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## Pericardial Fat and the Risk of Heart Failure

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### Abstract

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

**OBJECTIVES**—This study sought to examine the association between pericardial fat volume (PFV) and newly diagnosed HF.

**METHODS**—This study ascertained PFV using cardiac computed tomography in 6,785 participants (3,584 women and 3,201 men) without pre-existing cardiovascular disease from the MESA (Multi-Ethnic Study of Atherosclerosis). Cox proportional hazards regression was used to

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evaluate PFV as continuous and dichotomous variable, maximizing the J-statistic: (Sensitivity + Specificity – 1).

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

**CONCLUSIONS**—In this large, community-based, ethnically diverse, prospective cohort study, pericardial fat was associated with an increased risk of HF, particularly HF with preserved ejection fraction, 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, the amount of pericardial fat was lower in women than in men. After adjustment for established risk factors of heart failure, excess 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 and/or ethnicity. High pericardial fat predominantly augmented the risk of heart failure with preserved rather than reduced left ventricular ejection fraction.

## Keywords

adipose tissue; adiposity; heart failure; obesity; pericardial fat

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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 the myocardium and the visceral pericardium, has potential cardioprotective effects and cardiotoxic implications mediated by proinflammatory and profibrotic cytokines through paracrine and/or vasocrine 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 epidemiological 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 the risk of HF in a large, community-based, ethnically diverse, prospective cohort of women and men.

## **METHODS**

### **STUDY SAMPLE.**

The MESA (Multi-Ethnic Study of Atherosclerosis) is a prospective study of 6,814 participants (53% women and 47% men) from 4 different ethnic groups (38% White, 28% African American, 22% Hispanic, and 12% Chinese American), ages 45 to 84 years, 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 17, 2000, and August 31, 2002, from 6 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, 6,785 participants (3,584 women and 3,201 men) were eligible. An additional 29 participants (0.4% of eligible participants) were excluded due to missing information on newly diagnosed HF during follow-up.

### **STUDY OVERSIGHT.**

The MESA steering committee approved the research proposal, and the Mount Sinai Institutional Review Board designated the study as Not Human Subjects Research because deidentified datasets were used for analyses. All participants provided written informed consent for the overall study. The first author (S.K.) designed the study, 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.

### **EXPOSURE.**

We performed noncontrast cardiac CT scans using: 1) electron-beam CT (Imatron C-150 [General Electric Healthcare, Milwaukee, Wisconsin] at the Chicago, Los Angeles, and New York field centers) with voltage of 130 kVp, current of 630 mA, exposure time of 100 ms, slice thickness of 3.0 mm, and prospective electrocardiogram triggered at 80% of the RR interval; or 2) multidetector CT (LightSpeed QXi or Plus [General Electric Healthcare, Waukesha, Wisconsin] or Volume Zoom [Siemens Healthineers, Erlangen, Germany] at the Baltimore, Forsyth County, and St. Paul field centers) with voltage of 120 (LightSpeed systems) or 140 (Volume Zoom system) kVp, current of 139 to 400 mA, exposure time of 330 to 520 ms, 4 concurrent 2.5-mm slices per cardiac cycle, and prospective electrocardiogram triggered at 50% of the RR interval with the exception of the LightSpeed

QXi that utilized retrospective gating (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 the left main coronary artery with anterior border of the volume defined by the chest wall and posterior border by the aorta and the bronchus (16). We used volume analysis software in Advantage Workstation for Diagnostic Imaging (General Electric, Waukesha, Wisconsin) 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 1A) (11). We calculated PFV as the sum of all voxels containing fat. Our measurement of PFV around the proximal coronary arteries was highly reproducible; intraclass correlation coefficient was 0.99 for intrareader 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 volumes in a 30% random subsample of MESA participants (Supplemental Figure 1B), and interim myocardial infarction are shown in Supplemental Table 1.

## OUTCOME.

The MESA participants are contacted annually for the development of cardiovascular outcomes and death. At least 2 physicians who were blinded to the exposure status independently reviewed the medical records to ascertain the diagnosis of HF. Disagreements in the adjudication of HF between 2 reviewers were resolved by a third physician reviewer or, if required, by the 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 or 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 the diagnosis of HF and categorized newly diagnosed HF as heart failure with preserved ejection fraction (HFpEF) (LVEF  $\geq 50\%$ ), heart failure with mid-range ejection fraction (HFmrEF) (LVEF  $>40\%$  but  $<50\%$ ), and heart failure with reduced ejection fraction (HFrEF) (LVEF  $<40\%$ ) (17,18). We considered newly diagnosed HF without information on LVEF as heart failure with unknown ejection fraction (HFuEF).

## STATISTICAL ANALYSIS.

We summarized the distribution of PFV using mean  $\pm$  SD, median, interquartile range, 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 cutoff value determined using Youden statistic (19):

$$J = (\text{Sensitivity} + \text{Specificity} - 1)$$

. We calculated means  $\pm$  SD for continuous and proportions (expressed as percentage) for categorical variables. We compared the distribution of baseline variables between PFV categories using Student's ttest 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 the cumulative incidence of HF between groups using the log-rank test. We examined the shape of the 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 the 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. Furthermore, we examined Cox proportional hazards regression models with both linear and transformed PFV terms (logarithm, square root, cube root, quadratic, or cubic) to the risk of HF. 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 the attenuating influence of intermediary variables, we considered covariates as likely or not likely in the causal pathway based on *a priori* hypothesis. We constructed sex-specific and sex-stratified models adjusted for: 1) age (per year increase); 2) 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 the causal pathway); and 3) all above-mentioned covariates and hypertension, diabetes mellitus, and dyslipidemia at baseline and interim myocardial infarction as a time-dependent covariate during follow-up (variables likely in the causal pathway). We assessed for the correlation between PFV and anthropometric indicators of obesity such as BMI, waist circumference, hip circumference, and waist-to-hip ratio in the overall sample and abdominal fat depots such as subcutaneous and visceral fat volumes in the 30% random subsample using Pearson rank correlation and examined hierarchical statistical models with each anthropometric indicator of obesity or volume of abdominal fat depot included as a covariate.

