Pericardial Fat Volume and Incident Atrial Fibrillation in the Multi-Ethnic Study of Atherosclerosis and Jackson Heart Study

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Objective: To determine whether greater pericardial fat volume would be associated with increased risk of incident atrial fibrillation (AF).

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

Results: Among 7,991 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 the Multi-Ethnic Study of Atherosclerosis and 4.5 years in the Jackson Heart Study, 756 incident AF cases were identified. After adjustment for age, sex, study, race/ethnicity, height, glucose status, systolic blood pressure, treated hypertension, and BMI, greater pericardial fat volume was associated with higher AF risk in Hispanics (hazard ratio 1.24 per SD, 95% confidence interval 1.05-1.46) but not overall (hazard ratio 1.06, 95% confidence interval 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.

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

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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 (CT), and it 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 BMI, African Americans are known to have, on average, smaller pericardial fat depots (18) and lower rates of incident AF than white individuals (19-21). On the other hand, the limited data available in Hispanic individuals suggest a distribution of pericardial fat volume similar to that of white people (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 Multi-Ethnic 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 to 2002, MESA enrolled 6,814 participants 45 to 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 to 2004, JHS enrolled 5,301 African-American residents of three counties surrounding the Jackson, Mississippi, area. Participants were 20 to 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 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, Wisconsin). 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 intrareader 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 1,414 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 to 12 months in MESA and every 9 to 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 antihypertension 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 (standard deviation, 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 socio-demographic characteristics and characteristics known to be

| 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                | 1,308            | 1,855            | 2,568        | 1,472          | 788           |
| Age, y, mean (SD)              | 60 (11)          | 62 (10)          | 62 (10)      | 61 (10)        | 62 (10)       |
| Men, n (%)                     | 440 (34)         | 828 (45)         | 1,227 (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)         | 1,027 (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)      |

JHS, Jackson Heart Study; MESA, Multi-Ethnic Study of Atherosclerosis; CT, computed tomography; SD, standard deviation.

| 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 |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                | JHS African American | MESA African American | MESA White | MESA Hispanic | MESA Chinese |
| Overall                        | 72 (33)          | 67 (35)          | 85 (46)      | 88 (44)       | 74 (31)      |
| Age, y                         |                  |                  |              |                |               |
| 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/m²                     |                  |                  |              |                |               |
| <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)      |

JHS, Jackson Heart Study; MESA, Multi-Ethnic Study of Atherosclerosis; SD, standard deviation.
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 residual 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 nonlinear 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 SD units with one knot at a BMI of 30 kg/m², the cutoff used by the World Health Organization to classify individuals with versus without obesity. The overall SD for BMI was 6 kg/m². 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 1,500 bootstrap replications to compute bias-corrected confidence intervals, as implemented in Stata® v. 10.1 (StataCorp, College Station, Texas).

Results
A total of 7,991 participants had pericardial fat volume measured and had follow-up for incident AF; 6,683 in MESA and 1,308 in JHS (Table 1). Among MESA participants, 1,855 self-identified as African American, 2,568 as white, 1,472 as Hispanic, and 788 as Chinese; all JHS participants were African American. Overall, the mean age was 62 years, and 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% confidence interval [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 nonsignificant (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 three 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/m²) 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/m²) 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 substantially (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 1.12 (95% CI, 1.02-1.24).

Discussion

In a diverse population of 7,991 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 Hispanic but not in white, African-American, or Chinese-American participants. In Hispanic individuals, 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 Hispanics was different from that of other groups.

| TABLE 3 Association of pericardial fat volume with incident atrial fibrillation overall and in subgroups defined by race/ethnicity, age group, and sex |
| --- |
| **Hazard ratio** (95% CI) |
| **N with AF** |
| **Overall** |
| 756 |
| 1.15 (1.08-1.23) |
| 1.12 (1.05-1.20) |
| 1.06 (0.97-1.15) |
| **Subgroups** |
| **Interaction** |
| **P value** |
| **Race/ethnic group** |
| 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, y** |
| 30-54 |
| 29 |
| 1.51 (1.10-2.07) |
| 1.28 (0.89-1.84) |
| 0.96 (0.61-1.52) |
| 0.34 |
| 55-69 |
| 325 |
| 1.11 (1.00-1.23) |
| 1.07 (0.97-1.19) |
| 1.03 (0.91-1.17) |
| 0.30 |
| 70-94 |
| 402 |
| 1.14 (1.04-1.25) |
| 1.13 (1.02-1.24) |
| 1.07 (0.95-1.20) |
| 0.18 |
| **Sex** |
| Women |
| 352 |
| 1.29 (1.15-1.46) |
| 1.26 (1.11-1.43) |
| 1.13 (0.97-1.31) |
| 0.09 |
| Men |
| 404 |
| 1.09 (1.00-1.18) |
| 1.06 (0.97-1.15) |
| 1.01 (0.91-1.13) |
| 0.04 |

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**a**Hazard ratio per 1 standard deviation increment in pericardial fat volume (41 mL).

