The Long- and Short-Term Impact of Elevated Body Mass Index on the Risk of New Atrial Fibrillation

The WHS (Women’s Health Study)

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Objectives

The purpose of this study was to characterize the relationship between changes in body mass index (BMI) and incident atrial fibrillation (AF) in a large cohort of women.

Background

Obesity and AF are increasing public health problems. The importance of dynamic obesity-associated AF risk is uncertain, and mediators are not well characterized.

Methods

Cases of AF were confirmed by medical record review in 34,309 participants in the Women’s Health Study. Baseline and updated measures of BMI were obtained from periodic questionnaires.

Results

During 12.9 ± 1.9 years of follow-up, 834 AF events were confirmed. BMI was linearly associated with AF risk, with a 4.7% (95% confidence interval [CI]: 3.4 to 6.1, \( p < 0.0001 \)) increase in risk with each kilogram per square meter. Adjustment for inflammatory markers minimally attenuated this risk. When updated measures of BMI were used to estimate dynamic risk, overweight (hazard ratio [HR]: 1.22; 95% CI: 1.02 to 1.45, \( p = 0.03 \)), and obesity (HR: 1.65; 95% CI: 1.36 to 2.00; \( p < 0.0001 \)) were associated with adjusted short-term increases in AF risk. Participants becoming obese during the first 60 months had a 41% adjusted increase in risk of the development of AF (\( p = 0.02 \)) compared with those maintaining BMI < 30 kg/m². The prevalence of overweight and obesity increased over time. The adjusted proportion of incident AF attributable to short-term elevations in BMI was substantial (18.3%).

Conclusions

In this population of apparently healthy women, BMI was associated with short- and long-term increases in AF risk, accounting for a large proportion of incident AF independent of traditional risk factors. A strategy of weight control may reduce the increasing incidence of AF. (Women’s Health Study [WHS]: A Randomized Trial of Low-Dose Aspirin and Vitamin E in the Primary Prevention of Cardiovascular Disease and Cancer; NCT00000479).

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Over the past 3 decades, there has been a rapid increase in the prevalence of atrial fibrillation (AF), which is not entirely explained by the aging of the population (1). At present, an estimated 2.3 million people are diagnosed with AF in the U.S., and AF accounts for between 75,000 and 100,000 strokes per year (2). If this rapid growth continues, the number of individuals with AF is expected to increase to 12.1 million by 2050 (3). Once AF develops, treatments aimed at eliminating AF are associated with limited long-term success and non-negligible risks (4,5). Even when treatment is apparently successful, asymptomatic AF may persist, and the risk of stroke may never be eliminated (6). Therefore, the identification of modifiable risk factors for development of AF is of paramount importance.

See page 2328
of women are extremely obese (BMI >40 kg/m²) (7). Several prospective studies have reported significant associations between obesity and incident AF (8–10). However, how weight change influences the risk of incident AF and what proportion of the rapid increase in AF prevalence is attributable to obesity are uncertain. In addition, the mechanism(s) by which obesity confers an elevated risk are not entirely clear. Previous studies identified left atrial size (9) and impaired left ventricular diastolic function (11) as potential mediators of the relationship between obesity and AF. However, other potential mediators of obesity-associated AF have not been well characterized. Measures of abdominal adiposity have been associated with markers of inflammation (12), and several lines of evidence support a link between markers of inflammation and initiation and maintenance of AF (13). However, it is unclear whether these inflammatory markers are mediators of obesity-associated AF risk.

To address these gaps in our knowledge, we examined the relationship between baseline and updated measures of BMI and incident AF over 12 years of follow-up in a large prospective cohort of women free of cardiovascular disease (CVD) at baseline, the WHS (Women’s Health Study). We used updated measures to account for changes in BMI over time and to characterize the short-term impact that BMI has on AF risk. This cohort also provided us with the unique opportunity to investigate the role inflammatory mediators might play in obesity-associated AF.