In secondary analyses, to determine the influence of biomarkers of inflammation (C-reactive protein and interleukin 6) and hemodynamic stress (N-terminal pro-B-type natriuretic peptide) on the association between PFV and incident HF, we included these intermediary variables in multivariable models. To assess for the effect modification of the association between PFV and newly diagnosed HF by baseline covariates, we introduced interaction terms in sexstratified and fully adjusted models and conducted subgroup analyses stratified by covariate levels of interest. To examine the association between PFV and HF subtypes, we constructed cumulative incidence curves for each HF subtype according to high and

normal PFV categories and compared the difference between groups using log-rank test. We performed sex-stratified and age-adjusted, partially adjusted, and fully adjusted Cox analyses to examine the association between PFV and incidence of individual subtype of HF where follow-up on other categories of HF were censored at the time of their onset.

In supplementary analyses, to examine the competing influence of all-cause death on the occurrence of HF, we constructed cumulative incidence curves of all-cause death using Kaplan-Meier estimation methods according to normal and high PFV categories, estimated the 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 the 2 cumulative incidence functions using the nonparametric Gray test for equality (20) and the 2 subdistribution hazard functions using the parametric multivariable Fine-and-Gray models (21). We adopted a similar approach to account for the competing risk of all-cause death on HF subtypes. For example, in models evaluating PFV and the risk of newly diagnosed HFpEF, we considered other HF subtypes and all-cause death as competing events. To determine the public health impact of high PFV, we calculated the population attributable risk (PAR) for HF with the use of proportion of cases exposed to high PFV (pd) and relative risk (RR) from fully adjusted models as:

$$\text{PAR} = \text{pd} \left( \frac{\text{RR} - 1}{\text{RR}} \right) \times 100$$

(22) Lastly, we examined the association between PFV and definite HF only using the same statistical approach we have detailed but with participants censored at the time of onset of probable but not definite HF.

We computed relative risks, 95% confidence intervals (CIs), and 2-tailed p values. We conducted all analyses using SAS software version 9.4 (SAS Institute, Cary, North Carolina).

## RESULTS

In the overall study sample of 6,785 individuals, mean PFV was  $80 \pm 42 \text{ cm}^3$ , median was  $71 \text{ cm}^3$ , interquartile range was 49 to  $100 \text{ cm}^3$ , and range was 7 to  $405 \text{ cm}^3$ . Women had lesser amount of PFV than men did ( $69 \pm 33 \text{ cm}^3$  vs.  $92 \pm 47 \text{ cm}^3$ ;  $p < 0.001$ ) (Supplemental Figure 2). During 90,686 person-years of follow-up (mean:  $13.4 \pm 4.6$  years; median: 15.7 years; interquartile range: 11.7 to 16.5 years; maximum: 17.5 years), 383 participants (5.7%, 164 women and 221 men) developed newly diagnosed HF. Optimal cutoff value (Youden index) to dichotomize PFV as normal or high was  $69.8 \text{ cm}^3$  (rounded to  $70 \text{ cm}^3$ ) in women and  $120.6 \text{ cm}^3$  (rounded to  $120 \text{ cm}^3$ ) for men (Supplemental Figure 3).

### 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 the

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 increment ( $42 \text{ cm}^3$ ) in PFV increased the risk of HF by 68% (95% CI: 42% to 98%;  $p < 0.001$ ) in women, 24% (95% CI: 12% to 37%;  $p < 0.001$ ) in men, and 34% (95% CI: 23% to 46%;  $p < 0.001$ ) in the overall sample (Table 2, **models 1A, 1B, and 1C**, respectively). Additional adjustment for variables in the causal pathway (fully adjusted models) decreased the hazard ratio from 1.68 to 1.44 in women and 1.24 to 1.13 in men, thus explaining 35% and 46% of the elevated risk in women and men, respectively. The association between PFV and newly diagnosed HF was stronger in women than in men (interaction  $p = 0.01$  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% to 187%;  $p < 0.001$ ) of HF in women, 53% (95% CI: 13% to 107%;  $p = 0.006$ ) in men, and 77% (95% CI: 42% to 120%;  $p < 0.001$ ) in the overall sample (Table 2, **models 2A, 2B, and 2C**, 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 ( $r = 0.50$ ;  $p < 0.001$ ). High PFV was noted in 10%, 29%, and 55% of lean, overweight, and obese participants, respectively; 11% and 50% of participants with normal and high waist circumference, respectively; 19% and 45% of participants with hip circumference <median and median value (104 cm), respectively; and 21% and 43% of participants with waist-to-hip ratio <median and median value (0.94), respectively. In sex-stratified and age-adjusted, partially adjusted, or fully adjusted models where each anthropometric indicator of obesity was individually introduced as a covariate, the association between PFV and newly diagnosed HF remained robust; 95% CIs did not cross the line of unity (Figure 1). Specifically, in sex-stratified and fully adjusted models, compared with normal PFV, high PFV was associated with hazard ratios of 1.47 (95% CI: 1.16 to 1.88;  $p = 0.002$ ) with BMI in the model, 1.39 (95% CI: 1.09 to 1.77;  $p = 0.008$ ) with waist circumference, 1.54 (95% CI: 1.21 to 1.95;  $p < 0.001$ ) with hip circumference, and 1.60 (95% CI: 1.28 to 2.01;  $p < 0.001$ ) with waist-to-hip ratio.

## INFLUENCE OF ABDOMINAL SUBCUTANEOUS AND VISCERAL FAT.

On abdominal CT scans performed at a mean of  $2.7 \pm 0.9$  years and a median of 3.1 years (interquartile range: 1.6 to 3.4 years) from the baseline examination, data on abdominal subcutaneous and visceral fat volumes were available for 1,616 (24%) and 1,917 (28%) of 6,785 participants, respectively. High PFV was evident in 19% and 36% of participants with abdominal subcutaneous fat volume <median and median value ( $816 \text{ cm}^3$ ), respectively; and 14% and 49% of participants with abdominal visceral fat volume <median and median value ( $455 \text{ cm}^3$ ), respectively. PFV was poorly correlated with abdominal subcutaneous fat volume ( $r = 0.18$ ;  $p < 0.001$ ) but moderately correlated with abdominal visceral fat volume ( $r = 0.65$ ;  $p < 0.001$ ). Newly diagnosed HF occurred in 93 of 1,616 participants (5.8%) with data on abdominal subcutaneous fat and 112 of 1,916 participants (5.8%) with data on abdominal visceral fat (information on HF was missing in 1 participant). In sex-stratified and age-adjusted, partially adjusted, and fully adjusted multivariable models where estimates of abdominal subcutaneous or visceral fat volumes were individually introduced as covariates, the association between PFV and newly diagnosed HF remained statistically significant (Figure 2). Particularly, in sex-stratified and fully adjusted models, compared with normal PFV, high PFV was associated with hazard ratios of 1.76 (95% CI: 1.11 to 2.78;  $p = 0.016$ ) with abdominal subcutaneous fat volume as an additional covariate and 1.68 (95% CI: 1.05 to 2.68;  $p = 0.030$ ) with abdominal visceral fat volume.

