Pericardial fat volume and incident atrial fibrillation in the Multi-Ethnic Study of Atherosclerosis and Jackson Heart Study

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Abstract

Objective—We hypothesized that greater pericardial fat volume would be associated with increased risk of incident atrial fibrillation (AF).

Methods—In the Multi-Ethnic Study of Atherosclerosis (MESA) and Jackson Heart Study (JHS), pericardial fat volume was quantified by computed tomography. Incident AF was identified from discharge diagnosis codes, study electrocardiograms, and Medicare claims.

Results—Among 7991 participants, 40% were African-American, 32% white, 18% Hispanic, and 10% Chinese-American; mean age was 62 years; 55% were women. During an average of 10.0 years of follow-up in MESA and 4.5 years in JHS, 756 incident AF cases were identified. After adjustment for age, sex, study, race/ethnicity, height, glucose status, systolic blood pressure,

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treated hypertension, and body mass index (BMI), greater pericardial fat volume was associated with higher AF risk in Hispanics (HR 1.24 per SD, 95%CI 1.05-1.46), but not overall (HR 1.06, 95%CI 0.97-1.15). In mediation analysis, pericardial fat volume partially mediated the association of BMI with incident AF in Hispanics.

Conclusions—After adjustment for BMI, greater pericardial fat volume was associated with incident AF in Hispanics but not overall. Additional research is needed on the mechanisms by which pericardial fat volume is related to increased AF risk and possible differences by race/ethnicity.

Keywords

pericardial fat; obesity; atrial fibrillation; epidemiology

introduction

Atrial fibrillation (AF), a common arrhythmia, is important because it is associated with substantially elevated risks of stroke,[1] cognitive decline,[2] dementia,[3] arterial emboli, heart failure,[4] and cardiovascular death.[5] Obesity is consistently associated with higher risk of incident AF, even after adjustment for diabetes, hypertension, and other cardiovascular risk factors.[6-8] However, the mechanisms by which obesity is related to AF are not completely understood. In obesity, excess adipose tissue is stored in part as pericardial fat, which includes both epicardial fat (located between the myocardium and the visceral pericardium) and paracardial fat (located superficial to the parietal pericardium).[9 10] Fat in the pericardial depot is metabolically active, producing cytokines that may contribute to atrial remodeling, and because some of the epicardial fat overlies and shares the same microcirculation with the atrial myocardium, it has been hypothesized that excess epicardial fat is causally related to increased risk of AF.[9-12]

In large population studies, pericardial fat volume can be readily quantified by computed tomography, and is highly correlated with epicardial fat volume (Spearman correlation coefficient, 0.92; p<0.0001).[13] Two community-based studies, the Heinz Nixdorf Recall and Framingham Heart Studies, found little evidence that greater epicardial or pericardial fat volume was associated with incident AF.[14 15] However, study power was limited in both analyses, with 50 and 162 AF cases respectively, and generalizability was limited because all participants were white.

Obesity is particularly prevalent in African-American[16] and Hispanic populations,[17] but the potential role of obesity in AF initiation in these groups has received little attention. Despite greater average body mass index (BMI), African Americans are known to have, on average, smaller pericardial fat depots[18] and lower rates of incident AF than whites.[19-21] On the other hand, the limited data available in Hispanics suggests a distribution of pericardial fat volume similar to that of whites,[18] but lower rates of incident AF.[17] Additional evaluation is needed of the possible association of pericardial fat volume with incident AF in adequately powered studies of diverse participants.

Therefore, we conducted an analysis in two large and diverse cohort studies, the MultiEthnic Study of Atherosclerosis (MESA) and the Jackson Heart Study (JHS). We hypothesized that greater pericardial fat volume would be associated with incident AF independent of BMI. In addition, we examined whether the association of BMI with incident AF is mediated by pericardial fat volume.

Methods

Setting

In 2000-2002, MESA enrolled 6814 participants 45-84 years of age and free of clinically recognized cardiovascular disease from six US communities.[22] Participants self-identified with one of four race/ethnic groups: African-American (28%), white (38%), Hispanic (22%) and Asian, of Chinese descent (12%); 53% were women. In 2000-2004, JHS enrolled 5301 African-American residents of three counties surrounding the Jackson, MS area. Participants were 20-95 years of age at baseline; 64% were women. In both studies, institutional review boards at each study center approved the study protocol, and written informed consent was obtained from every participant.

