Obesity and the Risk of New-Onset Atrial Fibrillation

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The prevalence of atrial fibrillation (AF), the most common cardiac dysrhythmia, is expected to increase several-fold in the coming decades. Because the onset of AF is associated with considerable morbidity and mortality despite contemporary therapies, the identification of potentially modifiable risk factors for AF is an important goal. Prior studies have demonstrated that advanced age, diabetes, hypertension, and cardiovascular disease increase the risk of developing AF. Obesity occurs in association with most of these conditions, but it is unclear whether obesity itself predisposes to AF. The rationale for hypothesizing such a link comes from experimental and clinical data suggesting that adiposity influences atrial and ventricular structure, autonomic tone, and ventricular diastolic function. Prior epidemiologic studies have yielded conflicting results regarding whether obesity is a risk factor for AF, but these studies were potentially limited by short-term follow-up, failure to account for interim cardiovascular events, and lack of echocardiographic data. The availability of long-term follow-up in the Framingham Heart Study provided an opportunity to examine the relationship between obesity and AF risk.

Objective To examine the association between body mass index (BMI) and the risk of developing new-onset AF.

Design, Setting, and Participants Prospective, community-based observational cohort in Framingham, Mass. We studied 5282 participants (mean age, 57 [SD, 13] years; 2898 women [55%]) without baseline AF (electrocardiographic AF or arterial flutter). Body mass index (calculated as weight in kilograms divided by square of height in meters) was evaluated as both a continuous and a categorical variable (normal defined as <25.0; overweight, 25.0 to <30.0; and obese, ≥30.0). In addition to adjusting for clinical confounders by multivariable techniques, we also examined models including echocardiographic left atrial diameter to examine whether the influence of obesity was mediated by changes in left atrial dimensions.

Main Outcome Measure Association between BMI or BMI category and risk of developing new-onset AF.

Results During a mean follow-up of 13.7 years, 526 participants (234 women) developed AF. Age-adjusted incidence rates for AF increased across the 3 BMI categories in men (9.7, 10.7, and 14.3 per 1000 person-years) and women (5.1, 8.6, and 9.9 per 1000 person-years). In multivariable models adjusted for cardiovascular risk factors and interim myocardial infarction or heart failure, a 4% increase in AF risk per 1-unit increase in BMI was observed in men (95% confidence interval [CI], 1%-7%; P = .02) and in women (95% CI, 1%-7%; P = .009). Adjusted hazard ratios for AF associated with obesity were 1.52 (95% CI, 1.09-2.13; P = .02) and 1.46 (95% CI, 1.03-2.07; P = .03) for men and women, respectively, compared with individuals with normal BMI. After adjustment for echocardiographic left atrial diameter in addition to clinical risk factors, BMI was no longer associated with AF risk (adjusted hazard ratios per 1-unit increase in BMI, 1.00 [95% CI, 0.97-1.04], P = .84 in men; 0.99 [95% CI, 0.96-1.02], P = .56 in women).

Conclusions Obesity is an important, potentially modifiable risk factor for AF. The excess risk of AF associated with obesity appears to be mediated by left atrial dilatation. These prospective data raise the possibility that interventions to promote normal weight may reduce the population burden of AF.

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Original Contribution

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proposed by the Boston Medical Center in-
imained eligible. All protocols were ap-
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isting medical condition. A total of 5282

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years (n=701), prior or current AF
erarchical fashion: age younger than 35
nations but still provided a long period
veloping AF, after adjustment for other
factors and interim events. Because
chardiograms were routinely per-
on study participants, we also had the
ability to investigate the hypothesis
obesity predisposes to AF through
its influence on left atrial structure.8

METHODS
Study Sample
The design and selection criteria of the
Framingham Heart Study and the
Framingham Offspring Study have been
detailed previously.14,15 Participants at-
tending the 16th examination of the
original cohort (n=2351; 1979-1982) or
the second examination of the off-
spring cohort (n=3867; 1979-1983)
were eligible for the present investiga-
tion. We chose these examinations
because they included routine echocar-
diograms and reflected more contem-
porary experience than earlier exami-
nations but still provided a long period
of follow-up. We excluded partici-
ants for the following reasons, in
hierarchical fashion: age younger than 35
years (n=701), prior or current AF
(n=127), or underweight (body mass in-
ex [BMI] <18.5, n=108). Under-
weight participants were excluded to
reduce the possibility of including
individuals with cachexia from an ex-
isting medical condition. A total of 5282
participants (2898 women [55%]) re-
ained eligible. All protocols were ap-
proved by the Boston Medical Center
institutional review board, and participants
provided written informed consent.