Methods

Study sample. The design of the WHS was described previously (14). Briefly, the WHS was initially a randomized, double-blind, and placebo-controlled trial of low-dose aspirin and vitamin E conducted in 39,876 female health professionals without previous CVD. Randomized treatment ended in March 2004, and the cohort has been followed subsequently. Of the original cohort, 4,324 opted to remain in the study. Participants were asked to report their weight and height on the 24-, 36-, 60-, 72-, and 108-month questionnaires, and at the beginning of the observational phase of the study. Participants were mailed out, and 1,324 questionnaires (93%) were used in regression analyses. Because distributions of ICAM-1, fibrinogen, and hsCRP are skewed, log-transformed levels were used in regression analyses.

Validation of incident AF. This female health professional cohort was asked to report diagnoses of incident AF at baseline, 48 months, and then annually. Beginning on September 19, 2006, those who reported an incident AF event on at least 1 annual questionnaire were sent an additional questionnaire to confirm the episode and collect additional information. They were also asked for permission to review their medical records, in particular, available electrocardiograms, rhythm strips, 24-h electrocardiograms, and information on cardiac structure and function. For deceased participants, we contacted family members to obtain consent and additional relevant information. A total of 1,425 self-reports of AF were made, 1,421 questionnaires were mailed out, and 1,324 questionnaires (93%) were received to identify patients for chart review. Of these, 834 cases of AF were confirmed by medical record review and 79 (9.5%) were asymptomatic at the time of diagnosis. An end-point committee of physicians reviewed medical records for reported events according to pre-defined criteria. An incident AF event was confirmed if there was electrocardiographic evidence of AF or if a medical report indicated a personal history of AF. The earliest date in the medical records when documentation was believed to have occurred was set as the date of onset of AF. Only confirmed events were included in the analysis.
Statistical analysis. For each woman, person-months of follow-up were calculated from the date of randomization to the date of AF, death, or March 1, 2008, whichever came first. Age-adjusted Kaplan-Meier curves were used to plot survival free of AF for the 3 WHO categories of BMI, and differences between curves were tested with the log-rank test. We calculated age and multivariable-adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) using Cox proportional hazards models. BMI was analyzed as a continuous variable and in WHO categories. All models were also adjusted for treatment arms of the randomized portion of the WHS (vitamin E, beta carotene, and aspirin use). The first model was age adjusted (continuous). The second was a multivariable model that additionally adjusted for ethnicity, hypertension (defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, or report of diagnosis of hypertension by a physician), hypercholesterolemia (self-reported cholesterol of at least 240 mg/dl [6.22 mmol/l]), diabetes, alcohol consumption (rarely/never, <1 drink/week, 1 to 6 drinks/week, ≥1 drink/day), smoking (never, past, current), and physical activity (<1,000 kcal/week, ≥1,000 kcal/week) (16). To test for deviation from linearity, we included a quadratic term in the Cox proportional hazard models containing continuous BMI and nonparametrically using restricted cubic spline transformations (20).

To evaluate the degree to which the association between BMI and AF may be mediated by the development of intercurrent cardiovascular events, we refitted the Cox age-adjusted and multivariable proportional hazards models after censoring all women with an intercurrent cardiovascular event at the date of the event. An intercurrent cardiovascular event was defined as confirmed myocardial infarction, stroke, or coronary revascularization. To examine effect mediation by inflammation, we repeated these age-adjusted and multivariable models among the 24,621 women in the biomarker cohort and then performed an additional multivariable model that also included log-transformed fibrinogen, hsCRP, and ICAM-1 levels.

To investigate the relationship between the short-term risk of BMI and subsequent risk of incident AF, we constructed time-varying Cox models in which BMI categories were updated at each follow-up and the most recent BMI measurement was used to estimate risk in the following time period. In multivariable models, other covariates were updated at various time points, and if data were missing at a given time point, the last observation was carried forward. Using these adjusted short-term relative risks and the updated prevalence of obesity among the cases, we then estimated the population-attributable risk proportion for overweight and obesity defined as: \( \frac{p \cdot d}{RR - 1} \), where \( p \) is the proportion of cases exposed to the risk factor and \( RR \) is the adjusted relative risk (21). We also evaluated effect modification through stratified analyses and multiplicative interaction terms. Multiplicative interaction terms between BMI and various baseline characteristics were evaluated in fully adjusted models using likelihood ratio tests. The proportional hazards assumption was examined for all models by including BMI by logarithm of time interaction into the model. No violation of this assumption was detected. All probability values were 2 tailed, and we considered \( p \leq 0.05 \) as statistically significant. All analysis was performed with SAS version 9 (SAS Institute Inc., Cary, North Carolina).