## 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 6,733 (99.2%), 6,593 (97.2%), and 6,762 (99.7%) of 6,785 participants, respectively, at baseline. Additional adjustment for these 3 biomarkers did not substantially change the association between PFV and newly diagnosed HF; specifically, in sex-stratified and full-adjusted models, the hazard ratios were 1.21 (95% CI: 1.10 to 1.33;  $p < 0.001$ ) for every 1-SD increase in PFV and 1.76 (95% CI: 1.40 to 2.22;  $p < 0.001$ ) for high compared with normal PFV.

## INTERACTION AND SUBGROUP ANALYSES.

The association between PFV and newly diagnosed HF was not modified by age, race, anthropometric indicators of obesity, vigorous physical activity, cigarette smoking, alcohol consumption, hypertension, diabetes mellitus, or dyslipidemia at baseline (interaction  $p = 0.10$  for all) (Figure 3).

## PERICARDIAL FAT AND THE RISK OF HF SUBTYPES.

Information on LVEF was available in 356 of 385 participants (92.5%) who developed newly diagnosed HF. In the overall sample comprising 6,756 individuals, 167 (2.5%) developed HFpEF, 38 (0.6%) HFmrEF, 151 (2.2%) HFrfEF, and 29 (0.4%) HFuEF. High PFV compared with normal PFV was associated with a higher cumulative incidence of HFpEF (logrank  $p < 0.001$ ), HFmrEF (log-rank  $p = 0.002$ ), and HFuEF (log-rank  $p = 0.001$ ) but not HFrfEF (log-rank  $p = 0.10$ ) (Figure 4). In sex-stratified and fully adjusted analyses, every 1-SD increase ( $42 \text{ cm}^3$ ) 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 1A and 1B**). However, the association between elevated PFV and newly diagnosed HFrEF did not reach statistical significance in partially adjusted models ( $p = 0.06$ ) and was further attenuated on additional adjustment for variables in the causal pathway ( $p = 0.31$ ) (Table 3, **models 2A and 2B**). 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 ( $p = 0.02$  in partially adjusted models and  $p = 0.05$  in fully adjusted models) (Table 3, **models 3 and 4**).

### COMPETING RISK ANALYSES.

During follow-up, death due to all causes occurred in 1,547 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 4). 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  $p < 0.001$ ) and subdistributional hazards of HF were greater in high versus 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 the competing risk of other HF subtypes and all-cause death ( $p < 0.001$  in Gray 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  $p = 0.005$ ; Fine-and-Gray  $p = 0.05$ ) but not with newly diagnosed HFrEF (Gray  $p = 0.20$  and Fine-and-Gray  $p = 0.42$ ) or HFuEF (Gray  $p = 0.002$ ; Fine-and-Gray  $p = 0.10$ ).

### POPULATION ATTRIBUTABLE RISK.

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

### PERICARDIAL FAT AND THE RISK OF DEFINITE HF.

Of the 382 participants with probable or definite HF, 291 participants (76%; 126 women and 165 men) met the criteria for definite HF. All analyses using this more stringent criteria for HF did not materially alter the association between PFV and newly diagnosed HF. For instance, in sex-stratified and fully adjusted models, hazard ratios for definite HF were 1.20 (95% CI: 1.08 to 1.33;  $p < 0.001$ ) for every 1-SD increase ( $42 \text{ cm}^3$ ) in PFV and 1.68 (95% CI: 1.30 to 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 a greater risk of HF in both women and men. Increasing amount of PFV was associated with a linear increase in the risk of HF without evidence of a threshold. Although the amount of PFV was lower in women than in men, the 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 the association between PFV and newly diagnosed HF in women and almost one-half in men. High, compared with normal, PFV doubled the risk of HF 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 volume, the association between PFV and newly diagnosed HF remained robust when accounting for these variables in multivariable statistical models. The effect of PFV on the occurrence of HF was not attenuated by biomarkers of inflammation and hemodynamic stress nor modified by race and/or ethnicity. The 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 the overall sample.

Elevated PFV was strongly associated with newly diagnosed HFpEF and modestly associated with HFmrEF. The absence of a statistically significant association between PFV and newly diagnosed HFfrEF in fully adjusted models should be interpreted in the context of a reduced number of events in analyses on HF subtypes and the attenuation of hazards due to the adjustment for variables in the causal pathway. Given the small number of newly diagnosed HFmrEF and HFuEF, multivariable analyses for the occurrence of these HF subtypes should be considered as exploratory or hypothesis-generating approaches.

#### **COMPARISON WITH PREVIOUS STUDIES.**

Sex-based differences in the amount of pericardial fat are 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 2 sexes (27). A prior study showed that pericardial fat, but not hepatic fat, was associated with cardiovascular events including HF (13). However, this study did not quantify the risk estimates by considering covariates in or not in the causal pathway, assess for sex-based differences in the association between PFV and newly diagnosed HF, or examine the implications of PFV on HF subtypes.

#### **MECHANISMS.**

Excess epicardial fat, perhaps owing to its proximity to the myocardium with no fascia separating the 2 tissues and a common blood supply (8), may contribute to myocardial steatosis (intracellular accumulation of fat; fatty degeneration of the heart) (28) or extend between myocardial bundles and muscle fibers (extracellular infiltration of fat; adiposity of the heart) (29), resulting in myocardial dysfunction. The association of epicardial fat 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 proinflammatory mediators (36) may predispose to coronary atherosclerosis and cardiomyopathy by paracrine and/or vasocrine pathways (6-8). In addition, the systemic effects of epicardial fat 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). Although the distinct role of pericardial mediastinal fat to the development of HF is not well elucidated, pericardial fat (comprising both epicardial and paracardial fat depots) 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).

### STUDY STRENGTHS.

Our study sample was large, community-based, and included similar numbers of women and men from 4 different racial and/or ethnic groups; thus increasing the generalizability of the 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 the diagnosis of HF 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 the competing risk of all-cause death are additional strengths of our investigation.