Study Design

Measurement of pericardial fat volume by computed tomography (CT)—
Consenting participants underwent CT scanning of the chest at Exam 1 (2000-2002) in MESA and at Exam 2 (2007-2009) in JHS. The two studies used the same methods and the same Wake Forest University Reading Center to measure pericardial fat volume.[23-25] Pericardial fat volume was measured rather than epicardial fat volume because it is often difficult to accurately visualize the normal parietal pericardium (which separates the epicardial and paracardial fat), especially in lean individuals, and the goal was to obtain unbiased measurements in participants across the spectrum of weight.[13] Pericardial fat was measured in eighteen 2.5-mm slices, from 15 mm above to 30 mm below the superior extent of the left main coronary artery, using Volume Analysis software (GE Healthcare, Waukesha, WI). The anterior border of the volume was defined by the chest wall and the posterior border by the aorta and the bronchus. This volume includes the pericardial fat located around the proximal coronary arteries, and includes both epicardial and paracardial fat.[13] Tissue with attenuation of -190 to -30 Hounsfield units was defined as fat. The pericardial fat volume was the sum of all voxels containing fat. The intra-reader reproducibility was excellent in both studies (intraclass correlation coefficients, 0.99 in MESA and 0.96 in JHS). All suitable CT scans in MESA were read for pericardial fat, but due to budgetary constraints, a random sample of 1414 CT scans were read for pericardial fat volume in JHS.

Incident atrial fibrillation during follow-up—AF was identified using similar methods in JHS and MESA. Participants were contacted by telephone during follow-up every 9-12 months in MESA and every 9-15 months in JHS to inquire about hospitalizations. Medical records were obtained for all reported hospitalizations and discharge diagnosis *International Classification of Diseases, Ninth Revision* (ICD-9) codes were obtained. In addition, in JHS, area hospitals reported hospital discharge diagnosis codes for all JHS participants. AF was

identified by an ICD-9 code for AF (427.31) or atrial flutter (427.32) in any position assigned at hospital discharge, by study electrocardiogram at a single follow-up visit (2010-2012 in MESA and 2009-2012 in JHS), or for those enrolled in fee-for-service Medicare, by an inpatient or outpatient claim with an AF or atrial flutter ICD-9 diagnosis code in any position, using methods adapted from the Cardiovascular Health Study.[26] Hospital discharge diagnosis data and Medicare claims data were available in both studies through December 2012. We defined the date of incident AF as the first date AF was noted either by study electrocardiogram or a single ICD-9 code in any position in cohort hospitalization monitoring or Medicare inpatient or outpatient claims data.

Assessment of participant characteristics—Participants in MESA and JHS underwent similar extensive evaluations at study exams, including measurement of height, waist circumference and weight, and assessment by questionnaire of smoking, educational attainment, current medications, and physician diagnoses of hypertension and diabetes.[16 22] Blood pressure was measured with the participant in a seated position; serum glucose and (in JHS only) hemoglobin A1c (HbA1c) were measured in a fasting blood sample. Treated hypertension was defined as use of an antihypertensive medication in combination with self-report of a physician diagnosis of hypertension. Glucose status was classified as normal (fasting glucose<100 mg/dL or HbA1c<5.7% with no use of diabetic medications), impaired fasting glucose (fasting glucose 100 and < 126 mg/dL or HbA1c 5.7 and < 6.5% with no use of diabetic medications), or diabetes (use of a diabetic medication, fasting glucose 126 mg/dL, or HbA1c 6.5%).

Statistical analysis

Included in the analysis were all participants with pericardial fat volume measured who were free of a history of AF at the time of CT and had follow-up for incident AF. Information about participant characteristics came from Exam 1 in MESA and from Exam 2 in JHS.

We described participant characteristics and provided the mean (SD) pericardial fat volume for participant groups defined by these same characteristics. Data were missing for fewer than 1.2% of participants for all covariates. Missing data were imputed using multiple imputation by chained equations.[27] We used Cox proportional hazards models to examine the association of pericardial fat volume with time to incident AF, adjusted for sociodemographic characteristics and characteristics known to be associated with both pericardial fat volume and incident AF.[28] Participants entered the analysis at the time of the chest CT, time to event was time to diagnosis of incident AF, and participants were treated as censored at death, loss to follow-up, or the end of follow-up, whichever came first. We examined scaled Schoenfeld residuals relationships to functions of time to test for violations of the proportional hazards assumption and found none.

