagnosis. Disagreements in adjudication of HF between two reviewers were resolved by third physician reviewer or, if required, by Endpoint Committee as a whole.

We classified HF as probable, definite, or absent. Probable HF required HF symptoms such as shortness of breath or signs such as edema and HF diagnosed by a physician and patient

receiving medical treatment for HF. Definite HF required all features of probable HF and one or more other criteria, such as pulmonary edema/congestion by chest radiography; dilated ventricle or poor left ventricular function by echocardiography or ventriculography; or evidence of left ventricular diastolic dysfunction. We considered participants not meeting any criteria, including just a physician diagnosis of HF without any other evidence, as having no HF.

We used information on left ventricular ejection fraction (LVEF) ascertained at or after HF diagnosis and categorized newly-diagnosed HF as HF with preserved EF (HFpEF, LVEF ≥ 50%), HF with mid-range EF (HFmrEF, LVEF >40% but <50%), and HF with reduced EF (HFrEF, LVEF ≤ 40%) (17,18). We considered newly-diagnosed HF without information on LVEF as HF with unknown EF (HFuEF).

STATISTICAL ANALYSIS. We summarized distribution of PFV using mean±standard deviation (SD), median, and range. In primary analyses, we defined HF as probable or definite HF. We conducted receiver operating curve analyses and categorized PFV as normal or high by means of sex-specific optimal cut-off value determined using Youden's statistic (19): $J = (Sensitivity + Specificity - 1)$. We calculated means±SD for continuous and proportions (expressed as percentage) for categorical variables. We compared distribution of baseline variables between PFV categories using t-test for continuous and chi-square test for categorical variables. We used Kaplan-Meier estimation method to construct cumulative incidence curves for HF according to PFV categories in women and men and compared cumulative incidence of HF between groups using log-rank test. We examined shape of association between PFV and newly-diagnosed HF using semiparametric generalized additive models to detect nonlinearity by fitting smoothing splines for PFV with 5 degrees of freedom (1 for linear portion of fit and 4 for

nonlinear spline portion) and specified binomial distribution, logit link function, generalized cross validation smoothing parameter, and alpha of 0.05 as model options. Further, we examined Cox proportional hazards regression models with both linear and transformed PFV terms (logarithm, square root, cube root, quadratic, or cubic) to HF risk. Thereafter, we evaluated PFV as continuous (per SD increase) and categorical variables (normal vs. high). To avoid underestimation of true hazards and to provide insight into attenuating influence of intermediary variables, we considered covariates as likely or not likely in causal pathway based on *a priori* hypothesis. We constructed sex-specific and sex-stratified models adjusted for (a) age (per year increase), (b) age, race (white [referent], Black, Hispanic, Chinese), cigarette smoking (no [referent], past, current), alcohol consumption (no or past [referent], mild-to-moderate, heavy), and vigorous physical activity at baseline (potential confounders not likely in causal pathway), (c) all above covariates and hypertension, diabetes mellitus, and dyslipidemia at baseline and interim myocardial infarction as a time-dependent covariate during follow-up (variables likely in causal pathway). We assessed for correlation between PFV and anthropometric indicators of obesity such as BMI, waist circumference, hip circumference, and waist-to-hip ratio in overall sample using Pearson rank correlation and examined hierarchical statistical models with each anthropometric indicator of obesity included as a covariate.

In secondary analyses, we examined the correlation between PFV and estimates of abdominal subcutaneous and visceral fat areas, at the level of L4/L5 intervertebral disc space and individually included these covariates in multivariable models to examine their impact on the association between PFV and incident HF. Similarly, to determine influence of biomarkers of inflammation (C-reactive protein and interleukin-6) and hemodynamic stress (N-terminal pro-B-type natriuretic peptide) on association between PFV and incident HF, we included these

intermediary variables in multivariable models. To assess for effect modification of association between PFV and newly-diagnosed HF by baseline covariates, we introduced interaction terms in sex-stratified and fully-adjusted models and conducted subgroup analyses stratified by covariate levels of interest. To examine association between PFV and HF subtypes, we constructed cumulative incidence curves for each HF subtype according to high and normal PFV categories and compared difference between groups using log-rank test. We performed sex-stratified and age-adjusted, partially-adjusted, and fully-adjusted Cox analyses to examine association between PFV and incidence of individual subtype of HF where follow-up on other categories of HF were censored at time of onset.

In supplementary analyses, to examine competing influence of all-cause death on HF occurrence, we constructed cumulative incidence curves of all-cause death using Kaplan-Meier estimation methods according to normal and high PFV categories, estimated cumulative incidence rates of HF in normal and high PFV groups using Kaplan-Meier-like method where all-cause death was coded as a competing event, and compared two cumulative incidence functions using nonparametric Gray's test for equality (20) and two subdistribution hazard functions using parametric multivariable Fine-and-Gray's models (21). We adopted a similar approach to account for competing risk of all-cause death on HF subtypes. For example, in models evaluating PFV and newly-diagnosed HFpEF risk, we considered other HF subtypes and all-cause death as competing events. To determine public health impact of high PFV, we calculated population attributable risk (PAR) for HF using proportion of cases exposed to high PFV (pd) and relative risk (RR) from fully-adjusted models as (22): $PAR = pd([RR-1]/RR)\,x\,100$. Lastly, we examined association between PFV and definite HF

only using same statistical approach detailed above but with participants censored at time of onset of probable but not definite HF.

We computed relative risks, 95 percent confidence intervals (CI), and two-tailed p-values. We conducted all analyses using SAS software version 9.4 (SAS Institute).

