Obesity and the Risk of New-Onset Atrial Fibrillation

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Context Obesity is associated with atrial enlargement and ventricular diastolic dysfunction, both known predictors of atrial fibrillation (AF). However, it is unclear whether obesity is a risk factor for AF.

Objective To examine the association between body mass index (BMI) and the risk of developing 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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THE PREVALENCE OF ATRIAL FIbrillation (AF), the most common cardiac dysrhythmia, is expected to increase several-fold in the coming decades.[1] 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.[2,3] Prior studies have demonstrated that advanced age, diabetes, hypertension, and cardiovascular disease increase the risk of developing AF.[4-7] 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,[8-11] autonomic tone,[12] and ventricular diastolic function.[13] 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.[4-7]

The availability of long-term follow-up in the Framingham Heart Study provided an opportunity to examine the

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association of obesity with the risk of developing AF, after adjustment for other risk factors and interim events. Because echocardiograms were routinely performed on study participants, we also had the ability to investigate the hypothesis that 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 attending the 16th examination of the original cohort (n=2351; 1979-1982) or the second examination of the offspring cohort (n=3867; 1979-1983) were eligible for the present investigation. We chose these examinations because they included routine echocardiograms and reflected more contemporary experience than earlier examinations but still provided a long period of follow-up. We excluded participants for the following reasons, in hierarchical fashion: age younger than 35 years (n=701), prior or current AF (n=127), or underweight (body mass index [BMI] <18.5, n=108). Underweight participants were excluded to reduce the possibility of including individuals with cachexia from an existing medical condition. A total of 5282 participants (2898 women [55%]) remained eligible. All protocols were approved 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 routinely administered at each Framingham Heart Study examination.[14,15] Height and weight were directly measured using 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 glucose level of 200 mg/dL (11.1 mmol/L) or greater, or use of insulin or medications used to treat hyperglycemia. Electrocardiographic left ventricular hypertrophy was defined as increased voltage with accompanying lateral repolarization abnormalities.[16] A standardized 2-dimensional guided M-mode echocardiogram 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 related to cardiovascular disease during follow-up and were reviewed by a committee of 3 investigators. Atrial fibrillation was diagnosed if AF or atrial flutter was present on an electrocardiogram obtained from a hospital or physician chart, or from 1 of the routine Framingham clinic examinations (every 2 years in the original cohort and every 4 years in the offspring cohort). The electrocardiographic interpretation of AF was confirmed by 1 of 2 Framingham Heart Study cardiologists (D.L., E.J.B.). Criteria for other cardiovascular events, including myocardial infarction (MI) and congestive heart failure, have been described previously.[19]

Statistical Analyses

Body mass index was analyzed as both a continuous and a categorical variable, using the World Health Organization/National Institutes of Health classification scheme (normal defined as <25.0; overweight, 25.0 to <30.0; and obese, ≥30.0).[20] Sex-specific Kaplan-Meier curves were plotted to depict the probability of developing AF according to BMI category.

We examined the association between BMI or BMI category and the risk of developing new-onset AF using sex-specific Cox proportional hazards regressions.[21] Death was treated as a censoring event. Follow-up was also censored after 16 years, with the final participant censored in this manner in October 1999. There was no significant interaction between follow-up time and BMI for prediction of AF in the primary Cox model, suggesting that the proportional hazards assumption was appropriate. We estimated age-adjusted models as well as multivariable models. Covariates selected for adjustment were based on prior reports[4] and included age, systolic blood pressure, use of antihypertensive therapy, diabetes mellitus, electrocardiographic left ventricular hypertrophy, 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 categories were modeled with 2 dichotomous predictor variables (for overweight and obese); we also estimated separate models with an ordinal predictor 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 interim (ie, occurring after the baseline examination 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 including multiplicative interaction terms with these variables and BMI. We assessed the influence of different degrees of obesity by incorporating categorical variables for stage 1 obesity (BMI 30 to <35) and stage 2 or 3 obesity (BMI ≥35). 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 eliminated the exclusion of younger individuals (<35 years) or underweight individuals (BMI <18.5), adjusted for alcohol use (as a continuous or dichotomous variable), adjusted for cohort status (original cohort vs offspring cohort), 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.[22]

We hypothesized that the relation between obesity and AF may be mediated by the influence of obesity on left atrial structure.[8,9] 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 1. Baseline Characteristics, by Body Mass Index Category*