We used linear splines to evaluate the possibility of non-linear associations between participant characteristics, pericardial fat volume, and log hazard for AF. Based on change in the hazard ratio (HR) of interest, we found evidence for a nonlinear association for BMI with AF, but no evidence for nonlinearity for other characteristics. BMI was therefore modeled as a linear spline in standard deviation (SD) units with one knot at a BMI of 30

kg/m^2, the cutoff used by the World Health Organization to classify individuals with vs. without obesity. The overall SD for BMI was 6 kg/m^2. Pericardial fat volume was modeled as a continuous linear variable in SD units. The overall SD for pericardial fat volume was 41 ml. After confirming that the association of pericardial fat volume with AF did not differ significantly in African Americans by study, we pooled data from the two studies and examined the association overall and by race/ethnic group.

To examine the extent to which the higher risk of AF associated with obesity is explained by greater pericardial fat volume, we conducted a mediation analysis. We first estimated the HR for AF associated with a 1-SD difference in BMI separately in individuals with and without obesity, both overall and by race/ethnic group, after adjustment for age, sex, study, race/ethnicity, height, glucose status, systolic blood pressure, and treated hypertension. For subgroups in which BMI was significantly associated with incident AF, we then estimated the same HRs after further adjustment for pericardial fat volume. A larger change in HR toward the null would imply a larger mediating effect of pericardial fat volume. Finally, using the Judd and Kenny difference in coefficients method,[29] we calculated the ratio of the HRs for AF associated with a 1-SD difference in BMI, without compared to with adjustment for pericardial fat volume. We used 1500 bootstrap replications to compute bias-corrected confidence intervals, as implemented in Stata v. 10.1 (StataCorp, College Station, TX).

Results

A total of 7991 participants had pericardial fat volume measured and had follow-up for incident AF, 6683 in MESA and 1308 in JHS (Table 1). Among MESA participants, 1855 self-identified as African American, 2568 white, 1472 Hispanic, and 788 Chinese; all JHS participants were African American. Overall, the mean age was 62 years; 55% were women. Compared with white or Chinese participants, the prevalence of hypertension was higher in African-American participants, and the prevalence of obesity and diabetes was higher in both African-American and Hispanic participants.

Across the race/ethnic groups, African-American participants had, on average, the lowest pericardial fat volume; volume was greatest in white and Hispanic participants (Table 2). The distribution of pericardial fat volume was similar in the African-American participants in the two studies. Greater pericardial fat volume was also associated with older age, male sex, greater BMI, treated hypertension, impaired fasting glucose, and diabetes.

During an average of 10.0 years of follow-up in MESA and 4.5 years in JHS, a total of 756 cases of incident AF were identified, 721 in MESA and 35 in JHS. Among men, especially in the oldest age group, African American participants had lower AF incidence than white participants (Figure 1).

After adjustment for age, study, sex, and race/ethnicity, greater pericardial fat volume was associated with higher risk of incident AF in the pooled data (Model 1: HR, 1.15 per SD increment of pericardial fat volume; 95% CI, 1.08-1.23; Table 3). Additional adjustment for height, systolic blood pressure, treated hypertension, and glucose status changed the estimate only slightly (Model 2: HR, 1.12 per SD, 95% CI, 1.05-1.20). After further

adjustment for BMI (linear spline), the association was attenuated and became non-significant (Model 3: HR, 1.06 per SD; 95% CI, 0.97-1.15). In Model 3 analyses stratified by race/ethnic group, greater pericardial fat volume was associated with incident AF in Hispanics (HR, 1.24; 95% CI, 1.05-1.46) but not in the other 3 race/ethnic groups; the p-value for interaction by race/ethnicity was 0.03. There was no evidence for difference in the pericardial fat-AF association by age group or sex. When we adjusted for waist circumference as a measure of obesity instead of BMI in Model 3, the association of pericardial fat volume with AF was little changed, either overall (HR 1.04 per SD; 95% CI, 0.96-1.13), or in Hispanics (HR 1.16, 95% CI 0.98-1.38), and the p-value for interaction by race/ethnicity remained significant at 0.008.