Clinical Evaluation and Definitions
Medical history, physical examination,
and electrocardiography were rou-
tinely administered at each Framing-
ham Heart Study examination.14,15 Height
and weight were directly measured us-
ing a standardized protocol. Body mass
index was calculated by dividing weight
in kilograms by the square of the height
in meters. Hypertension was defined as
systolic blood pressure greater than or
equal to 140 mm Hg, diastolic blood
pressure greater than or equal to 90
mm Hg, or use of antihypertensive
therapy. Criteria for diabetes mellitus
were a fasting glucose level of 126 mg/dL
(7.0 mmol/L) or greater, random glu-
cose level of 200 mg/dL (11.1 mmol/L)
or greater, or use of insulin or medica-
tions used to treat hyperglycemia. Elec-
trocardiographic left ventricular hyper-
trophy was defined as increased voltage
with accompanying lateral repolariza-
tion abnormalities.16 A standardized 2-di-
mensional guided M-mode echocardi-
ogram was also performed at the baseline
examinations.17 Left atrial diameter at
end-systole was measured according to
American Society of Echocardiography
guidelines.18

Medical records were obtained for all
hospitalizations and physician visits re-
lated to cardiovascular disease during
follow-up and were reviewed by a com-
mittee of 3 investigators. Atrial fibril-
lation was diagnosed if AF or atrial flut-
ter was present on an electrocardiogram
obtained from a hospital or physician
chart, or from 1 of the routine Framing-
ham clinic examinations (every 2 years
in the original cohort and every 4 years
in the offspring cohort). The electro-
cardiographic interpretation of AF was
confirmed by 1 of 2 Framingham Heart
Study cardiologists (D.L., E.J.B.). Cri-
teria for other cardiovascular events, in-
cluding myocardial infarction (MI) and
congestive heart failure, have been de-
scribed previously.19

Statistical Analyses
Body mass index was analyzed as both
a continuous and a categorical vari-
able, using the World Health Organi-
zation/National Institutes of Health
classification scheme (normal defined as
<25.0; overweight, 25.0 to <30.0; and
obese, ³30.0).20 Sex-specific Kaplan-
Meier curves were plotted to depict the
probability of developing AF accord-
ing to BMI category.

We examined the association be-
 tween BMI or BMI category and the risk
of developing new-onset AF using sex-
specific Cox proportional hazards re-
gressions.21 Death was treated as a cen-
soring event. Follow-up was also
censored after 16 years, with the final par-
ticipant censored in this manner in Oc-
tober 1999. There was no significant in-
teraction between follow-up time and
BMI for prediction of AF in the primary
Cox model, suggesting that the propor-
tional hazards assumption was ap-
propriate. We estimated age-adjusted mod-
els as well as multivariable models.
Covariates selected for adjustment were
based on prior reports4 and included age,
systolic blood pressure, use of antihy-
pertensive therapy, diabetes mellitus,
electrocardioographic left ventricular hy-
pertrophy, history of MI or congestive
heart failure, regular use of cigarettes
in the prior year, and significant systolic
murmur (grade 3 out of 6 or greater) or
any diastolic murmur. The 3 BMI cat-
 egories were modeled with 2 dichoto-
mous predictor variables (for over-
weight and obese); we also estimated
separate models with an ordinal predic-
tor variable for BMI category to test for
a linear trend across BMI categories. In
additional models, we examined whether
obesity predisposed to AF through an in-
term (ie, occurring after the baseline ex-
amination and before the onset of AF)
MI or heart failure event (considered as
time-dependent covariates).

We tested for effect modification by
age, sex, or systolic blood pressure by in-
cluding multiplicative interaction terms
with these variables and BMI. We as-
essed the influence of different de-
gresses of obesity by incorporating cat-
egorical variables for stage 1 obesity (BMI
30 to <35) and stage 2 or 3 obesity (BMI
³35). We also performed an additional
analysis excluding individuals with BMI
of 30 or greater to determine whether an
association with BMI was observed in
nonobese individuals. This analysis was
sex-pooled (to maximize statistical
power) and adjusted for all covariates,
including sex. Additional secondary
analyses were performed that elimi-
nated the exclusion of younger individu-
als (<35 years) or underweight individu-
als (BMI <18.5), adjusted for alcohol use (as a continuous or dichoto-
mous variable), adjusted for cohort sta-
tus (original cohort vs offspring co-
hort), and excluded individuals who
developed atrial flutter. To remove the
contribution of parental history of AF,
we repeated the primary Cox analyses with stratification for cohort status.  
We hypothesized that the relation between obesity and AF may be mediated by the influence of obesity on left atrial structure. To examine this hypothesis, we constructed additional sex-specific models with adjustment for echocardiographic left atrial size measured at the baseline examination, before any of the participants had developed AF.