RESULTS

In overall study sample of 6785 individuals, mean±SD of PFV was 80±42 cm^3, median 71 cm^3, and range 7–405 cm^3. Women had lesser amount of PFV than men (mean±SD, 69±33 cm^3 vs. 92±47 cm^3, P<0.001) (**Supplemental Figure S2**). During 90,686 person-years of follow-up (mean±SD, 13.4±4.6 years; median [interquartile range], 15.7 [11.7–16.5] years; maximum 17.5 years), 383 participants (5.7%, 164 women and 221 men) developed newly-diagnosed HF. Optimal cut-off value (Youden's index) to dichotomize PFV as normal or high was 69.8 cm^3 (rounded to 70 cm^3) in women and 120.6 cm^3 (rounded to 120 cm^3) for men (**Supplemental Figure S3**).

BASELINE CHARACTERISTICS. In both sexes, participants with high PFV were older, had higher BMI, waist circumference, hip circumference, and waist-to-hip ratio, lesser amount of vigorous physical activity, higher prevalence of hypertension, diabetes mellitus and dyslipidemia, and increased levels of biomarkers of inflammation and hemodynamic stress (**Table 1**). A heterogeneity in distribution of race/ethnicity, cigarette smoking, and alcohol consumption was also evident between groups.

PERICARDIAL FAT AND THE RISK OF HEART FAILURE. The cumulative incidence of HF was higher in participants with high compared with normal PFV in both women and men (log-rank-*P*<0.001) (**Central Illustration**). In generalized additive models stratified by sex and adjusted for all baseline covariates in fully-adjusted models, PFV was linearly associated with newly-diagnosed HF (highly significant *P*<0.001 for parametric linear trend and insignificant *P*=0.22 for nonparametric spline component of PFV). In sex-stratified and fully-adjusted Cox models, linear PFV term was highly significant (*P*<0.001) but additional logarithm, square-root,

cube-root, quadratic, or cubic-transformed PFV terms were statistically insignificant ($P \geq 0.11$ for all). Overall, these results were consistent with a positive linear association rather than a nonlinear J-shaped or U-shaped association between PFV and newly-diagnosed HF.

In multivariable Cox models adjusting for age and potential confounders (partially-adjusted models), every 1 SD (42 cm^3) increment in PFV increased HF risk by 68% (95%CI 42%–98%, P<0.001) in women, 24% (95%CI 12%–37%, P<0.001) in men, and 34% (23%–46%, P<0.001) in overall sample (**Table 2, IA, IB, and IC,** respectively). Additional adjustment for variables in causal pathway (fully-adjusted models) decreased hazard ratio from 1.68 to 1.44 in women and 1.24 to 1.13 in men, thus explaining 35% and 46% of elevated risk in women and men, respectively. The association between PFV and HF risk was stronger in women than in men (P-for-interaction=0.01 in fully-adjusted models). Similarly, in fully-adjusted models evaluating PFV as a categorical variable, compared with normal PFV, high PFV was associated with a 2-fold greater risk (95%CI 48%–187%, P<0.001) of HF in women, 53% (95%CI 13%–107%, P=0.006) in men, and 77% (95%CI 42%–120%, P<0.001) in overall sample (**Table 2, Models IIA, IIB, and IIC,** respectively).

INFLUENCE OF ANTHROPOMETRIC INDICATORS OF OBESITY. A weak-to-moderate linear correlation was noted between PFV and BMI (r=0.44, P<0.001), waist circumference (r=0.54, P<0.001), hip circumference (r=0.32, P<0.001), and waist-to-hip ratio (r=0.50, P<0.001). In sex-stratified and age-adjusted, partially-adjusted, or fully-adjusted models where each anthropometric indicator of obesity was individually introduced as a covariate, association between PFV and newly-diagnosed HF remained robust; 95%CIs did not cross line of unity (**Figure 1**). Specifically, in sex-stratified and fully-adjusted models, compared

with normal PFV, high PFV was associated with a hazard ratio of 1.47 (95%CI 1.16–1.88, *P*=0.002) with BMI in model, 1.39 (95%CI 1.09–1.77, *P*=0.008) with waist circumference, 1.54 (95%CI 1.21–1.95, *P*<0.001) with hip circumference, and 1.60 (95%CI 1.28–2.01, *P*<0.001) with waist-to-hip ratio.

INFLUENCE OF ABDOMINAL SUBCUTANEOUS AND VISCERAL FAT. Data on abdominal subcutaneous and visceral fat at the level of L4/L5 intervertebral disc space was available on 1616 (24%) and 1917 (28%) of 6785 participants, respectively, on abdominal CT scans performed at 2.7±0.9 (mean±SD) years from the baseline examination. PFV was poorly correlated with abdominal subcutaneous fat area (r=0.21, *P*<0.001) but moderately correlated with abdominal visceral fat area (r=0.67, *P*<0.001). Incident HF occurred in 93 (5.8%) of 1616 with data on abdominal subcutaneous fat and 112 (5.8%) of 1917 participants with data on abdominal visceral fat. In sex-stratified and age-adjusted, partially-adjusted, and fully-adjusted multivariable models where estimates of abdominal fat depots were individually introduced as covariates, the association between PFV and incident HF remained statistically significant (**Supplemental Figure S4**). Particularly, in sex-stratified and fully-adjusted models, compared with normal PFV, high PFV was associated with a hazard ratio of 1.78 (95%CI 1.13-2.83, *P*=0.014) with abdominal subcutaneous fat area as an additional covariate and 1.73 (95% CI 1.08-2.77, *P*=0.023) with abdominal visceral fat area.

INFLUENCE OF BIOMARKERS OF INFLAMMATION AND HEMODYNAMIC STRESS AS INTERMEDIARY VARIABLES. Information on C-reactive protein, interleukin-6, and N-Terminal-pro-B-type natriuretic peptide was available in 6733 (99.2%), 6593 (97.2%), and 6762 (99.7%) of 6785 participants, respectively, at baseline. Additional

adjustment for these three biomarkers did not substantially change the association between PFV and newly-diagnosed HF; specifically, in sex-stratified and full-adjusted models, hazard ratio was 1.21 (95%CI 1.10–1.33, *P*<0.001) for every 1SD increase in PFV and 1.76 (95%CI 1.40–2.22, *P*<0.001) for high compared with normal PFV.