	Men			Women		
	Normal (n = 755)	Overweight (n = 1216)	Obese (n = 413)	Normal (n = 1536)	Overweight (n = 898)	Obese (n = 464)
Age, mean (SD), y	55 (13)	56 (13)	55 (12)	55 (14)	61 (13)	60 (13)
Body mass index, mean (SD)*	23.2 (1.4)	27.2 (1.4)	32.8 (2.8)	22.3 (1.6)	27.2 (1.4)	34.2 (4.0)
Smoker, No. (%)†	265 (35)	328 (27)	117 (29)	496 (32)	238 (27)	95 (21)
Blood pressure, mean (SD), mm Hg						
Systolic	129 (19)	132 (18)	137 (17)	126 (21)	133 (21)	138 (18)
Diastolic	78 (9)	81 (9)	85 (9)	75 (9)	77 (9)	80 (9)
Antihypertensive therapy, No. (%)	92 (12)	195 (16)	118 (29)	201 (13)	250 (28)	165 (36)
Diabetes, No. (%)	50 (7)	106 (9)	55 (13)	45 (3)	49 (6)	63 (14)
Electrocardiographic LVH, No. (%)	11 (2)	10 (1)	6 (2)	19 (1)	8 (1)	9 (2)
Significant heart murmur, No. (%)	17 (2)	27 (2)	13 (3)	38 (3)	33 (4)	7 (2)
Heavy alcohol use, No. (%)‡	192 (26)	308 (26)	103 (25)	353 (23)	126 (14)	61 (13)
Prior MI, No. (%)	41 (5)	60 (5)	26 (6)	14 (1)	14 (2)	7 (2)
Prior CHF, No. (%)	4 (1)	10 (1)	2 (1)	9 (1)	16 (2)	6 (1)

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.

Table 2. Incidence of Atrial Fibrillation, by Body Mass Index Category

	Men			Women		
	Normal	Overweight	Obese	Normal	Overweight	Obese
No. of events/person-years	77/9934	149/16 278	66/5280	89/22 070	91/12 331	54/6284
Age-adjusted incidence per 1000 person-years (95% CI)	9.7 (7.5-11.9)	10.7 (9.0-12.5)	14.3 (10.8-17.7)	5.1 (4.1-6.2)	8.6 (6.8-10.3)	9.9 (7.2-12.5)

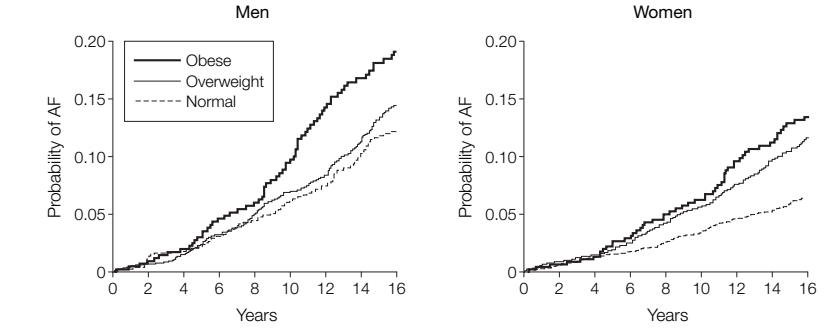
Abbreviation: CI, confidence interval.

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 underweight individuals (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; $P=.02$).

Figure. Kaplan-Meier Curves Showing Cumulative Hazards of Developing Atrial Fibrillation (AF) in Men and Women, by Baseline Body Mass Index Category



No. at Risk										
Obese	413	380	336	280	238	464	444	397	345	299
Overweight	1216	1143	1023	908	776	898	852	776	696	614
Normal	755	699	614	557	482	1536	1476	1394	1282	1180

Horizontal axis represents time since the baseline examination. Body mass index categories were as follows: normal, <25.0; overweight, 25.0 to <30.0; and obese, ≥30.0.

Table 3. Body Mass Index and Risk of Incident Atrial Fibrillation, Multivariable Models*

	Men		Women	
Model	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
With BMI as a continuous variable (+1 unit)				
Age-adjusted	1.05 (1.02-1.08)	.002	1.04 (1.02-1.07)	.001
Adjusted for clinical variables†	1.04 (1.01-1.07)	.02	1.04 (1.01-1.07)	.01
Adjusted for clinical variables and interim MI/CHF†	1.04 (1.01-1.07)	.02	1.04 (1.01-1.07)	.009
With BMI as a categorical variable				
Age-adjusted				
Normal	1.00		1.00	
Overweight	1.12 (0.85-1.48)	.41	1.20 (0.90-1.62)	.21
Obese	1.69 (1.22-2.35)	.002	1.59 (1.13-2.22)	.008
Trend across categories	1.29 (1.09-1.53)	.003	1.25 (1.06-1.48)	.009
Adjusted for clinical variables†				
Normal	1.00		1.00	
Overweight	1.09 (0.82-1.43)	.56	1.11 (0.83-1.50)	.49
Obese	1.49 (1.06-2.09)	.02	1.45 (1.03-2.05)	.04
Trend across categories	1.22 (1.02-1.44)	.03	1.20 (1.00-1.42)	.046
Adjusted for clinical variables and interim MI/CHF†				
Normal	1.00		1.00	
Overweight	1.10 (0.84-1.46)	.49	1.13 (0.84-1.52)	.42
Obese	1.52 (1.09-2.13)	.02	1.46 (1.03-2.07)	.03
Trend across categories	1.23 (1.03-1.46)	.02	1.20 (1.01-1.43)	.04