All analyses were performed with SAS version 8.0 (SAS Institute, Cary, NC). A 2-sided *P*<.05 was considered statistically significant.

**RESULTS**

**Study Sample**

Baseline characteristics of the 5282 participants in the study sample are provided in Table 1. The mean age was 56 (range, 35 to 90) years in men and 58 (range, 35 to 90) years in women. Of the 2384 men, 1216 (51%) were overweight and 413 (17%) were obese; of the 2898 women, 898 (31%) were overweight and 464 (16%) were obese.

**Incidence of AF**

During a mean of 13.7 years of follow-up, 292 men and 234 women developed AF. Prior to developing AF, 43 men and 22 women had experienced an MI, and 36 men and 29 women had experienced congestive heart failure. During the follow-up period, 1452 participants (715 women) died, of whom 1168 (572 women) were free of AF.

Age-adjusted incidence rates for AF increased across categories of BMI in both men and women (Table 2). The figure displays Kaplan-Meier curves showing that the probability of developing AF over time increased across categories of BMI.

**Multivariable Analyses**

Results of the multivariable Cox proportional hazards regressions are shown in Table 3. After adjustment for age alone, each 1-unit increase in BMI was associated with increases of 5% in the risk of AF for men (*P* = .002) and 4% for women (*P* = .001). These relations remained significant in multivariable-adjusted models, with a 4% increase in risk of AF per 1-unit increase in BMI for both men (*P* = .02) and women (*P* = .01). Similarly, age-adjusted and fully-adjusted hazard ratios (HRs) for AF increased across BMI categories in both men and women (Table 3). Multivariable-adjusted HRs for AF were 1.49 (95% confidence interval [CI], 1.06-2.09) for obese men and 1.45 (95% CI, 1.03-2.05) for obese women, compared with men and women with normal BMI. These findings were not attenuated in models adjusting for interim MI or congestive heart failure in addition to baseline covariates. Each 1-unit increase in BMI was associated with a 4% increase in AF risk in men (*P* = .02) and women (*P* = .009). The multivariable-

<table>
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<tr>
<th>Table 1. Baseline Characteristics, by Body Mass Index Category*</th>
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<tr>
<td><strong>Men</strong></td>
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<tr>
<td>Normal (n = 755)</td>
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<tr>
<td>Age, mean (SD), y</td>
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<tr>
<td>Body mass index, mean (SD)*</td>
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<tr>
<td>Smoker, No. (%)†</td>
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<td>Blood pressure, mean (SD), mm Hg</td>
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<td>Systolic</td>
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<td>Antihypertensive therapy, No. (%)</td>
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<td>Diabetes, No. (%)</td>
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<td>Electrocardiographic LVH, No. (%)</td>
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<td>Significant heart murmur, No. (%)</td>
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<tr>
<td>Heavy alcohol use, No. (%)‡</td>
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<td>Prior MI, No. (%)</td>
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<td>Prior CHF, No. (%)</td>
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<tr>
<th>Table 2. Incidence of Atrial Fibrillation, by Body Mass Index Category</th>
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<tr>
<td><strong>Men</strong></td>
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<tr>
<td>Normal</td>
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<tr>
<td>No. of events/person-years</td>
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<td>Age-adjusted incidence per 1000 person-years (95% CI)</td>
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Abbreviations: CHF, congestive heart failure; LVH, left ventricular hypertrophy; MI, myocardial infarction.

*Body mass index was calculated as weight in kilograms divided by the square of height in meters. Categories were as follows: normal, <25.0; overweight, 25.0 to <30.0; obese, ≥30.0.

†Regular use of cigarettes in the prior year.