INTERACTION AND SUBGROUP ANALYSES. The association between PFV and HF risk was not modified by age, race, anthropometric indicators of obesity, vigorous physical activity, cigarette smoking, alcohol consumption, hypertension, diabetes mellitus, or dyslipidemia at baseline (*P*-for-interaction ≥ .10 for all) (**Figure 2**).

PERICARDIAL FAT AND THE RISK OF HEART FAILURE SUBTYPES. Information on LVEF was available in 356 of 385 participants (92.5%) who developed newly-diagnosed HF. In overall sample comprising 6756 individuals, 167 (2.5%) developed HFpEF, 38 (0.6%) HFmrEF, 151 (2.2%) HFrEF, and 29 (0.4%) HFuEF. High PFV compared with normal PFV was associated with a higher cumulative incidence of HFpEF (log-rank-P<0.001), HFmrEF (log-rank-*P*=0.002), and HFuEF (log-rank-*P*=0.001) but not HFrEF (log-rank-*P*=0.10) (**Figure 3**). In sex-stratified and fully-adjusted analyses, every 1 SD (42 cm^3) increase in PFV was associated with a 42% greater risk of HFpEF (*P*<0.001) and high PFV compared with normal PFV conferred a 2.3-fold greater risk of HFpEF (*P*<0.001) (**Table 3 Models IA and IB**). However, association between elevated PFV and risk of HFrEF did not reach statistical significance in partially-adjusted models (*P*=0.06) and was further attenuated on additional adjustment for variables in causal pathway (*P* ≥ 0.31) (**Table 3 Models IIA and IIB**). Of note, despite small numbers of HFmrEF and HFuEF, high PFV compared with normal PFV was modestly or

borderline associated with over a 2-fold greater risk of HFmrEF and HFuEF ($P \leq 0.02$ in partially-adjusted models and ≤ 0.05 in fully-adjusted models) (**Table 3 Models III and IV**).

COMPETING RISK ANALYSES. During follow up, death due to all causes occurred in 1547 individuals (689 women and 858 men). The cumulative incidence of all-cause death was higher in participants with high compared with normal PFV in both sexes (log-rank-P<0.001) (**Supplemental Figure S5**). The cumulative incidence of HF with all-cause death as a competing event was greater among high compared with normal PFV in both women and men (Gray's P<0.001) and subdistributional hazards of HF were greater in high vs. normal PFV in fully-adjusted Fine-and-Gray models in both sexes (P<0.001). Elevated PFV was significantly associated with newly-diagnosed HFpEF after accounting for competing risk of other HF subtypes and all-cause death (P<0.001 in Gray's test and P<0.001 in sex-stratified and fully-adjusted Fine-and-Gray models). In similar models, elevated PFV was borderline associated with HFmrEF (Gray's P=0.005, Fine-and-Gray's P=0.05) but not with newly-diagnosed HFrEF (Gray's P=0.20 and Fine-and-Gray's P=0.42) or HFuEF (Gray's P=0.002, Fine-and-Gray's P=0.10).

POPULATION ATTRIBUTABLE RISK. Among MESA participants, HF risk attributable to high PFV was 21% (95%CI 14%–27%) in overall sample. It was higher in women (33%, 95%CI 21%–42%) than men (13%, 95%CI 4%–19%).

PERICARDIAL FAT AND THE RISK OF DEFINITE HEART FAILURE. Of 382 participants with probable or definite HF, 291 participants (76%, 126 women and 165 men) met criteria for definite HF. All analyses using this more stringent HF criteria did not materially alter association between PFV and newly-diagnosed HF. For instance, in sex-stratified and fully

adjusted models, hazard ratio for definite HF was 1.20 (95%CI 1.08–1.33, $P<0.001$) for every 1SD (42 cm^3) increase in PFV and 1.68 (95%CI 1.30–2.15, $P<0.001$) for high compared with normal PFV.

DISCUSSION

PRINCIPAL FINDINGS. In our large, community-based, ethnically-diverse, prospective cohort of 45-to-84-year-old participants free of cardiovascular disease at baseline, higher PFV was associated with greater HF risk in both women and men. Increasing amount of PFV was associated with a linear increase in HF risk without evidence of a threshold. Although amount of PFV was lower in women than in men, relative risk of newly-diagnosed HF associated with elevated PFV was higher in women than in men. Hypertension, diabetes mellitus, dyslipidemia, and interim myocardial infarction explained about one-third of association between PFV and newly-diagnosed HF in women and almost one-half in men. High, compared with normal, PFV doubled HF risk in women and conferred about a 50% greater risk in men. Although PFV was weakly-to-moderately correlated with anthropometric indicators of obesity and abdominal visceral fat area, association between PFV and newly-diagnosed HF remained robust when accounting for these variables in multivariable statistical models. Effect of PFV on occurrence of HF was not attenuated by biomarkers of inflammation and hemodynamic stress, or modified by race/ethnicity. Proportion of all cases of HF that is attributable to high PFV among MESA participants was 32% in women, 13% in men, and 21% in overall sample.

Elevated PFV was strongly associated with newly-diagnosed HFpEF and modestly associated with HFmrEF. Absence of statistically significant association between PFV and newly-diagnosed HFrEF in fully-adjusted models should be interpreted in context of reduced number of events in analyses on HF subtypes and attenuation of hazards due to adjustment for variables in causal pathway. Given small number of newly-diagnosed HFmrEF and HFuEF,

multivariable analyses for occurrence of these HF subtypes should be considered as exploratory or hypothesis-generating approaches.