Abbreviations: BMI, body mass index; CHF, congestive heart failure; CI, confidence interval; HR, hazard ratio; 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.
†Clinical variables were age, systolic blood pressure, use of antihypertensive therapy, diabetes mellitus, electrocardiographic left ventricular hypertrophy, prior MI or CHF, regular use of cigarettes in the prior year, and significant heart murmur.

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)

($P<.001$). The difference in left atrial diameter between overweight men and those with normal BMI was also significant ($P<.001$). Similarly, mean left atrial diameter was higher in obese women (4.0 [0.4] cm) compared with overweight women (3.8 [0.5] cm) ($P<.001$) and those with normal BMI (3.5 [0.5] cm) ($P<.001$) and higher in overweight women compared with those with normal BMI ($P<.001$). Adjustment for left atrial diameter markedly attenuated the effect of BMI on risk of AF, rendering it statistically nonsignificant (adjusted HRs per 1-unit increment in BMI: men, 1.00; 95% CI, 0.97-1.04; $P=.84$; women, 0.99; 95% CI, 0.96-1.02; $P=.56$). Similarly, after adjustment for left atrial diameter, there was no significant trend in multivariable-adjusted HRs across BMI categories in men (1.00, 0.90 [95% CI, 0.66-1.21], and 1.11 [95% CI, 0.76-1.61]; $P=.66$ for trend) or women (1.00, 0.87 [95% CI, 0.64-1.20], and 0.89 [95% CI, 0.59-1.32]; $P=.47$ for trend). Left atrial diameter was strongly associated with incident AF (multivariable-adjusted HRs per 1-mm increment in left atrial diameter: 1.06 [95% CI, 1.04-1.09] in men, and 1.10 [95% CI, 1.07-1.13] in women; both $P<.001$).

COMMENT

These prospective, community-based data indicate that obesity is a risk factor for AF. The association of obesity with subsequent development of AF persists even after accounting for concomitant conditions such as hypertension, diabetes, and MI. The validity of our results is supported by the large sample size, long duration of follow-up, and their consistency in multiple analyses adjusting for known confounders in men and women. Furthermore, our findings have biological plausibility because obesity is associated with an important "intermediate" phenotype for AF, left atrial enlargement.[9,23] Indeed, the results of our analyses suggest that the excess risk of AF associated with obesity may be attributable to differences in left atrial size between lean and obese individuals.

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.[24] 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 $\geq$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.[8,9,25] Elevated plasma volume,[26] ventricular diastolic dysfunction,[13] and enhanced neurohormonal activation[27] 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 stress[28] or lipoapoptosis.[11]

Extracardiac factors that may increase atrial arrhythmogenicity in obese individuals include autonomic dysfunction[12] and sleep apnea.[29] Kanagala et al[29] 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.[4] 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,[5,7] 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,[30] 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.[31,32] 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.[33,34] 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.[22] 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,[4] 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.[24] 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.[35] 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.

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Study concept and design: Wang, D'Agostino, Wolf, Vasan, Benjamin.
Acquisition of data: Wang, Levy, D'Agostino, Wolf, Benjamin.
Analysis and interpretation of data: Wang, Parise, Levy, D'Agostino, Vasan, Benjamin.
Drafting of the manuscript: Wang, Parise, D'Agostino, Vasan, Benjamin.
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REFERENCES

1. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA*. 2001;285:2370-2375.
2. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation*. 1998;98:946-952.
3. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med*. 2002;347:1825-1833.
4. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort: the Framingham Heart Study. *JAMA*. 1994;271:840-844.
5. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-up Study. *Am J Med*. 1995;98:476-484.
6. Ruigomez A, Johansson S, Wallander MA, Rodriguez LA. Incidence of chronic atrial fibrillation in general practice and its treatment pattern. *J Clin Epidemiol*. 2002;55:358-363.
7. Wilhelmsen L, Rosengren A, Lappas G. Hospitalizations for atrial fibrillation in the general male population: morbidity and risk factors. *J Intern Med*. 2001; 250:382-389.
8. Vaziri SM, Larson MG, Lauer MS, Benjamin EJ, Levy D. Influence of blood pressure on left atrial size: the Framingham Heart Study. *Hypertension*. 1995;25: 1155-1160.
9. Pritchett AM, Jacobsen SJ, Mahoney DW, Rodeheffer RJ, Bailey KR, Redfield MM. Left atrial volume as an index of left atrial size: a population-based study. *J Am Coll Cardiol*. 2003;41:1036-1043.
10. Lauer MS, Anderson KM, Kannel WB, Levy D. The impact of obesity on left ventricular mass and geometry: the Framingham Heart Study. *JAMA*. 1991;266: 231-236.
11. Zhou YT, Grayburn P, Karim A, et al. Lipotoxic heart disease in obese rats: implications for human obesity. *Proc Natl Acad Sci U S A*. 2000;97:1784-1789.
12. Pelat M, Verwaerde P, Merial C, et al. Impaired atrial M(2)-cholinoceptor function in obesity-related hypertension. *Hypertension*. 1999;34:1066-1072.
13. Iacobellis G, Ribaudo MC, Leto G, et al. Influence of excess fat on cardiac morphology and func-