In the mediation analysis, we first examined the adjusted HR for AF associated with each 1-SD increment [6 kg/m^2] in BMI, separately in individuals with and without obesity. In individuals without obesity, greater BMI was not associated with higher risk of incident AF, and mediation analysis was not pursued further. In individuals with obesity (BMI 30 kg/m^2) overall, greater BMI was significantly associated with higher AF risk (HR, 1.50; 95% CI, 1.30-1.73; Table 4). After further adjustment for pericardial fat volume, this HR did not change substantively (HR, 1.46; 95% CI, 1.26-1.70), and mediation analysis in the overall population provided little evidence that the association of BMI with AF was mediated by pericardial fat volume. In the overall population, the ratio of the HRs for AF associated with a 1-SD increment in BMI, without compared to with adjustment for pericardial fat volume, was 1.02 (95% CI, 0.99-1.06). However, in Hispanic individuals with obesity, where the association of BMI with AF was relatively strong (HR, 1.92; 95% CI, 1.45-2.55), there was attenuation of the association after additional adjustment for pericardial fat volume (HR, 1.71; 95% CI, 1.27-2.31), and the mediation analysis suggested that pericardial fat volume partially mediated the association of BMI with AF. In Hispanic individuals with obesity, the ratio of the HRs for AF associated with a 1-SD increment in BM, without compared to with adjustment for pericardial fat volume, was 1.12 (95% CI, 1.02-1.24).

Discussion

In a diverse population of 7991 Americans, after adjustment for sociodemographic characteristics, BMI, and other AF risk factors, greater pericardial fat volume was significantly associated with the risk of incident AF in Hispanics, but not in whites, African Americans, or Chinese Americans. In Hispanics, mediation analysis in the subgroup with obesity suggested that pericardial fat volume partially mediates the association of BMI with AF.

Strengths of our analysis include the large and diverse study population with consistent methods across studies for measurement of pericardial fat volume and ascertainment of incident AF, the extensive, high-quality information on participant characteristics, and the large number of participants (N=756) who developed clinically-recognized incident AF during follow-up. However, several limitations should be recognized. Using ICD-9 codes to identify incident AF has a high positive predictive value, but imperfect sensitivity.[30] Because AF is often paroxysmal and may be asymptomatic, some participants who experienced AF

may not have sought medical attention and would have been missed by our ascertainment methods. AF ascertainment methods were identical across race/ethnic groups in MESA, but it remains possible that the likelihood of seeking care for arrhythmia symptoms or the recognition of AF by medical personnel varied by race/ethnicity or by study. Both MESA and JHS measured pericardial fat rather than epicardial fat, the depot hypothesized to be causally related to AF. However, pericardial fat can be measured more consistently and accurately than epicardial fat across the spectrum of weight, and pericardial fat volume is very highly correlated with epicardial fat volume.[13] We did not have measures of left atrial size in most participants, thus we were unable to investigate the role of left atrial enlargement in the associations we studied. Analysis of the pericardial fat-AF association by race/ethnic group was prespecified in our analysis plan, and while statistically significant, the differences in association by race/ethnicity we observed were not large, thus our findings in Hispanics require replication. Finally, the validity of the mediation analysis rests on the assumptions that obesity is causally related to incident AF, that there is no unmeasured and unaccounted-for exposure-mediator, mediator-outcome, or exposure-outcome confounding, and that there is no interaction between exposure and mediator on the outcome. These assumptions are difficult to prove definitively.

Several lines of evidence suggest mechanisms by which excess pericardial fat deposition could affect AF risk. Pericardial fat is metabolically active and releases pro-inflammatory cytokines.[31] Since epicardial fat and the underlying myocardium share the same blood supply and there is no fibrous fascial layer between the fat and the myocardium or coronary vessels, these mediators diffuse freely into vasa vasorum and into thin-walled structures such as the atrial and right ventricular walls. In a rat atrial tissue model, adipofibrokines released by epicardial fat were shown to promote fibrosis,[32] which may lead to AF. In addition, adipocyte infiltration into myocardial tissue and fat accumulation in droplets in the cytosol of cardiomyocytes may increase mechanical pumping effort in individuals with obesity and cause autonomic dysfunction, electrocardiographic abnormalities, and arrhythmogenesis, possibly predisposing to AF.[9,10,33,34] Finally, obesity is strongly linked to sleep apnea, which may promote initiation or maintenance of AF through hypoxemia, intrathoracic pressure changes, and development of diastolic dysfunction.[10]