COMPARISON WITH PREVIOUS STUDIES. Sex-based differences in amount of pericardial fat is unclear. One autopsy study of normal hearts has reported that women have lower amount of epicardial fat tissue than men (23); however, other studies have reported greater amount in women (24,25). Women were noted to have thicker epicardial fat tissue on histological specimens from normal hearts (26), but an echocardiographic study showed no significant difference in epicardial fat thickness in the two sexes (27). A prior study showed that pericardial fat but not hepatic fat was associated with cardiovascular events including heart failure (13). However, this study did not quantify risk estimates by considering covariates in or not in causal pathway, assess for sex-based differences in association between PFV and newly-diagnosed HF, or examine implications of PFV on HF subtypes.

MECHANISMS. Excess epicardial fat, perhaps owing to its proximity to myocardium with no fascia separating the two tissues and common blood supply (8), may contribute to myocardial steatosis (fatty degeneration of heart) (28) or extend between myocardial bundles and muscle fibers (adiposity of heart) (29) resulting in myocardial dysfunction. Its association with essential hypertension (30), ventricular hypertrophy (25), diastolic dysfunction (31), and altered hemodynamics (32) may precipitate symptoms and signs of HF (33) and contribute to a distinct obese-HFpEF phenotype (34). Promotion of oxidative stress (35) and pro-inflammatory mediators (36) may predispose to coronary atherosclerosis and cardiomyopathy by paracrine and/or vasocrine pathways (6-8), Its systemic effects include increased susceptibility to insulin resistance (37), diabetes mellitus type 2 (38), and metabolic syndrome (39). Modified secretory

profile of epicardial fat in diabetics may promote cardiomyocyte dysfunction (40). Pericardial fat is correlated with coronary atherosclerotic plaques (11) and obstructive coronary artery disease (41), and is prospectively associated with myocardial infarction (12), a potent risk factor for HF (42).

STRENGTHS. Our study sample was large, community-based, and included similar number of women and men from four different racial/ethnic groups; thus increasing generalizability of results of our investigation. Prospective study design, volumetric measurement of pericardial fat rather than ascertainment of its unidimensional thickness, good reproducibility of exposure measurement, outcome adjudication by physician reviewers and an endpoint committee, application of uniform criteria for HF diagnosis during the course of the study, very little missing information on covariates of interest, long duration of follow up, and multivariable adjustment for potential confounders with close attention to correlated variables, intermediary factors, and competing risk of all-cause death are additional strengths of our investigation.

LIMITATIONS. We acknowledge several limitations. First, our measurement of PFV was limited to heart region encompassing proximal coronary arteries rather than entire extent of heart. This is unlikely to adversely impact overall findings of our study because our measurement of PFV around proximal coronaries was well-correlated with total amount of PFV around heart (correlation coefficient=0.93, $P<0.001$, in a random sample of 10 participants of Diabetes Heart Study) (16). Second, we could not separately quantify epicardial and paracardial fat repositories around the heart because of challenges with adequately delineating the pericardium separating these two fat depots particularly in individuals with lean or normal BMI. However, because epicardial and paracardial fat volumes were highly correlated (Spearman

correlation coefficient=0.92, $P<0.001$, in a random sample of 159 MESA participants) (12), we surmised that composite of these two fat depots, pericardial fat, is an adequate measure for an epidemiological investigation. Our use of this composite variable may have underestimated the magnitude of effect. Third, data on abdominal subcutaneous and visceral fat was available in only 24% and 28%, respectively, of the overall study and that too a few years after the baseline examination. Nonetheless, the presence of a statistically significant association between PFV and incident HF in multivariable analyses accounting for abdominal fat depots even in this relatively small noncontemporary sample lends credence to the possibility that pericardial fat is not just a surrogate for abdominal fat depot but its specific location around the heart may have a causal implication for the development of HF. Fourth, cut-off values to categorize PFV as normal or high in women and men using Youden's *J-statistic* need further validation in other cohort studies. Lastly, exposure to radiation is always a matter of concern in CT-based estimation of PFV. In this regard, non-radiation-based technologies such as echocardiography, *albeit* limited to measurement of pericardial fat thickness, and cardiovascular magnetic resonance imaging for quantification of PFV are good alternatives for future studies.

CONCLUSIONS

In our prospective cohort of middle-aged to elderly participants without clinically apparent cardiovascular disease, greater amount of pericardial fat was associated with a higher HF risk in both women and men and about one-fifth of newly-diagnosed HF (approximately one-third in women and over one-tenth in men) was attributable to high PFV. Excess pericardial fat should be considered as a novel risk factor for HF. Our findings must be replicated in cohorts not as healthy as MESA participants. Future studies are warranted to differentiate the relative contribution of epicardial and paracardial fat depots, particularly given known differences in

their embryological, anatomical, biochemical, biomolecular, and physiopathological profiles (6-8), to HF risk. Effect of lifestyle modification and target therapies to reduce regional fat depot around coronary arteries and heart and, in turn, reduce incidence of HF also need further investigation.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: High pericardial fat volume (≥ 70 cm^3 in women and ≥ 120 cm^3 in men) increases the risk of developing heart failure by approximately 2-fold in women and about 50% in men.

TRANSLATIONAL OUTLOOK: Future studies are warranted to assess this relationship in other cohorts, differentiate the relative contribution of epicardial and paracardial fat depots to the risk of heart failure, examine the impact of lifestyle modification, and evaluate specific therapies that reduce pericardial fat deposition.