### STUDY LIMITATIONS.

First, our measurement of PFV was limited to the region of the heart encompassing the proximal coronary arteries rather than the entire extent of the heart. This is unlikely to adversely impact the overall findings of our study because our measurement of PFV around proximal coronaries was well-correlated with the total amount of PFV around the heart (correlation coefficient = 0.93;  $p < 0.001$ , in a random sample of 10 participants of the 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 2 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 the composite of these 2 fat depots, pericardial fat, is an adequate measure for an epidemiological investigation. Our use of this composite variable may have underestimated the magnitude of the effect of epicardial fat on the risk of HF. 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 newly diagnosed HF in multivariable analyses accounting for abdominal fat depots, even in this relatively small representative but noncontemporary sample, lends credence to the possibility that pericardial fat is not just a surrogate for abdominal fat depot, but that its specific location around the heart may have a causal implication for the development of HF. Fourth, cutoff values to categorize PFV as normal or high in women and men using the Youden *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 the 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-age to elderly participants without clinically apparent cardiovascular disease, greater amount of pericardial fat was associated with a higher risk of HF 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 that are not as healthy as MESA participants are. Future studies are warranted to differentiate the relative contribution of epicardial and paracardial fat depots, particularly given known differences in their embryological, anatomic, biochemical, biomolecular, and physiopathological profiles (6-8), to the risk of HF. Effect of lifestyle modification and target therapies to reduce regional fat depot around the coronary arteries and the heart and, in turn, reduce the incidence of HF also need further investigation.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## ABBREVIATIONS AND ACRONYMS

<b>BMI</b>	body mass index
<b>CI</b>	confidence interval
<b>CT</b>	computed tomography
<b>HF</b>	heart failure
<b>HFmrEF</b>	heart failure with mid-range ejection fraction
<b>HFpEF</b>	heart failure with preserved ejection fraction
<b>HFrfEF</b>	heart failure with reduced ejection fraction
<b>HFuEF</b>	heart failure with unknown ejection fraction

<b>LVEF</b>	left ventricular ejection fraction
<b>PFV</b>	pericardial fat volume

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## PERSPECTIVES

### COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

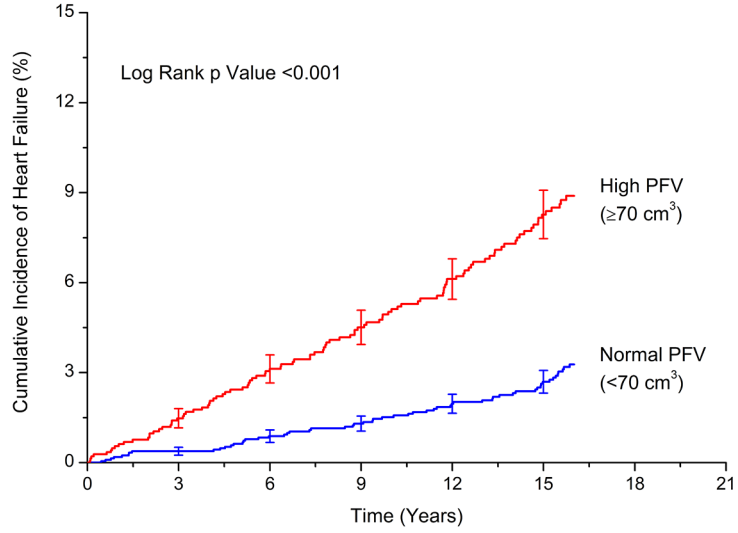
High pericardial fat volume ( 70 cm<sup>3</sup> in women and 120 cm<sup>3</sup> in men) increases the risk of developing heart failure by approximately 2-fold in women and about 50% in men.

### 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.

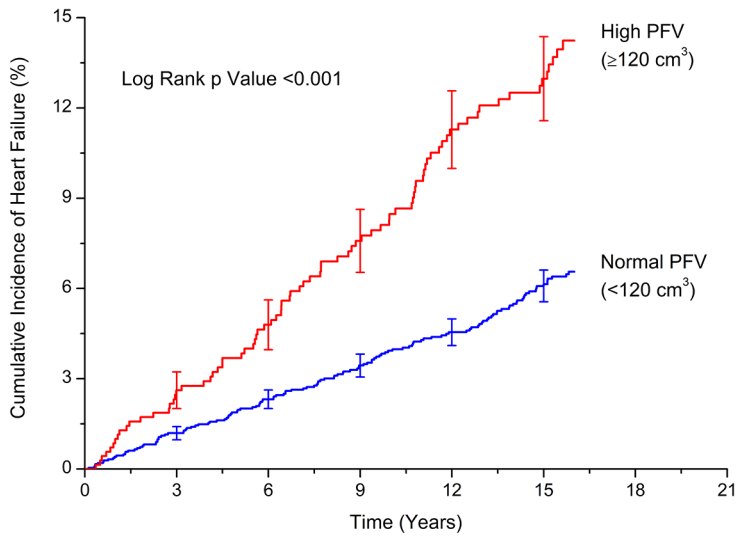


**A. Women**



No. at Risk	0	3	6	9	12	15
Normal PFV	2130	2051	1944	1838	1727	1501
High PFV	1462	1360	1249	1127	1005	812