To date, limited information has been available about the association of pericardial fat depots with incident AF. In the Heinz Nixdorf Recall[14] and Framingham Heart Studies,[15] greater epicardial or pericardial fat volume was associated with incident AF after adjustment for age and sex only, but not after further adjustment for AF risk factors including BMI (OR 1.19, 95% CI 0.88 - 1.61 and HR 1.09, 95% CI 0.94-1.27, respectively). Our findings in white participants are similar to these earlier findings. We are not aware of any previous analyses in race/ethnic groups other than whites. In our analysis, it is not clear why there was stronger evidence for an association between pericardial fat volume and AF in Hispanics than in the other race/ethnic groups studied. Further study will be required to clarify whether pericardial fat is associated with changes that may differ in various race/ethnic subgroups, such as increased left atrial size or changes in cardiac conduction or function.

In an analysis of time trends in AF incidence in the Mayo Clinic population, it was estimated that 60% of the increase in AF incidence observed between 1980 and 2000 may be due to

the obesity epidemic.[8] A clinical trial of weight management vs. general lifestyle advice in patients with overweight or obesity and with symptomatic AF found that active weight management led to greater weight loss, reduced AF symptoms, and reduced AF burden, suggesting that weight reduction may reduce AF-related morbidity.[35] Because obesity is particularly prevalent in African Americans and Hispanics, research into the role of obesity in AF initiation is a high priority for the health of these communities. The findings of our study support the hypothesis that greater pericardial fat volume may be one mechanism by which obesity increases the risk of incident AF in the Hispanic subgroup. An understanding of the details of this association will require further study. However, based on the well-established association of obesity with incident AF, our results are consistent with the notion that maintaining a healthy body weight may play a role in AF prevention in all race/ethnic groups.

Acknowledgments

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What Is Already Known About This Subject?

- Obesity is associated with a higher risk of atrial fibrillation (AF), but the mechanisms of this association are not completely understood.

- In obesity, adipose tissue is stored as paracardial and epicardial fat, which shares microcirculation with the atrial myocardium. Cytokines released from this metabolically active fat depot may contribute to atrial remodeling and predispose to arrhythmia.

What Does This Study Add?

- In this large study of two ethnically diverse cohorts, after adjustment for body mass index, greater pericardial fat volume was not associated with incident AF overall but was associated with AF in Hispanic participants, and mediation analysis suggested that pericardial fat volume may partially mediate the association of obesity with AF in that group.

- Obesity was associated with incident AF in all race/ethnic groups, supporting the conclusion that maintenance of a healthy body weight may play a role in AF prevention in everyone. Further study will be required to understand whether the effects of pericardial fat volume on atrial structure and function differ by race/ethnic group.