REFERENCES

1. Kenchaiah S, Evans JC, Levy D et al. Obesity and the risk of heart failure. N Engl J Med 2002;347:305-13.
2. Kenchaiah S, Gaziano JM, Vasan RS. Impact of obesity on the risk of heart failure and survival after the onset of heart failure. Med Clin North Am 2004;88:1273-94.
3. Lee DS, Massaro JM, Wang TJ et al. Antecedent blood pressure, body mass index, and the risk of incident heart failure in later life. Hypertension 2007;50:869-76.
4. Bahrami H, Bluemke DA, Kronmal R et al. Novel metabolic risk factors for incident heart failure and their relationship with obesity: the MESA (Multi-Ethnic Study of Atherosclerosis) study. J Am Coll Cardiol 2008;51:1775-83.
5. Kenchaiah S, Sesso HD, Gaziano JM. Body mass index and vigorous physical activity and the risk of heart failure among men. Circulation 2009;119:44-52.
6. Rabkin SW. Epicardial fat: properties, function and relationship to obesity. Obes Rev 2007;8:253-61.
7. Sacks HS, Fain JN. Human epicardial adipose tissue: a review. Am Heart J 2007;153:907-17.
8. Iacobellis G. Local and systemic effects of the multifaceted epicardial adipose tissue depot. Nat Rev Endocrinol 2015;11:363-71.
9. Bos D, Shahzad R, van Walsum T et al. Epicardial fat volume is related to atherosclerotic calcification in multiple vessel beds. Eur Heart J Cardiovasc Imaging 2015;16:1264-9.
10. Sacks H, Symonds ME. Anatomical locations of human brown adipose tissue: functional relevance and implications in obesity and type 2 diabetes. Diabetes 2013;62:1783-90.

11. Ding J, Kritchevsky SB, Harris TB et al. The association of pericardial fat with calcified coronary plaque. Obesity (Silver Spring) 2008;16:1914-9.
12. Ding J, Hsu FC, Harris TB 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.
13. Shah RV, Anderson A, Ding J et al. Pericardial, But Not Hepatic, Fat by CT Is Associated With CV Outcomes and Structure: The Multi-Ethnic Study of Atherosclerosis. JACC Cardiovasc Imaging 2017;10:1016-1027.
14. Bild DE, Bluemke DA, Burke GL et al. Multi-Ethnic Study of Atherosclerosis: objectives and design. Am J Epidemiol 2002;156:871-81.
15. Carr JJ, Nelson JC, Wong ND 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.
16. Ding J, Kritchevsky SB, Hsu FC et al. Association between non-subcutaneous adiposity and calcified coronary plaque: a substudy of the Multi-Ethnic Study of Atherosclerosis. Am J Clin Nutr 2008;88:645-50.
17. Yancy CW, Jessup M, Bozkurt B et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2013;128:1810-52.
18. Ponikowski P, Voors AA, Anker SD et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment

of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:891-975.

19. Youden WJ. Index for rating diagnostic tests. Cancer 1950;3:32-5.
20. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 1988;16:1141-53.
21. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496-509.
22. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. Am J Public Health 1998;88:15-9.
23. Shirani J, Berezowski K, Roberts WC. Quantitative measurement of normal and excessive (cor adiposum) subepicardial adipose tissue, its clinical significance, and its effect on electrocardiographic QRS voltage. Am J Cardiol 1995;76:414-8.
24. Reiner L, Mazzoleni A, Rodriguez FL. Statistical analysis of the epicardial fat weight in human hearts. AMA Arch Pathol 1955;60:369-73.
25. Corradi D, Maestri R, Callegari S et al. The ventricular epicardial fat is related to the myocardial mass in normal, ischemic and hypertrophic hearts. Cardiovasc Pathol 2004;13:313-6.
26. Schejbal V. [Epicardial fatty tissue of the right ventricle--morphology, morphometry and functional significance]. Pneumologie 1989;43:490-9.
27. Iacobellis G, Assael F, Ribaudo MC et al. Epicardial fat from echocardiography: a new method for visceral adipose tissue prediction. Obes Res 2003;11:304-10.

28. Laennec RTH. De l'auscultation médiate, ou, Traité du diagnostic des maladies des poumons et du coeur : fondé principalement sur ce nouveau moyen d'exploration. Paris: J.-A. Brosson, et J.-S. Chaudé, 1819.
29. Smith HL, Willius FA. Adiposity of the heart - A clinical and pathologic study of one hundred and thirty-six obese patients. Archives of Internal Medicine 1933;52:911-931.
30. Austys D, Dobrovolskij A, Jablonskiene V, Dobrovolskij V, Valeviciene N, Stukas R. Epicardial Adipose Tissue Accumulation and Essential Hypertension in Non-Obese Adults. Medicina (Kaunas) 2019;55.
31. Iacobellis G, Leonetti F, Singh N, A MS. Relationship of epicardial adipose tissue with atrial dimensions and diastolic function in morbidly obese subjects. Int J Cardiol 2007;115:272-3.
32. Koepp KE, Obokata M, Reddy YNV, Olson TP, Borlaug BA. Hemodynamic and Functional Impact of Epicardial Adipose Tissue in Heart Failure With Preserved Ejection Fraction. JACC Heart Fail 2020;8:657-666.
33. Kawel-Boehm N, Kronmal R, Eng J et al. Left Ventricular Mass at MRI and Long-term Risk of Cardiovascular Events: The Multi-Ethnic Study of Atherosclerosis (MESA). Radiology 2019;293:107-114.
34. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence Supporting the Existence of a Distinct Obese Phenotype of Heart Failure With Preserved Ejection Fraction. Circulation 2017;136:6-19.
35. Salgado-Somoza A, Teijeira-Fernandez E, Fernandez AL, Gonzalez-Juanatey JR, Eiras S. Proteomic analysis of epicardial and subcutaneous adipose tissue reveals differences in proteins involved in oxidative stress. Am J Physiol Heart Circ Physiol 2010;299:H202-9.