Results

Baseline BMI and AF. Baseline characteristics of the cohort by BMI WHO categories are shown in Table 1. At baseline, 6,185 women (18% of the population) were categorized as obese (BMI >30 kg/m²). Compared with women with a normal BMI (<25 kg/m²), obese women were more likely to have a history of diabetes, hypertension, and hyperlipidemia and were less physically active and less likely to consume alcoholic beverages.

When examined as a continuous variable, BMI measured at baseline was associated with subsequent AF risk in age-adjusted and multivariable-adjusted Cox proportional hazards models (Table 2). Each 1-U increase in BMI was associated with a 4.7% increase in AF risk (95% CI: 3.4% to 6.1%, \( p < 0.0001 \)) even after controlling for the obesity-associated covariates age, ethnicity, diabetes, hypertension, hyperlipidemia, alcohol use, smoking, and physical activity, as well as aspirin, vitamin E, and beta carotene randomization arm. When baseline BMI was divided into the WHO categories for obesity and overweight, a significant association with AF was observed for both the overweight and obese women in age-adjusted models (Table 2), and the survival curves for freedom from AF continued to diverge over the course of the study (Fig. 1) (log-rank \( p = 0.001 \)). However, the risk was not significantly increased among overweight women (BMI 25 to 29.99 kg/m²) after multivariable adjustment. A quadratic term added to the model was not significant (\( p \) for quadratic term = 0.58) suggesting a lack of nonlinearity, and multivariable spline regression confirmed that the relationship between BMI and AF was linear (\( p \) for linear trend <0.0001, \( p \) for deviation from linearity = 0.58).

When women in whom interim CVD developed were censored from the analysis, the relationship between BMI and AF was minimally changed (Table 2). To examine effect mediation by inflammation, age-adjusted and multivariable-adjusted models limited to women who donated blood samples at baseline were performed (Table 2), and relationships between BMI and AF were similar to those observed in the entire cohort. Further adjustment for fibrinogen, hsCRP, and ICAM-1 levels resulted in an 8.9% attenuation of the HR for developing AF associated with obesity (HR: 1.68, 95% CI: 1.37 to 2.07 reduced to 1.53; 95% CI: 1.22 to 1.91, multivariable adjusted model II) (Table 2).
Updated measures of BMI and AF risk. We next examined the dynamic association between BMI and AF by updating measures of BMI, and BMI in the overweight range was now associated with a significant increase in the risk of AF. Even after adjustment for updated measures of potential biological intermediaries including diabetes, hypertension, and physical activity, overweight status remained significantly associated with short-term increases in AF risk (HR: 1.22, 95% CI: 1.02 to 1.45, \( p = 0.03 \)). Again, the significant increase in risk persisted for the obese even after adjustment for these updated biological intermediaries (HR: 1.65, 95% CI: 1.36 to 2.00, \( p < 0.0001 \)).

To further investigate the relationship change in BMI and AF, we examined whether a change in BMI over the first 60 months of the study influenced risk of AF after that time point (Table 3). The majority of women did not change categories, and the 5,095 women who remained obese had a trend toward a higher risk of AF after 60 months, whereas the 2,411 women who were newly obese had a significantly higher adjusted risk of incident AF after year 5 (HR: 1.41, 95% CI: 1.05 to 1.90, \( p = 0.02 \)) compared with those who maintained a BMI <30 kg/m² over the same period. In contrast, women who were obese at baseline but then attained a BMI <30 kg/m² by year 5 no longer had a significantly increased risk of subsequent AF in adjusted analyses (HR: 1.01, 95% CI: 0.58 to 1.79, \( p = 0.96 \)) compared with those who maintained a BMI <30 kg/m² over the same period. However, these analyses were limited by small numbers of women (\( n = 599 \)) who achieved this degree of weight loss, and as a result CIs are wide.