**b**Adjusted for age, study, sex, and race/ethnicity (except in analyses stratified by these characteristics).

**c**Adjusted for Model 1 variables plus height, systolic blood pressure (linear), treated hypertension, and glucose status (normal, impaired fasting glucose, diabetes).

**d**Adjusted for Model 2 variables plus BMI (linear spline).

AF, atrial fibrillation; CI, confidence interval.
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African American group

| Race/ethnicity | N with | HR^a (95% CI) for AF per SD increment in BMI | N with | HR^a (95% CI) for AF per SD increment in BMI, after adjustment for pericardial fat volume | Ratio of the HRs^a for AF associated with a 1-SD increment in BMI, without to with adjustment for pericardial fat volume (95% CI) |
|---------------|-------|--------------------------------------------|-------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| Overall       | 5,125 | 1.01 (0.86-1.19)                            | 2866  | 1.50 (1.30-1.73)                                                                                     | 1.46 (1.26-1.70)                                                                                     | 1.02 (0.99-1.06)                                                                                     |
| African American group | 1,611 | 0.91 (0.64-1.28)                            | 1552  | 1.32 (1.05-1.67)                                                                                     | 1.27 (1.00-1.62)                                                                                     | 1.04 (0.97-1.11)                                                                                     |
| White         | 1,856 | 1.08 (0.85-1.38)                            | 712   | 1.57 (1.20-2.05)                                                                                     | 1.64 (1.24-2.16)                                                                                     | 0.96 (0.88-1.04)                                                                                     |
| Hispanic      | 903   | 0.93 (0.59-1.48)                            | 569   | 1.92 (1.45-2.55)                                                                                     | 1.71 (1.27-2.31)                                                                                     | 1.12 (1.02-1.24)                                                                                     |
| Chinese       | 755   | 0.97 (0.64-1.47)                            | 33    | A^0                                                                                                  | A^0                                                                                                  | A^0                                                                                                  |

^aAll 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 adjusted for study and race/ethnicity, and the analysis in African Americans was also adjusted for study. |  |
^bHR not calculated because the small number of AF cases in Chinese participants with obesity led to unstable estimates. |  |
SD of BMI = 6 kg/m^2. |  |
AF, atrial fibrillation; HR, hazard ratio; CI, confidence interval; SD, standard deviation. |  |

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). Because 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, adipocyte brokines 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 study (14) and Framingham Heart Study (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 (odds ratio 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 white people. In our analysis, it is not clear why there was stronger evidence for an association between pericardial fat volume and AF in Hispanic individuals 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 versus 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.