tion: study in uncomplicated obesity. *Obes Res*. 2002; 10:767-773.
14. Dawber TR, Meadors GF, Moore FEJ. Epidemiological approaches to heart disease: the Framingham Study. *Am J Public Health*. 1951;41:279-286.
15. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families: the Framingham Offspring Study. *Am J Epidemiol*. 1979;110:281-290.
16. Kannel WB, Gordon T, Offutt D. Left ventricular hypertrophy by electrocardiogram: prevalence, incidence, and mortality in the Framingham Study. *Ann Intern Med*. 1969;71:89-105.
17. Savage DD, Garrison RJ, Kannel WB, Anderson SJ, Feinleib M, Castelli WP. Considerations in the use of echocardiography in epidemiology: the Framingham Study. *Hypertension*. 1987;9:II40-II44.
18. Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation*. 1978;58: 1072-1083.
19. Kannel WB, Wolf PA, Garrison RJ, eds. *Some Risk Factors Related to the Annual Incidence of Cardiovascular Disease and Death in Pooled Repeated Biennial Measurements: Framingham Heart Study, 30 Year Follow-up*. Bethesda, Md: US Dept of Health and Human Services; 1987. Section 34.
20. *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*. Bethesda, Md: National Heart, Lung, and Blood Institute; 1998.
21. Cox DR. Regression models and life tables. *J R Stat Soc [B]*. 1972;34:187-220.
22. Fox CS, Parise H, D'Agostino RB Sr, et al. Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring. *JAMA*. 2004;291:2851-2855.
23. Vaziri SM, Larson MG, Benjamin EJ, Levy D. Echocardiographic predictors of nonrheumatic atrial fibrillation: the Framingham Heart Study. *Circulation*. 1994; 89:724-730.
24. Mokdad AH, Ford ES, Bowman BA, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA*. 2003;289:76-79.
25. Gerdts E, Oikarinen L, Palmieri V, et al. Correlates of left atrial size in hypertensive patients with left ventricular hypertrophy: the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) Study. *Hypertension*. 2002;39:739-743.
26. Messerli FH, Ventura HO, Reisin E, et al. Borderline hypertension and obesity: two prehypertensive states with elevated cardiac output. *Circulation*. 1982; 66:55-60.
27. Engeli S, Sharma AM. The renin-angiotensin system and natriuretic peptides in obesity-associated hypertension. *J Mol Med*. 2001;79:21-29.
28. Vincent HK, Powers SK, Stewart DJ, Shanely RA, Demirel H, Naito H. Obesity is associated with increased myocardial oxidative stress. *Int J Obes Relat Metab Disord*. 1999;23:67-74.
29. Kanagala R, Murali NS, Friedman PA, et al. Obstructive sleep apnea and the recurrence of atrial fibrillation. *Circulation*. 2003;107:2589-2594.
30. Halligan SC, Gersh BJ, Brown RD Jr, et al. The natural history of lone atrial flutter. *Ann Intern Med*. 2004; 140:265-268.
31. Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. *Cardiovasc Res*. 2002;54:230-246.
32. Kistler PM, Sanders P, Fynn SP, et al. Electrophysiologic and electroanatomic changes in the human atrium associated with age. *J Am Coll Cardiol*. 2004;44:109-116.
33. Rexrode KM, Carey VJ, Hennekens CH, et al. Abdominal adiposity and coronary heart disease in women. *JAMA*. 1998;280:1843-1848.
34. Rimm EB, Stampfer MJ, Giovannucci E, et al. Body size and fat distribution as predictors of coronary heart disease among middle-aged and older US men. *Am J Epidemiol*. 1995;141:1117-1127.
35. Alaud-din A, Meterissian S, Lisbona R, MacLean LD, Forse RA. Assessment of cardiac function in patients who were morbidly obese. *Surgery*. 1990;108: 809-818.

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)