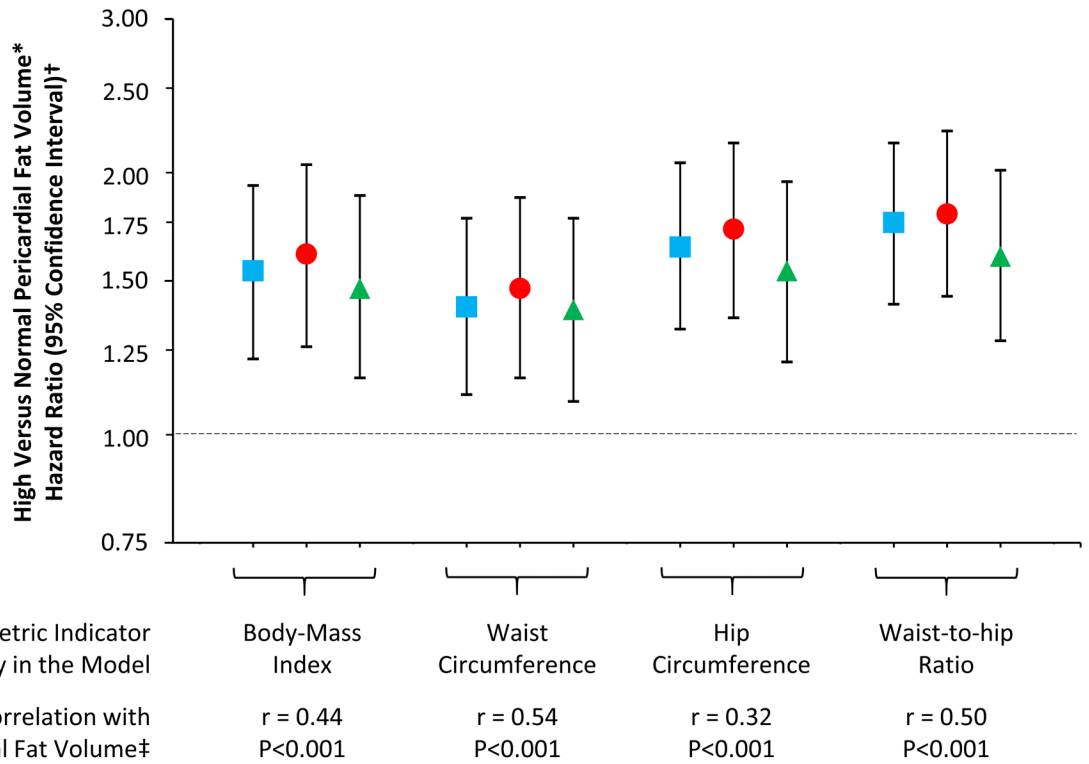
**B. Men**



No. at Risk	0	3	6	9	12	15
Normal PFV	2483	2353	2180	1987	1813	1538
High PFV	710	653	598	530	459	370

**Central Illustration: Cumulative Incidence of Heart Failure by Categories of Pericardial Fat Volume at Baseline**

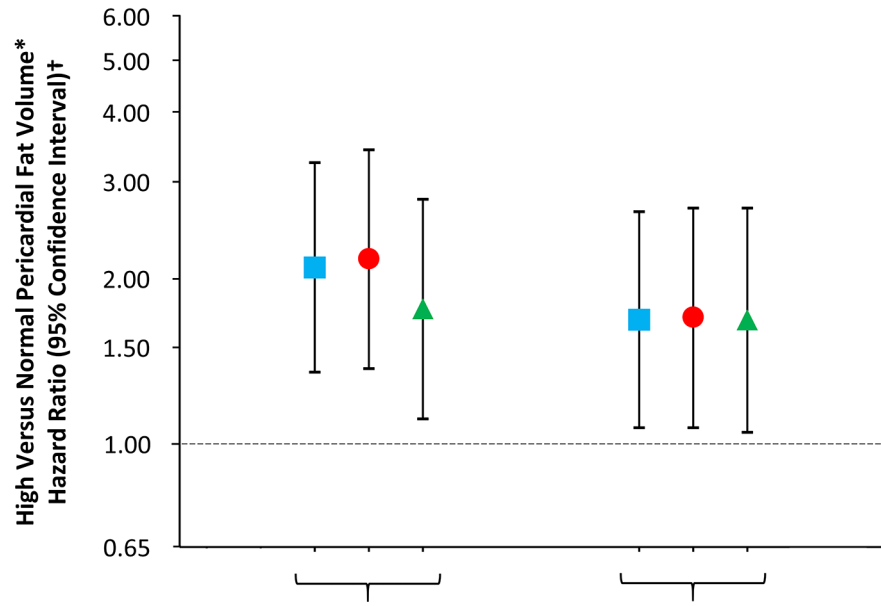
In MESA (Multi-Ethnic Study of Atherosclerosis), newly diagnosed heart failure (HF) occurred more frequently among participants with high compared with normal pericardial fat volume (PFV) in both women (A) and men (B). Vertical bars represent standard errors. Data shown are truncated at 16 years of follow-up.



**All Statistical Models Were Sex-Stratified and Adjusted for an Anthropometric Indicator of Obesity§ and**

- Age
- Age and Other Confounders||
- ▲ Age, Other Confounders, || and Intermediary Variables#

**FIGURE 1. PFV and the Risk of HF Adjusted for Anthropometric Indicators of Obesity**  
 Elevated pericardial fat volume (PFV) was associated with a greater risk of heart failure (HF) after adjustment for anthropometric indicators of obesity in multivariable models. \*High PFV was defined as  $70 \text{ cm}^3$  in women and  $120 \text{ cm}^3$  in men. †Hazard ratios are shown on a logarithmic scale. Vertical bars denote 95% confidence intervals. ‡r denotes correlation coefficient. §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.



Computed Tomographic Estimate in the Model‡	Abdominal Subcutaneous Fat Volume	Abdominal Visceral Fat Volume
Pearson Correlation with PFV§	r = 0.18 P<0.001	r = 0.65 P<0.001
No. of Events/Risk (%)		
Normal PFV	52/1,179 (4.4)	58/1,317 (4.4)
High PFV	41/437 (9.4)	54/599 (9.0)
Py (Rate/10,000 Py)		
Normal PFV	17,037 (30.5)	19,033 (30.5)
High PFV	6,096 (67.3)	8,287 (65.2)

**All Statistical Models were Sex-Stratified and Adjusted for Abdominal Subcutaneous or Visceral Fat Volume|| and**

- Age
- Age and Other Confounders#
- ▲ Age, Other Confounders,# and Intermediary Variables\*\*

**Figure 2. PFV and the Risk of HF Adjusted for Abdominal Fat Depots**

Elevated PFV was associated with a greater risk of HF after adjustment for abdominal fat depots in multivariable models. \*High PFV was defined as 70 cm<sup>3</sup> in women and 120 cm<sup>3</sup> in men. †Hazard ratios are shown on a logarithmic scale. Vertical bars denote 95% confidence intervals. ‡Abdominal subcutaneous and visceral fat volumes were computed from a total of 6 axial slices, 2 adjacent slices each at the level of L2-L3, L3-L4, and L4-L5 intervertebral disc spaces, in 1,616 (24%) and 1,917 (28%) of 6,785 participants, respectively, on abdominal computed tomographic scans performed at 2.7 ± 0.9 years from the baseline examination. §r denotes correlation coefficient. ||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