36. Mazurek T, Zhang L, Zalewski A et al. Human epicardial adipose tissue is a source of inflammatory mediators. Circulation 2003;108:2460-6.

37. Iacobellis G, Leonetti F. Epicardial adipose tissue and insulin resistance in obese subjects. J Clin Endocrinol Metab 2005;90:6300-2.

38. Li Y, Liu B, Li Y et al. Epicardial fat tissue in patients with diabetes mellitus: a systematic review and meta-analysis. Cardiovasc Diabetol 2019;18:3.

39. Iacobellis G, Ribaudo MC, Assael F et al. Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: a new indicator of cardiovascular risk. J Clin Endocrinol Metab 2003;88:5163-8.

40. Greulich S, Maxhera B, Vandenplas G et al. Secretory products from epicardial adipose tissue of patients with type 2 diabetes mellitus induce cardiomyocyte dysfunction. Circulation 2012;126:2324-34.

41. Zhou J, Chen Y, Zhang Y et al. Epicardial Fat Volume Improves the Prediction of Obstructive Coronary Artery Disease Above Traditional Risk Factors and Coronary Calcium Score. Circ Cardiovasc Imaging 2019;12:e008002.

42. Kannel WB, D'Agostino RB, Silbershatz H, Belanger AJ, Wilson PW, Levy D. Profile for estimating risk of heart failure. Arch Intern Med 1999;159:1197-204.

FIGURE LEGENDS

CENTRAL ILLUSTRATION Cumulative Incidence of Heart Failure by Categories of Pericardial Fat Volume at Baseline.

PFV denotes pericardial fat volume. Vertical bars represent standard errors.

FIGURE 1 Pericardial Fat Volume and the Risk of Heart Failure in Regression Models Including Anthropometric Indicators of Obesity.

* Introduced as a continuous variable in statistical models.

† Race, cigarette smoking, alcohol consumption, and vigorous physical activity at baseline.

‡ Hypertension, diabetes mellitus, and dyslipidemia at baseline and interim myocardial infarction during follow-up.

§ High pericardial fat volume was defined as ≥ 70 cm^3 in women and ≥ 120 cm^3 in men

¶ Hazard ratios are shown on a logarithmic scale. Vertical bars denote 95% confidence intervals.

‖ 'r' denotes correlation co-efficient.

FIGURE 2 Pericardial Fat Volume and the Risk of Heart Failure According to Subgroups.

N denotes number at risk and Py person years.

*All analyses were stratified by sex and adjusted for age, race, cigarette smoking, alcohol consumption, vigorous physical activity, hypertension, diabetes mellitus, and dyslipidemia at baseline and interim myocardial infarction during follow-up.

†Risk estimates were for every 1 SD (42 cm^3) increase in pericardial fat volume. Size of squares are proportional to the number of events in the specified subgroup. Hazard ratios are shown on a logarithmic scale. Horizontal error bars indicate 95% confidence intervals.

FIGURE 3 Cumulative Incidence of Heart Failure Subtypes by Categories of Pericardial Fat Volume at Baseline.

HFpEF denotes heart failure with preserved ejection fraction, HFrEF heart failure with reduced ejection fraction, HFmrEF heart failure with mid-range ejection fraction, HFuEF heart failure with unknown ejection fraction, LVEF left ventricular ejection fraction, and PFV pericardial fat volume. High PFV was defined as ≥ 70 cm^3 in women and ≥ 120 cm^3 in men. Vertical bars represent standard errors. In panels C and D, the inset shows the same data on an enlarged y-axis.

TABLE 1 Baseline Characteristics According to Categories of Pericardial Fat Volume in Women and Men*

Characteristic	Women			Men		
	Normal PFV (N=2130)	High PFV (N=1462)	P value	Normal PFV (N=2483)	High PFV (N=710)	P value
Age, y	60.2 ± 10.2	64.9 ± 9.7	<0.001	61.6 ± 10.3	64.5 ± 9.5	<0.001
Race, No. (%)			<0.001			<0.001
White	796 (37)	664 (39)		885 (36)	370 (52)	
Black	720 (34)	329 (23)		737 (30)	98 (14)	
Hispanic	379 (18)	394 (27)		519 (21)	197 (28)	
Chinese	235 (11)	175 (12)		342 (14)	45 (6)	
Body mass index , kg/m^2†	26.7 ± 5.3	31.7 ± 6.3	<0.001	26.8 ± 3.9	31.4 ± 4.3	<0.001
Lean, No. (%)	913 (43)	172 (12)		832 (34)	27 (4)	
Overweight, No. (%)	737 (35)	478 (33)		1157 (47)	283 (40)	
Obese, No. (%)	480 (23)	812 (56)		494 (20)	400 (56)	
Waist circumference , cm	91.1 ± 13.8	105.9 ± 14.9	<0.001	96.3 ± 10.7	109.7 ± 11.5	<0.001
High, No. (%)‡	1167 (55)	1300 (89)		679 (27)	528 (74)	
Hip circumference, cm	104.1 ± 11.1	112.5 ± 13.6	<0.001	101.8 ± 8.4	109.4 ± 9.4	<0.001
≥ Median (≥ 104 cm)	985 (46)	1044 (71)	<0.001	912 (37)	484 (68)	<0.001
Waist-to-hip ratio	0.87 ± 0.08	0.94 ± 0.07	<0.001	0.95 ± 0.06	1.00 ± 0.06	<0.001
≥ Median (≥ 0.94)	519 (24)	802 (55)	<0.001	1425 (57)	645 (91)	<0.001
Abdominal computed tomography at L4/L5 intervertebral disc space§						
Subcutaneous fat area, cm^2	284 ± 115 (N=513)	348 ± 132 (N=290)	<0.001	218 ± 93 (N=666)	277 ± 106 (N=147)	<0.001
Visceral fat area, cm^2	102 ± 44 (N=567)	175 ± 58 (N=391)	<0.001	146 ± 62 (N=750)	229 ± 69 (N=209)	<0.001
Vigorous physical activity, No. (%)¶	526 (25)	220 (15)	<0.001	1120 (45)	268 (38)	<0.001
Cigarette smoking, No. (%)			0.51			<0.001