A. Men
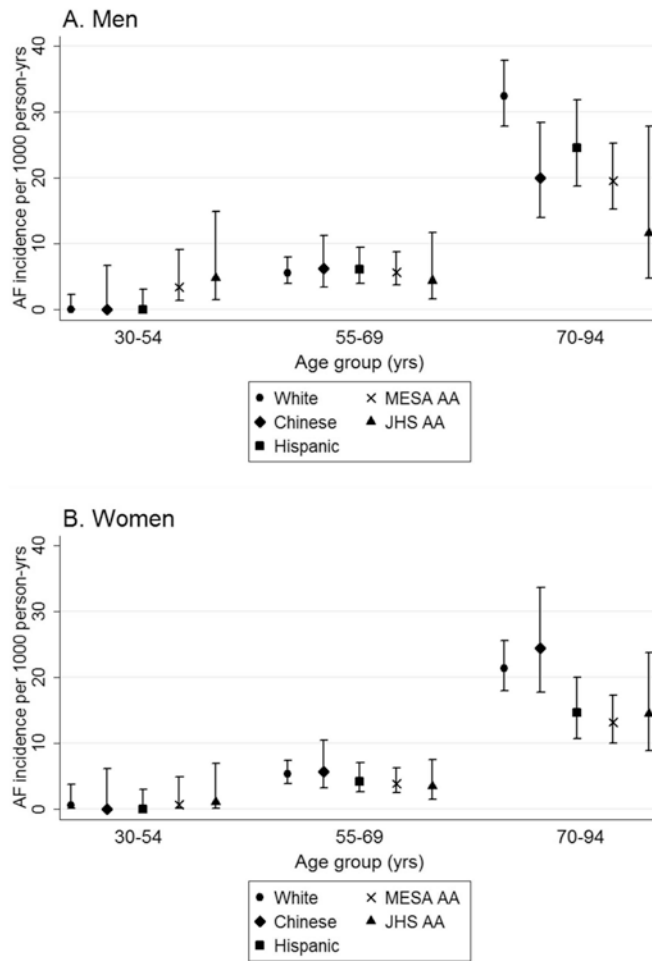
B. Women

Figure 1.
Incidence per 1000 person-years of atrial fibrillation by age group, race/ethnicity, and study, in men (Panel A) and women (Panel B). Bars show 95% confidence intervals. In the youngest age group, all whites, Hispanics, and Chinese were 45-54 years of age. AF = atrial fibrillation, MESA = Multi-Ethnic Study of Atherosclerosis, JHS = Jackson Heart Study, AA = African American

Table 1

Characteristics of Jackson Heart Study and Multi-Ethnic Study of Atherosclerosis participants at the time of the chest CT scan from which pericardial fat volume was measured

	JHS African American	MESA African American	MESA White	MESA Hispanic	MESA Chinese
Participants, n	1308	1855	2568	1472	788
Age, yrs, mean (SD)	60 (11)	62 (10)	62 (10)	61 (10)	62 (10)
Men, N (%)	440 (34)	828 (45)	1227 (48)	710 (48)	384 (49)
BMI, kg/m², N (%)					
<25.0	146 (11)	328 (18)	829 (32)	247 (17)	512 (65)
25.0-29.9	449 (35)	682 (37)	1027 (40)	656 (45)	243 (31)
>=30.0	703 (54)	845 (46)	712 (28)	569 (39)	33 (4)
Systolic blood pressure, mmHg, mean (SD)	127 (18)	132 (22)	123 (20)	127 (22)	125 (22)
Diastolic blood pressure, mmHg, mean (SD)	77 (10)	75 (10)	70 (10)	72 (10)	72 (10)
Treated hypertension, N (%)	864 (66)	871 (47)	691 (27)	423 (29)	198 (25)
Current smoking, N (%)	115 (9)	331 (18)	298 (12)	202 (14)	45 (6)
Impaired fasting glucose, N (%)	577 (45)	277 (15)	289 (11)	233 (16)	135 (17)
Diabetes, N (%)	345 (27)	317 (17)	151 (6)	255 (17)	101 (13)
High school education or less, N (%)	403 (31)	569 (31)	557 (22)	955 (65)	318 (40)

BMI = body mass index

Table 2

Mean (SD) pericardial fat volume (ml) by race/ethnic group and study in relation to age, sex, BMI, treated hypertension, and glucose status

Characteristic	JHS African American	MESA African American	MESA White	MESA Hispanic	MESA Chinese
Overall	72 (33)	67 (35)	85 (46)	88 (44)	74 (31)
Age, yrs					
30-54	61 (27)	58 (30)	70 (40)	75 (40)	61 (27)
55-69	77 (34)	70 (34)	89 (49)	91 (43)	75 (32)
70-94	77 (32)	73 (39)	94 (44)	100 (46)	84 (32)
Sex					
Women	67 (29)	61 (29)	70 (35)	76 (34)	69 (29)
Men	80 (37)	75 (40)	101 (51)	101 (49)	78 (34)
BMI, kg/m^2					
<25.0	47 (20)	44 (22)	54 (25)	57 (25)	63 (22)
25.0-29.9	64 (27)	62 (28)	87 (37)	83 (38)	91 (35)
>=30.0	82 (34)	81 (38)	119 (52)	108 (47)	112 (35)
Treated hypertension					
No	63 (29)	63 (34)	79 (43)	85 (44)	69 (30)
Yes	76 (33)	73 (35)	102 (50)	96 (43)	87 (32)
Glucose status					
Normal	61 (29)	62 (32)	80 (43)	80 (39)	68 (28)
Impaired fasting glucose	70 (29)	80 (37)	107 (45)	105 (48)	81 (35)
Diabetes	85 (37)	78 (38)	120 (59)	105 (47)	93 (33)