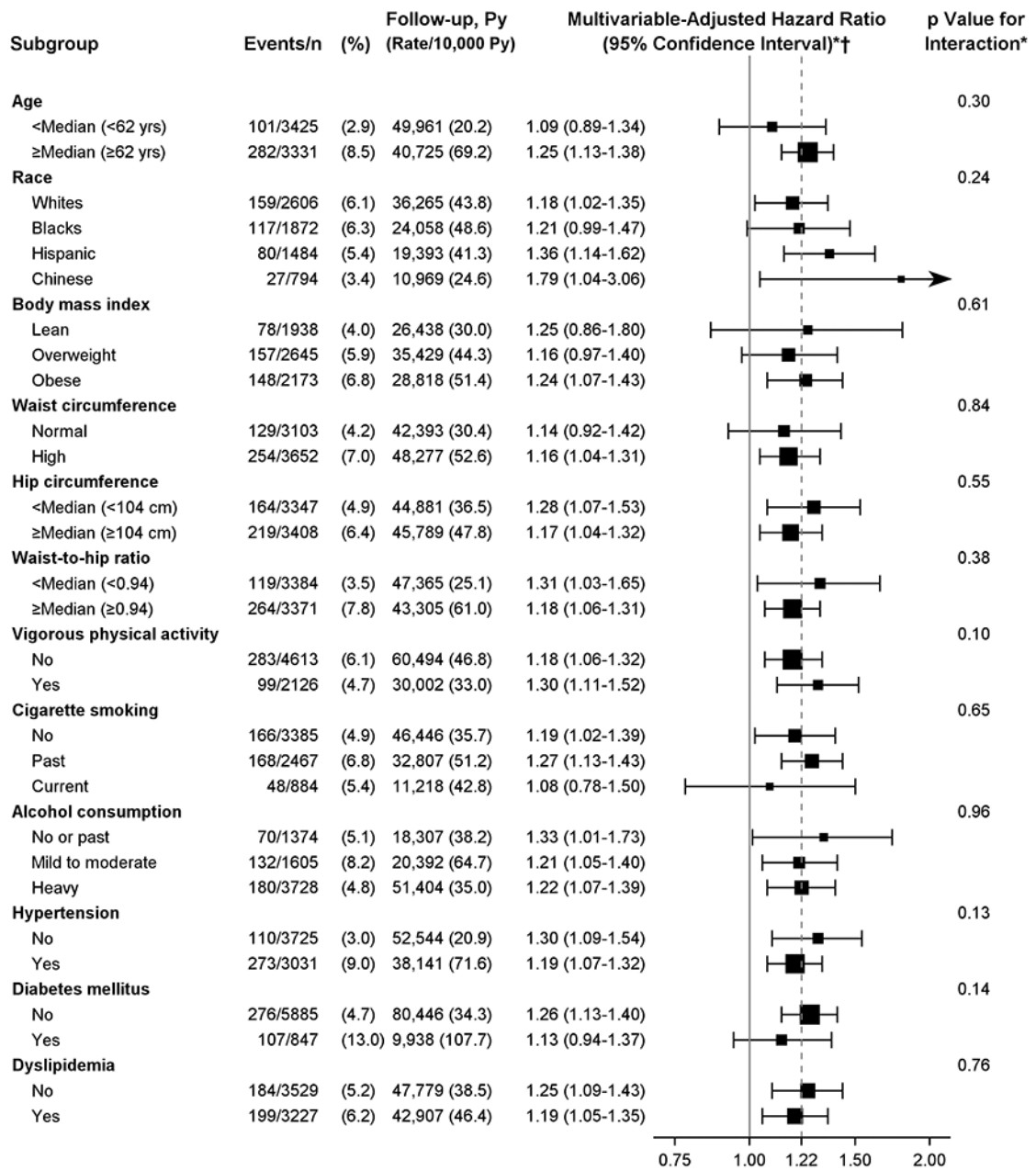
and interim myocardial infarction during follow-up. Py = person-years of follow-up; other abbreviations as in Figure 1.

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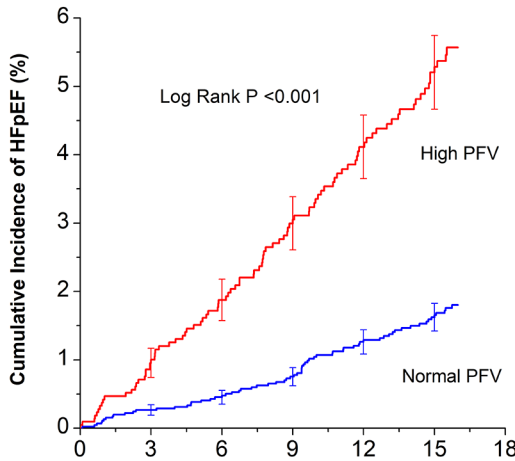
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**Figure 3: PFV and the Risk of HF According to Subgroups**

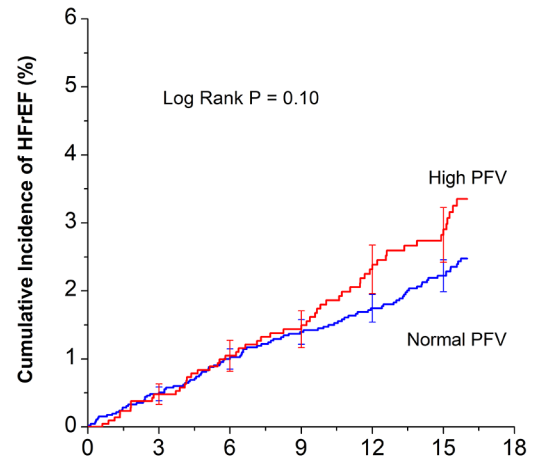
Effect of PFV on the risk of HF was similar in various subgroups. \*All analyses were sex-stratified and adjusted for age, race, cigarette smoking, alcohol consumption, vigorous physical activity, hypertension, diabetes mellitus, and dyslipidemia at baseline and interim myocardial infarction during follow-up. †Risk estimates were for every 1-SD increase (42 cm<sup>3</sup>) in PFV. 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. n = number at risk; other abbreviations as in Figures 1 and 2.