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References

1. Wolf PA, Dawber TR, Thomas HE, Jr., et al. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. *Neurology* 1978;28:973-977.
2. Thacker EL, McKnight B, Psaty BM, et al. Atrial fibrillation and cognitive decline: a longitudinal cohort study. *Neurology* 2011;81:119-125.
3. Kwok CS, Loke YK, Hale R, et al. Atrial fibrillation and incidence of dementia: a systematic review and meta-analysis. *Neurology* 2011;76:914-922.
4. Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation* 2003;107:2920-2925.
5. Benjamin EJ, Wolf PA, D’Agostino RB, et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 1998;98:946-952.
6. Dublin S, French B, Glazer NL, et al. Risk of new-onset atrial fibrillation in relation to body mass index. *Arch Intern Med* 2006;166:2322-2328.
7. Wang TJ, Parise H, Levy D, et al. Obesity and the risk of new-onset atrial fibrillation. *JAMA* 2004;292:2471-2477.
8. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation* 2006;114:119-125.
9. Sacks HS, Fain JN. Human epicardial adipose tissue: a review. *Am Heart J* 2007;153:907-917.
10. Wong CW, Ganesan AN, Selvanayagam JB. Epicardial fat and atrial fibrillation: current evidence, potential mechanisms, clinical implications, and future directions [published online March 1, 2016]. *Eur Heart J* 2016; doi:10.1093/eurheartj/ehw045.
11. Scridon A, Dobreanu D, Chevalier P, et al. Inflammation, a link between obesity and atrial fibrillation. *Inflamm Res* 2015;64:383-393.
12. Arora R, Knight BP. Epicardial atrial fat: not quite as idle as it looks. *Heart Rhythm* 2015;12:266-267.
13. Carr JJ, Ding J. Response to “Epicardial and pericardial fat: close, but very different” [letter]. *Obesity* 2009;17:626-627.
14. Mahabadi AA, Lehmann N, Kalisch H, et al. Association of epicardial adipose tissue and left atrial size on non-contrast CT with atrial fibrillation: the Heinz Nixdorf Recall Study. *Eur Heart J Cardiovasc Imaging* 2014;15:863-869.
15. Lee JJ, Yin X, Hoffmann U, et al. Relation of pericardial fat, intrathoracic fat, and abdominal visceral fat with incident atrial fibrillation (from the Framingham Heart Study). *Am J Cardiol* 2016;118:1486-1492.
16. Taylor HA, Wilson JG, Jr., Jones DW, et al. Toward resolution of cardiovascular health disparities in African Americans: design and methods of the Jackson Heart Study. *Ethn Dis* 2005;15:864-17.
17. Rodriguez CJ, Soliman EZ, Alonso A, et al. Atrial fibrillation incidence and risk factors in relation to race-ethnicity and the population attributable fraction of atrial fibrillation risk factors: the Multi-Ethnic Study of Atherosclerosis. *Ann Epidemiol* 2015;25:71-76.
18. Brinkley TE, Hsu FC, Carr JJ, et al. Pericardial fat is associated with carotid stiffness in the Multi-Ethnic Study of Atherosclerosis. *Nutr Metab Cardiovasc Dis* 2011;21:332-338.
19. Alonso A, Agarwal SK, Soliman EZ, et al. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J* 2009;158:111-117.
20. JENSEN PN, THACKER EL, DUBLIN S, et al. Racial differences in the incidence of and risk factors for atrial fibrillation in older adults: the Cardiovascular Health Study. *J Am Geriatr Soc* 2013;61:276-280.
21. Perez MV, Wang PJ, Larson JC, et al. Risk factors for atrial fibrillation and their population burden in postmenopausal women: the Women’s Health Initiative Observational Study. *Heart* 2013;99:1173-1178.
22. BILD DE, BLAEMKE DA, BURKE GL, et al. Multi-Ethnic Study of Atherosclerosis: objectives and design. *Am J Epidemiol* 2002;156:871-881.
23. 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.
24. 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.
25. Loo J, Fox CS, Hickson D, et al. Pericardial adipose tissue, atherosclerosis, and cardiovascular disease risk factors: the Jackson Heart Study. *Diabetes Care* 2010;33:1635-1639.
26. Wallace ER, Siscovick DS, Sitlani CM, et al. Incident atrial fibrillation and disability-free survival in the Cardiovascular Health Study. *J Am Geriatr Soc* 2016;64:838-843.
27. Carlin JB, Galati JC, Royston P. A new framework for managing and analyzing multiply imputed data in Stata. *Stata* 2006;8:49-67.
28. Alonso A, Krijthe BP, Aspelund T, et al. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. *J Am Heart Assoc* 2013;2:e000102. doi: 10.1161/JAHA.112.000102.
29. Judd CM, Kenny DA. Process analysis: estimating mediation in treatment evaluations. *Eval Rev* 1981;5:602-619.
30. JENSEN PN, JOHNSON K, FLOYD J, et al. A systematic review of validated methods for identifying atrial fibrillation using administrative data. *Pharmacoepidemiol Drug Saf* 2012;21(Suppl 1):141-147.
31. Sacks HS, Fain JN. Human epicardial fat: what is new and what is missing? *Clin Exp Pharmacol Physiol* 2011;38:879-887.
32. Ventecler N, Guglielm V, Balse E, et al. Human epicardial adipose tissue induces fibrosis of the atrial myocardium through the secretion of adipokines. *Eur Heart J* 2015;36:795-805a.
33. Poirier P, Gils TD, Bray GA, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss. *Atheroscler Thromb Vasc Biol* 2006;26:968-976.
34. Al-Rawahi M, Proietti R, Thanssoulis G. Pericardial fat and atrial fibrillation: epidemiology, mechanisms and interventions. *Int J Cardiol* 2015;195:98-103.
35. Abed HS, Wittert GA, Leong DP, et al. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. *JAMA* 2013;310:2050-2060.