No	1267 (60)	847 (58)		1053 (43)	234 (33)	
Past	605 (28)	441 (30)		1044 (42)	386 (54)	
Current	252 (12)	168 (12)		377 (15)	89 (13)	
Alcohol consumption, No. (%)‖			<0.001			0.04
No or past	990 (47)	834 (58)		935 (38)	240 (34)	
Mild to moderate	1028 (49)	559 (39)		1390 (56)	414 (58)	
Heavy	98 (5)	53 (4)		139 (6)	54 (8)	
Blood pressure, mm Hg						
Systolic	123.7 ± 23.0	132.0 ± 22.6	<0.001	124.8 ± 19.3	130.3 ± 18.7	<0.001
Diastolic	68.9 ± 10.3	69.4 ± 9.9	<0.001	74.8 ± 9.4	76.1 ± 9.3	<0.001
Hypertension, No. (%)**	831 (39)	843 (58)	<0.001	975 (39)	392 (55)	<0.001
Diabetes mellitus, No. (%)††	159 (7)	250 (17)	<0.001	304 (12)	143 (20)	<0.001
Dyslipidemia, No. (%)‡‡	704 (33)	753 (52)	<0.001	1299 (52)	486 (68)	<0.001
Biomarkers						
C-reactive protein, mg/L	3.8 ± 5.6	5.7 ± 6.5	<0.001	2.7 ± 5.6	3.7 ± 5.0	<0.001
Interleukin-6, pg/mL	1.4 ± 1.1	2.0 ± 1.3	<0.001	1.4 ± 1.1	1.9 ± 1.4	<0.001
Log-NT-proBNP, pg/mL	4.1 ± 1.0	4.2 ± 1.0	0.004	3.6 ± 1.2	3.7 ± 1.2	0.001

* PFV denotes pericardial fat volume. High PFV value was defined as ≥ 70 cm^3 in women and ≥ 120 cm^3 in men. N denotes number of participants. Plus–minus values are means ± standard deviation. Log-NT-proBNP denotes logarithm-transformed N-Terminal pro-B-type natriuretic peptide. By design, none of the participants had clinically apparent cardiovascular disease at baseline (see text for details).

† The body-mass index was calculated as the weight in kilograms (kg) divided by the square of the height in meters (m^2). The body-mass index was <25 kg/m^2 in lean participants, 25 to 29.9 kg/m^2 in overweight participants, and ≥ 30 kg/m^2 in obese participants.

‡ High waist circumference was defined as >88 cm in women and >102 cm in men.

§ Data on abdominal subcutaneous and visceral fat areas at the level of L4/L5 intervertebral disc space was available on 1616 (24%) and 1917 (28%) of 6785 participants, respectively, on abdominal CT scans performed at 2.7±0.9 (mean±SD) years from the baseline examination.

¶ Vigorous physical activity was considered as present if a participant reported heavy-intensity exercise such as high impact aerobics, fast bicycling, running, jogging, fast swimming, health club machines, judo, kickboxing, and karate every week.

‖ Mild-to-moderate alcohol consumption was defined as up to 1 drink per day in women and up to 2 drinks per day in men; heavy consumption was defined as >1 drink per day in women and >2 drinks per day in men.

** Hypertension was defined as history of treated hypertension or untreated systolic blood pressure of ≥ 140 mm Hg or untreated diastolic blood pressure of ≥ 90 mm Hg.

†† Diabetes mellitus was defined as treatment with insulin or oral hypoglycemic agents or fasting glucose of ≥ 126 mg/dL.

‡‡ Dyslipidemia was defined as current lipid-lowering therapy or abnormal fasting lipid profile (total cholesterol of ≥ 240 mg/dL, LDL cholesterol of ≥ 160 mg/dL, HDL cholesterol of <40 mg/dL, or triglycerides of ≥ 200 mg/dL).

TABLE 2 Cox Proportional Hazards Regression Analyses Evaluating the Association between Pericardial Fat Volume and the Risk of Heart Failure*

	No. of events/ No. at risk (%)	Follow-up, Py (Rate/10,000 Py)	Hazard ratio (95% confidence interval), P Value		
			Age-Adjusted	Partially-Adjusted†	Fully-Adjusted‡
I. PFV as a continuous variable					
(per increment of 1 SD)§					
A. Women	164/3575 (4.6)	48,907 (33.5)	1.68 (1.43-1.98)	1.68 (1.42-1.98)	1.44 (1.21-1.71)
			<0.001	<0.001	<0.001
B. Men	219/3181 (6.9)	41,778 (52.4)	1.25 (1.13-1.38)	1.24 (1.12-1.37)	1.13 (1.01-1.27)
			.0001	<0.001	0.03
C. All (sex-stratified)	383/6756 (5.7)	90,686 (42.2)	1.34 (1.24-1.46)	1.34 (1.23-1.46)	1.22 (1.12-1.34)
			<0.001	<0.001	<0.001
II. PFV as a categorical variable					
A. Women					
Normal PFV	59/2120 (2.8)	30,195 (19.5)	1.00 (referent)	1.00 (referent)	1.00 (referent)
High PFV¶	105/1455 (7.2)	18,713 (56.1)	2.15 (1.56-2.97)	2.15 (1.55-2.99)	2.06 (1.48-2.87)
			<0.001	<0.001	<0.001
B. Men					
Normal PFV	137/2478 (5.5)	32,981 (41.5)	1.00 (referent)	1.00 (referent)	1.00 (referent)
High PFV¶	82/703 (12.0)	8,797 (93.2)	1.89 (1.44-2.49)	1.91 (1.43-2.54)	1.53 (1.13-2.07)
			<0.001	<0.001	0.006
C. All (sex-stratified)					
Normal PFV	196/4598 (4.3)	63,176 (31.0)	1.00 (referent)	1.00 (referent)	1.00 (referent)
High PFV¶	187/2158 (8.7)	27,510 (68.0)	2.00 (1.63-2.46)	2.04 (1.65-2.52)	1.77 (1.42-2.20)
			<0.001	<0.001	<0.001

* Py denotes person-years, PFV pericardial fat volume, and SD standard deviation.