**A. HFpEF (LVEF  $\geq$ 50%)**



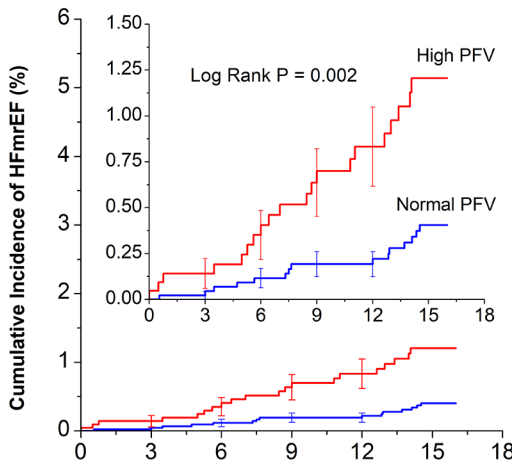
No. at risk	Time (years)					
Normal PFV	2158	2013	1847	1657	1464	1182
High PFV	4598	4404	4124	3825	3540	3039

**B. HFrEF (LVEF  $\leq$ 40%)**



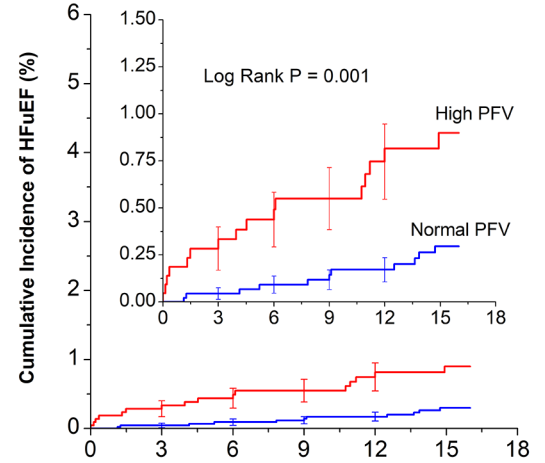
No. at risk	Time (years)					
Normal PFV	2158	2013	1847	1657	1464	1182
High PFV	4598	4404	4124	3825	3540	3039

**C. HFmrEF (LVEF >40% and <50%)**



No. at risk	Time (years)					
Normal PFV	2158	2013	1847	1657	1464	1182
High PFV	4598	4404	4124	3825	3540	3039

**D. HFuEF (LVEF Unknown)**



No. at risk	Time (years)					
Normal PFV	2158	2013	1847	1657	1464	1182
High PFV	4598	4404	4124	3825	3540	3039

**Figure 4: Cumulative Incidence of HF Subtypes by Categories of PFV at Baseline.**

High versus normal PFV and the cumulative incidence of (A) heart failure with preserved ejection fraction (HFpEF); (B) heart failure with reduced ejection fraction (HFrEF); (C) heart failure with mid-range ejection fraction (HFmrEF); (D) heart failure with unknown ejection fraction (HFuEF). High PFV was defined as 70 cm<sup>3</sup> in women and 120 cm<sup>3</sup> in men. Vertical bars represent standard errors. (C, D) The insets show the same data on an enlarged y-axis. Data shown are truncated at 16 years of follow-up. LVEF = left ventricular ejection fraction; other abbreviations as in Figure 1.

**TABLE 1**

Baseline Characteristics According to Categories of PFV in Women and Men

	Women			Men		
	Normal PFV (n = 2,130)	High PFV (n = 1,462)	P value	Normal PFV (n = 2,483)	High PFV (n = 710)	p Value
Age, yrs	60.2 ± 10.2	64.9 ± 9.7	<0.001	61.6 ± 10.3	64.5 ± 9.5	<0.001
Race			<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 <sup>2</sup> †	26.7 ± 5.3	31.7 ± 6.3	<0.001	26.8 ± 3.9	31.4 ± 4.3	<0.001
Lean	913 (43)	172 (12)		832 (34)	27 (4)	
Overweight	737 (35)	478 (33)		1,157 (47)	283 (40)	
Obese	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 ‡	1,167 (55)	1,300 (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)	1,044 (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 §						
Subcutaneous fat volume, cm <sup>3</sup>	956 ± 389 (513)	1,138 ± 421 (290)	<0.001	723 ± 302 (666)	898 ± 341 (147)	<0.001
Visceral fat volume, cm <sup>3</sup>	341 ± 146 (567)	194 ± 176 (391)	<0.001	484 ± 204 (750)	749 ± 237 (209)	<0.001
Vigorous physical activity	526 (25)	220 (15)	<0.001	1,120 (45)	268 (38)	<0.001
Cigarette smoking			0.51			<0.001
No	1,267 (60)	847 (58)		1,053 (43)	234 (33)	
Past	605 (28)	441 (30)		1,044 (42)	386 (54)	
Current	252 (12)	168 (12)		377 (15)	89 (13)	
Alcohol consumption #			<0.001			0.04
No or past	990 (47)	834 (58)		935 (38)	240 (34)	

	Women		Men		p Value
	Normal PFV (n = 2,130)	High PFV (n = 1,462)	Normal PFV (n = 2,483)	High PFV (n = 710)	
Mild to moderate	1,028 (49)	559 (39)	1,390 (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	124.8 ± 19.3	130.3 ± 18.7	<0.001
Diastolic	68.9 ± 10.3	69.4 ± 9.9	74.8 ± 9.4	76.1 ± 9.3	<0.001
Hypertension**	831 (39)	843 (58)	975 (39)	392 (55)	<0.001
Diabetes mellitus <sup>††</sup>	159 (7)	250 (17)	304 (12)	143 (20)	<0.001
Dyslipidemia <sup>‡‡</sup>	704 (33)	753 (52)	1,299 (52)	486 (68)	<0.001
Biomarkers					
C-reactive protein, mg/L	3.8 ± 5.6	5.7 ± 6.5	2.7 ± 5.6	3.7 ± 5.0	<0.001
Interleukin-6, pg/mL	1.4 ± 1.1	2.0 ± 1.3	1.4 ± 1.1	1.9 ± 1.4	<0.001
Log-NT-proBNP, pg/mL	4.1 ± 1.0	4.2 ± 1.0	3.6 ± 1.2	3.7 ± 1.2	0.001

Values are mean ± SD, n (%), or mean ± SD (n). By design, none of the participants had clinically apparent cardiovascular disease at baseline (see text for details).

\* High PFV value was defined as 70 cm<sup>3</sup> in women and 120 cm<sup>3</sup> in men.

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

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

<sup>§</sup> Data on abdominal subcutaneous and visceral fat volume computed from a total of 6 axial slices, 2 adjacent slices each at the level of L2-L3, L3-L4, and L4-L5 intervertebral disc spaces, was available on 1,616 (24%) and 1,917 (28%) of 6,785 participants, respectively, on abdominal computed tomography scans performed at 2.7 ± 0.9 years from the baseline examination. Number of participants with available data in each subgroup is shown in parentheses.