‡Defined as >1 drink/d in women and >2 drinks/d in men.
adjusted HRs for AF were 1.52 (95% CI, 1.09-2.13) for obese men and 1.46 (95% CI, 1.03-2.07) for obese women. The association between BMI and risk of AF did not vary by age, sex, or systolic blood pressure (P > .10 for all interaction terms). To assess the influence of different degrees of obesity, we estimated regressions with 4 BMI categories (normal, overweight, stage 1 obesity, and stage 2 or 3 obesity). Age-adjusted HRs for AF increased progressively across these 4 BMI categories in men (1.00, 1.12 [95% CI, 0.85-1.48], 1.61 [95% CI, 1.14-2.27], 2.30 [95% CI, 1.22-4.33]; P = .001 for trend) and women (1.00, 1.20 [95% CI, 0.90-1.61], 1.46 [95% CI, 1.00-2.15], 1.93 [95% CI, 1.15-3.25]; P = .005 for trend). After adjustment for clinical variables and interim MI or heart failure, these findings remained significant in men (1.00, 1.10 [95% CI, 0.84-1.46], 1.48 [95% CI, 1.04-2.10], 1.88 [95% CI, 0.93-3.79]; P = .01 for trend) and women (1.00, 1.13 [95% CI, 0.84-1.52], 1.39 [95% CI, 0.94-2.05], 1.67 [95% CI, 0.98-2.85]; P = .03 for trend).

In a secondary analysis restricted to nonobese individuals (BMI < 30), the association between BMI and risk for AF remained significant (sex-pooled multivariable-adjusted HR per 1-unit increase in BMI, 1.06; 95% CI, 1.02-1.10; P = .002). Results were also unchanged when analyses were repeated to include younger individuals (< 35 years) or obese individuals with BMI < 18.5 and in analyses adjusting for cohort status (original cohort vs offspring cohort) or alcohol use. Multivariable-adjusted HRs for AF associated with BMI were also similar after excluding the 49 individuals who developed atrial flutter. We repeated the Cox analyses with stratification for cohort status, with findings similar to those in the original model (adjusted HR per 1-unit increase in BMI: men, 1.04; 95% CI, 1.01-1.07; P = .02; women, 1.03; 95% CI, 1.01-1.06; P = .02).

### Echocardiographic Analyses

Because we hypothesized that the influence of obesity on risk of AF may be mediated by left atrial enlargement, we performed subsequent analyses adjusting for echocardiographic left atrial diameter (available in 2229 men [93%] and 2698 women [93%]) in addition to clinical covariates. Mean (SD) left atrial diameter was higher in obese men (4.4 [0.5] cm) compared with overweight men (4.1 [0.4] cm) (P < .001) and those with normal BMI (3.8 [0.4] cm).
We observed that obesity was associated with a 50% increase in the risk of AF. This value may underestimate the aggregate impact of obesity on AF risk, because it adjusts for conditions such as hypertension and diabetes that predispose to AF and are common sequelae of obesity. Furthermore, whereas the influence of obesity on the chances of developing AF in any given patient may be modest, the implication of these results for the population burden of AF may be substantial, because obesity is highly prevalent and potentially modifiable.23 Thus, even a small decrease in the prevalence of obesity could lead to a large reduction in the incidence of AF.

The observation that HRs for overweight did not reach statistical significance may reflect either a threshold effect or reduced statistical power to find an effect among overweight individuals (given the smaller relative risk associated with being overweight). We estimate that the statistical power to detect the observed HRs in the overweight group ranged from 40% (men) to 69% (women). Furthermore, when we excluded individuals with obesity (BMI >30) from the sample, BMI remained significantly associated with risk of AF, which suggests that the elevated AF risk was not restricted to obese individuals.

Potential Mechanisms

Left atrial enlargement is an important precursor of AF,23 and prior studies have shown that BMI is one of the most powerful determinants of left atrial size.9,25 Elevated plasma volume,26 ventricular diastolic dysfunction,13 and enhanced neurohormonal activation27 accompany obesity and may contribute to left atrial enlargement and electrical instability. Furthermore, recent studies suggest that adiposity may have a direct influence on myocardial structure, perhaps via increased oxidative stress28 or lipoapoptosis.11

Extracardiac factors that may increase atrial arrhythmogenicity in obese individuals include autonomic dysfunction12 and sleep apnea.29 Kanagala et al29 reported an association between obstructive sleep apnea and recurrence of AF after cardioversion, postulating that hypoxemia, increased afterload, or pulmonary vasoconstriction may play roles.

Comparison With Prior Studies

A previous report from the Framingham Heart Study did not find a significant association between BMI and the risk of AF, but that study pooled repeated observations over a 2-year follow-up period.24 Relations of BMI with the short-term risk of AF may be weak, in part because AF is a disease of elderly individuals and BMI frequently decreases with age and illness. A few epidemiologic studies have suggested an association between BMI and AF, but these studies were retrospective,6 limited to men,7 or the diagnosis of AF was based on hospital admission codes.7

The present investigation extends the results of prior studies to a large, prospective, community-based cohort that has been under continuous surveillance for AF and cardiovascular events for several decades. We used contemporary criteria for categorizing BMI as recommended by the World Health Organization and National Institutes of Health.20 Another important feature of this investigation was the ability to adjust for interim cardiovascular events and baseline echocardiographic data.