† Adjusted for age (for every one year increase), race (white [referent], Black, Hispanic, Chinese), cigarette smoking (no [referent], past,

current), alcohol consumption (no or past [referent], mild-to-moderate, heavy), and vigorous physical activity at baseline. Excluded 51 participants (31 women and 20 men) comprising 0.8% of 6756 participants (one heart failure event) because of missing information on covariates in the model.

‡ Adjusted for all the above covariates and presence or absence of hypertension, diabetes mellitus, and dyslipidemia at the baseline examination and interim myocardial infarction as a time-dependent variable during follow-up. Excluded 78 participants (46 women and 32 men) comprising 1.2% of 6756 participants (one heart failure event) because of missing information on covariates in the model.

§ 1 SD was 42 cm^3.

¶ High PFV value was ≥ 70 cm^3 in women and ≥ 120 cm^3 in men.

TABLE 3 Pericardial Fat Volume and the Risk of Heart Failure Subtypes in Sex-Stratified Cox Proportional Hazards Regression Models*

	No. of events/ No. at risk (%)	Follow-up, Py (Rate/10,000 Py)	Hazard ratio (95% confidence interval), P Value		
			Age-Adjusted	Partially-Adjusted†	Fully-Adjusted‡
I. HF with preserved EF (LVEF ≥ 50%)					
A. PFV as a continuous variable (per increment of 1 SD)§	167/6756 (2.5%)	90686 (18.4)	1.54 (1.37-1.73) <0.001	1.52 (1.35-1.72) <0.001	1.42 (1.25-1.62) <0.001
B. PFV as a categorical variable					
Normal PFV	71/4598 (1.5%)	63176 (11.2)	1.00 (referent)	1.00 (referent)	1.00 (referent)
High PFV¶	96/2158 (4.4%)	27510 (34.9)	2.57 (1.87-3.53) <0.001	2.55 (1.85-3.53) <0.001	2.32 (1.66-3.23) <0.001
II. HF with reduced EF (LVEF ≤ 40%)					
A. PFV as a continuous variable (per increment of 1 SD)§	151/6756 (2.2%)	90686 (16.7)	1.13 (0.97-1.30) 0.11	1.15 (1.00-1.33) 0.06	1.04 (0.89-1.21) 0.65
B. PFV as a categorical variable					
Normal PFV	96/4598 (2.1%)	63176 (15.2)	1.00 (referent)	1.00 (referent)	1.00 (referent)
High PFV¶	55/2158 (2.5%)	27510 (20.0)	1.33 (0.95-1.87) 0.10	1.40 (0.99-1.99) 0.06	1.20 (0.84-1.73) 0.31
III. HF with mid-range EF (LVEF >40% and <50%)					
A. PFV as a continuous variable (per increment of 1 SD)§	38/6756 (0.6%)	90686 (4.2)	1.41 (1.11-1.81) 0.006	1.44 (1.12-1.85) 0.004	1.25 (0.95-1.65) 0.11
B. PFV as a categorical variable					
Normal PFV	18/4598 (0.4%)	63176 (2.8)	1.00 (referent)	1.00 (referent)	1.00 (referent)
High PFV¶	20/2158 (0.9%)	27510 (7.3)	2.51 (1.30-4.84) .006	2.68 (1.37-5.27) 0.004	2.05 (1.02-4.11) 0.04

IV. HF with unknown EF					
A. PFV as a continuous variable	27/6756 (0.4%)	90686 (3.0)	1.35 (0.99-1.84)	1.23 (0.89-1.70)	1.09 (0.77-1.56)
(per increment of 1 SD)§			0.06	0.21	0.62
B. PFV as a categorical variable					
Normal PFV	11/4598 (0.2%)	63176 (1.7)	1.00 (referent)	1.00 (referent)	1.00 (referent)
High PFV¶	16/2158 (0.7%)	27510 (5.8)	2.91 (1.31-6.45)	2.66 (1.17-6.03)	2.36 (1.01-5.52)
			0.009	0.02	0.05

* Py denotes person-years, HF heart failure, EF ejection fraction, PFV pericardial fat volume, and SD standard deviation.

† Adjusted for age (for every one year increase), race (white [referent], Black, Hispanic, Chinese), cigarette smoking (no [referent], past, current), alcohol consumption (no or past [referent], mild-to-moderate, heavy), and vigorous physical activity at baseline. Excluded 51 participants (31 women and 20 men) comprising 0.8% of 6756 participants (one heart failure event) because of missing information on covariates in the model.

‡ Adjusted for all the above covariates and presence or absence of hypertension, diabetes mellitus, and dyslipidemia at the baseline examination and interim myocardial infarction as a time-dependent variable during follow-up. Excluded 78 participants (46 women and 32 men) comprising 1.2% of 6756 participants (one heart failure event) because of missing information on covariates in the model.

§ 1 SD was 42 cm^3.

¶ High PFV value was $\geq$ 70 cm^3 in women and $\geq$ 120 cm^3 in men.