BMI = body mass index

Table 3

Association of pericardial fat volume with incident atrial fibrillation overall and in subgroups defined by race/ethnicity, age group, and sex

	N with AF	Model 1[†]	Model 2[‡]	Model 3[§]	Interaction p-value
			Hazard ratio* (95% CI)		
Overall	756	1.15 (1.08-1.23)	1.12 (1.05-1.20)	1.06 (0.97-1.15)	
Subgroups:					
Race/ethnic group					0.03
African American	191	1.19 (1.02-1.37)	1.15 (0.99-1.33)	1.12 (0.94-1.33)	
White	344	1.06 (0.96-1.17)	1.04 (0.94-1.15)	0.93 (0.82-1.05)	
Hispanic	131	1.36 (1.19-1.55)	1.33 (1.15-1.53)	1.24 (1.05-1.46)	
Chinese	90	0.99 (0.75-1.30)	0.97 (0.73-1.30)	0.84 (0.58-1.22)	
Age, yrs					0.34
30-54	29	1.51 (1.10-2.07)	1.28 (0.89-1.84)	0.96 (0.61-1.52)	
55-69	325	1.11 (1.00-1.23)	1.07 (0.97-1.19)	1.03 (0.91-1.17)	
70-94	402	1.14 (1.04-1.25)	1.13 (1.02-1.24)	1.07 (0.95-1.20)	
Sex					0.18
Women	352	1.29 (1.15-1.46)	1.26 (1.11-1.43)	1.13 (0.97-1.31)	
Men	404	1.09 (1.00-1.18)	1.06 (0.97-1.15)	1.01 (0.91-1.13)	

AF = atrial fibrillation

*
HR per 1 standard deviation increment in pericardial fat volume (41 ml)

[†]
Model 1: adjusted for age, study, sex and race/ethnicity (except in analyses stratified by these characteristics

[‡]
Model 2: adjusted for Model 1 variables plus height, systolic blood pressure (linear), treated hypertension, and glucose status (normal, impaired fasting glucose, diabetes)

[§]
Model 3: adjusted for Model 2 variables plus body mass index (linear spline)

Table 4

Association of body mass index with incident atrial fibrillation in individuals without and with obesity, and analysis of pericardial fat volume as a mediator of that association in individuals with obesity, overall and by race/ethnic group

	Without obesity: BMI <30 kg/m²			With obesity: BMI ≥30 kg/m²			
	Total N	N with incident AF	HR* (95% CI) for AF per SD increment in BMI	Total N	N with incident AF	HR* (95% CI) for AF per SD increment in BMI	HR* (95% CI) for AF per SD increment in BMI, after adjustment for pericardial fat volume	Ratio of the HRs* for AF associated with a 1-SD increment in BMI, without to with adjustment for pericardial fat volume (95% CI)
Overall	5125	506	1.01 (0.86-1.19)	2866	250	1.50 (1.30-1.73)	1.46 (1.26-1.70)	1.02 (0.99-1.06)
Race/ethnic group								
African American	1611	101	0.91 (0.64-1.28)	1552	90	1.32 (1.05-1.67)	1.27 (1.00-1.62)	1.04 (0.97-1.11)
White	1856	254	1.08 (0.85-1.38)	712	90	1.57 (1.20-2.05)	1.64 (1.24-2.16)	0.96 (0.88-1.04)
Hispanic	903	64	0.93 (0.59-1.48)	569	67	1.92 (1.45-2.55)	1.71 (1.27-2.31)	1.12 (1.02-1.24)
Chinese	755	87	0.97 (0.64-1.47)	33	3	†	†	†

BMI = body mass index; AF = atrial fibrillation; HR = hazard ratio; CI = confidence interval; SD of BMI = 6 kg/m²

*
All models are adjusted for age, sex, height, systolic blood pressure (linear), treated hypertension, and glucose status (normal, impaired fasting glucose, diabetes); the overall analysis was also adjusted for study and race/ethnicity; and the analysis in African Americans was also adjusted for study.

†
HR not calculated because the small N of AF cases in Chinese participants with obesity led to unstable estimates