<sup>||</sup> 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 machine use, judo, kickboxing, and karate every week.

<sup>#</sup> 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.

<sup>\*\*</sup> 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.

<sup>††</sup> Diabetes mellitus was defined as treatment with insulin or oral hypoglycemic agents or fasting glucose of 126 mg/dl.

<sup>‡‡</sup> Dyslipidemia was defined as current lipid-lowering therapy or abnormal fasting lipid profile (total cholesterol of 240 mg/dl, low-density lipoprotein cholesterol of 160 mg/dl, high-density lipoprotein cholesterol of <40 mg/dl, or triglycerides of 200 mg/dl).



Log-NT-proBNP = logarithm-transformed N-terminal pro-B-type natriuretic peptide; PFV = pericardial fat volume.

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**TABLE 2**  
Cox Proportional Hazards Regression Analyses Evaluating the Association between PFV and the Risk of HF

	No. of Events/ No. at Risk (%)	Follow-up, Py (Rate/10,000 Py)	HR (95% CI), p Value	
			Age-Adjusted	Partially-Adjusted* Fully-Adjusted <sup>†</sup>
Model 1. PFV as a continuous variable (per 1-SD increment) <sup>‡</sup>				
A. Women	164/3575 (4.6)	48,907 (33.5)	1.68 (1.43-1.98), <0.001	1.68 (1.42-1.98), <0.001
B. Men	219/3181 (6.9)	41,778 (52.4)	1.25 (1.13-1.38), 0.0001	1.24 (1.12-1.37), <0.001
C. All (sex-stratified)	383/6756 (5.7)	90,686 (42.2)	1.34 (1.24-1.46), <0.001	1.34 (1.23-1.46), <0.001
Model 2. PFV as a categorical variable				
A. Women				
Normal PFV	59/2120 (2.8)	30,195 (19.5)	1.00 (referent)	1.00 (referent)
High PFV <sup>§</sup>	105/1455 (7.2)	18,713 (56.1)	2.15 (1.56-2.97), <0.001	2.15 (1.55-2.99), <0.001
B. Men				
Normal PFV	137/2478 (5.5)	32,981 (41.5)	1.00 (referent)	1.00 (referent)
High PFV <sup>§</sup>	82/703 (12.0)	8,797 (93.2)	1.89 (1.44-2.49), <0.001	1.91 (1.43-2.54), <0.001
C. All (sex-stratified)				
Normal PFV	196/4598 (4.3)	63,176 (31.0)	1.00 (referent)	1.00 (referent)
High PFV <sup>§</sup>	187/2158 (8.7)	27,510 (68.0)	2.00 (1.63-2.46), <0.001	2.04 (1.65-2.52), <0.001

\* Adjusted for age (for every 1-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 6,756 participants (1 HF event) because of missing information on covariates in the model.

<sup>†</sup> Adjusted for all the above-mentioned 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 6,756 participants (1 HF event) because of missing information on covariates in the model.

<sup>‡</sup> 1 SD = 42 cm<sup>3</sup>.

<sup>§</sup> High PFV value was 70 cm<sup>3</sup> in women and 120 cm<sup>3</sup> in men.

CI = confidence interval; HF = heart failure; HR = hazard ratio; Py = person-years; PFV = pericardial fat volume.

**TABLE 3**  
**PFV and the Risk of HF Subtypes in Sex-Stratified Cox Proportional Hazards Regression Models**

	No. of Events/ No. at Risk (%)	Follow-up, Py (Rate/10,000 Py)	HR (95% CI), p Value
		Age-Adjusted	Partially-Adjusted* Fully-Adjusted <sup>‡</sup>
<b>Model 1. HFpEF (LVEF 50%)</b>			
A. PFV as a continuous variable (per 1-SD increment) <sup>‡</sup>	167/6,756 (2.5%)	1.54 (1.37-1.73), <0.001	1.52 (1.35-1.72), <0.001
B. PFV as a categorical variable			
Normal PFV	71/4,598 (1.5%)	1.00 (referent)	1.00 (referent)
High PFV <sup>§</sup>	96/2,158 (4.4%)	2.57 (1.87-3.53), <0.001	2.55 (1.85-3.53), <0.001
<b>Model 2. HFmrEF (LVEF 40%)</b>			
A. PFV as a continuous variable (per 1-SD increment) <sup>‡</sup>	151/6,756 (2.2%)	1.13 (0.97-1.30), 0.11	1.15 (1.00-1.33), 0.06
B. PFV as a categorical variable			
Normal PFV	96/4,598 (2.1%)	1.00 (referent)	1.00 (referent)
High PFV <sup>§</sup>	55/2,158 (2.5%)	1.33 (0.95-1.87), 0.10	1.40 (0.99-1.99), 0.06
<b>Model 3. HFmrEF (LVEF &gt;40% and &lt;50%)</b>			
A. PFV as a continuous variable (per 1-SD increment) <sup>‡</sup>	38/6,756 (0.6%)	1.41 (1.11-1.81), 0.006	1.44 (1.12-1.85), 0.004
B. PFV as a categorical variable			
Normal PFV	18/4,598 (0.4%)	1.00 (referent)	1.00 (referent)
High PFV <sup>§</sup>	20/2,158 (0.9%)	2.51 (1.30-4.84), 0.006	2.68 (1.37-5.27), 0.004
<b>Model 4. HFuEF</b>			
A. PFV as a continuous variable (per 1-SD increment) <sup>‡</sup>	27/6,756 (0.4%)	1.35 (0.99-1.84), 0.06	1.23 (0.89-1.70), 0.21
B. PFV as a categorical variable			
Normal PFV	11/4,598 (0.2%)	1.00 (referent)	1.00 (referent)
High PFV <sup>§</sup>	16/2,158 (0.7%)	2.91 (1.31-6.45), 0.009	2.66 (1.17-6.03), 0.02

\* Adjusted for age (for every 1-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 6,756 participants (1 HF event) because of missing information on covariates in the model.

<sup>‡</sup> Adjusted for all the above-mentioned 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 6,756 participants (1 HF event) because of missing information on covariates in the model.

<sup>§</sup> 1 SD = 42 cm<sup>3</sup>.

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§ High PFV value was 70 cm<sup>3</sup> in women and 120 cm<sup>3</sup> in men.

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; other abbreviations as in Tables 1 and 2.