Limitations

Despite the strengths listed above, several limitations deserve mention. Although ascertainment of AF was based on electrocardiograms obtained directly from physician offices, hospitals, and routine Framingham Heart Study examinations, we cannot exclude the possibility that some episodes of AF were missed because they were asymptomatic or minimally symptomatic and transient. However, such misclassification would not be expected to affect obese and nonobese individuals differentially; random misclassification might have led to a conservative bias. Additionally, we included all episodes of new-onset AF and did not distinguish between chronic and...
paroxysmal AF. It is possible that the influence of obesity differed according to the type of AF. Similarly, we included both atrial flutter and AF in our end point; we had too few cases of atrial flutter to study this arrhythmia separately. Whereas many individuals with atrial flutter subsequently experience AF, the former may have a distinct pathogenesis and risk factors.

Atrial electrophysiological changes may play a critical role in the pathogenesis and maintenance of AF. Given the observational nature of our cohort, we were limited to characterizing atrial size (with echocardiography). Thus, further studies are necessary to understand the atrial changes in obese individuals that precede AF. Although we adjusted for interim MI and heart failure, we did not account for the development of other events or noncardiac surgeries that may have affected the risk of AF. Because variation in baseline left atrial size appeared to account for the link between obesity and AF, we do not believe that there was substantial confounding from these unmeasured risk factors. Additionally, we did not study the influence of changes in BMI over time. Participants attending multiple examinations, in whom serial BMI measurements would be available, may be healthier and less likely to develop AF than those attending fewer examinations. Also, standardized echocardiographic data were not available at every follow-up examination.

Because we used BMI as a surrogate measure of adiposity, it is possible that we misclassified individuals with high muscle mass. This misclassification may have affected men more than women, particularly in the overweight category. Although we did not find evidence of effect modification by sex in analyses incorporating sex interaction terms, these analyses may have been underpowered to detect modest interactions. Also, we did not measure waist-hip ratio or waist circumference at these examinations; these measures of abdominal adiposity may add incremental information to BMI in the prediction of cardiovascular risk. Because parental history may be a risk factor for AF, we performed stratified analyses separating parents and offspring who were members of the Framingham original and offspring cohorts, respectively. While these analyses did not account for sibling influences, the lack of attenuation of our findings in the stratified analyses suggests that the association with BMI is not explained by AF heritability.

The results of this study may not be generalizable to individuals with very advanced age or those with severe hypertension, because of the low prevalence of these characteristics in the study sample. Because age and age-related risk factors are powerfully related to the risk of AF, we cannot exclude the possibility that our findings would have differed in a substantially older population. Also, our cohort is predominantly white; thus, our findings may not apply to nonwhite individuals.

CONCLUSIONS

Obesity has become increasingly prevalent in the United States. Our findings suggest that obesity is a risk factor for AF, the most common disturbance of cardiac rhythm. Because management of AF remains a difficult clinical challenge, the identification of potentially modifiable risk factors may have important public health implications.

Although our study was observational, it raises the intriguing possibility that weight reduction may decrease the risk of AF. In this regard, it is interesting to note that weight reduction has been linked to regression of left atrial enlargement. Further studies are needed to understand the influence of adiposity on cardiac remodeling, to document the effects of weight loss on the risk of new AF, and to investigate the interaction between obesity and therapies for chronic or paroxysmal AF.

Author Contributions: Dr Benjamin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses. Drs Vasan and Benjamin contributed equally to this article.

Study concept and design: Wang, D’Agostino, Wolf, Vasan, Benjamin.

Acquisition of data: Wang, Levy, D’Agostino, Wolf, Vasan, Benjamin.

Analysis and interpretation of data: Wang, Parise, Levy, D’Agostino, Vasan, Benjamin.

Critical revision of the manuscript for important intellectual content: Parise, Levy, D’Agostino, Wolf, Vasan, Benjamin.

Statistical analysis: Parise, D’Agostino.

Obtained funding: Wolf, Benjamin.

Administrative, technical, or material support: Levy, Benjamin.

Study supervision: Vasan, Benjamin.

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References


If we had no winter, the spring would not be so pleasant: if we did not sometimes taste adversity, prosperity would not be so welcome.
—Anne Bradstreet (1612-1672)