Population-attributable risk proportion. The prevalence of overweight and obesity increased over the course of the study. At baseline, the prevalence of overweight and obesity was 30.8% and 18.0%, respectively, which increased to 34.2% and 24.2%, respectively, by the last time period, and over the same time period, the incidence of new AF increased as well (Fig. 2). Using a weighted average over time periods, the average prevalence of overweight and obesity over the course of the study was 34.1% and 23.2%, respectively. Using updated measures of BMI, the age-adjusted population-attributable risk proportion associated with obesity and overweight were estimated to be 0.153 and 0.074, respectively. Even after accounting for other potential confounders, some of which might be in the causal pathway (hypertension and diabetes), the estimated population-attributable risk proportion remained substantial at 0.122 and 0.061 for obesity and overweight, respectively, with a total of 18.3% of AF cases attributable to short-term increases in BMI >25 kg/m².

Subgroup analyses. In pre-specified stratified analyses (Fig. 3), the association between BMI and incident AF was stronger among women 60 years of age or younger compared with those older than age 60 years at baseline (\( p \) for interaction = 0.0005). In the younger women, the HRs for incident AF were 1.36 (95% CI: 1.08 to 1.72, \( p = 0.01 \)) and 2.16 (95% CI: 1.69 to 2.76, \( p < 0.0001 \)) among the overweight and obese, respectively, compared with the nonobese. Alternatively, overweight and obesity were not significantly associated with incident AF in multivariable models among the smaller subgroup of women who were older than

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline Characteristics According to BMI Categories</th>
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<tbody>
<tr>
<td>Total Population (n = 34,309)</td>
<td>BMI &lt;25 kg/m² (n = 17,544, 51.1%)</td>
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<tr>
<td>Weight, kg</td>
<td>70.2 ± 14.5</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>54.6 ± 7.0</td>
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<tr>
<td>Ethnicity, % white</td>
<td>32,389 (95.1)</td>
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<tr>
<td>Diabetes</td>
<td>928 (2.7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8,667 (25.3)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>9,980 (29.1)</td>
</tr>
<tr>
<td>Alcohol use</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>15,160 (44.2)</td>
</tr>
<tr>
<td>&lt;1 drink/week</td>
<td>4,541 (13.2)</td>
</tr>
<tr>
<td>1–6 drinks/week</td>
<td>11,043 (32.2)</td>
</tr>
<tr>
<td>≥1 drink/day</td>
<td>3,555 (10.4)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>17,689 (51.6)</td>
</tr>
<tr>
<td>Past</td>
<td>12,355 (36.0)</td>
</tr>
<tr>
<td>Current</td>
<td>4,239 (12.4)</td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
</tr>
<tr>
<td>≥1,000 kcal/week</td>
<td>11,728 (34.2)</td>
</tr>
<tr>
<td>&lt;1,000 kcal/week</td>
<td>22,580 (65.8)</td>
</tr>
</tbody>
</table>

Values are mean ± SD or n (%). Hypertension is defined as self-reported systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg or report of diagnosis of hypertension by a physician; history of hypercholesterolemia is self-reported cholesterol of at least 240 mg/dl (6.22 mmol/l). BMI = body mass index.
In this cohort of female health care professionals without previous evidence of CVD, BMI is strongly associated with subsequent development of AF even after accounting for the interim development of CVD and other important AF risk factors such as diabetes and hypertension. The relationship is linear, with a 4.7% increase in risk of incident AF for each kg/m² increase in BMI. In our full multivariable models, 1.65- to 1.77-fold increases in AF risk were observed among the obese (BMI ≥30 kg/m²), with greater than 2-fold increases in risk among obese women who were 60 years of age or younger at study entry. Adjustment for inflammatory markers measured at baseline in the biomarker cohort only minimally attenuated the obesity-associated risk of AF, suggesting that inflammation is not a major mediator of the AF risk associated with obesity.

When BMI was updated over the course of the study, significant short-term elevations in risk were associated with elevated BMI in both the overweight and obese ranges, even after adjustment for updated biological intermediaries.
Study participants who became obese during the first 60 months of follow-up had a 41% adjusted increase in risk of the development of AF (p = 0.02) compared with those who maintained a BMI <30 kg/m². These results on short-term risk suggest that the AF risk associated with obesity may be modifiable by weight change.

To our knowledge, this is one of the first studies examining the short-term influence of BMI changes over time and subsequent risk of AF. Our results using updated BMI measures are consistent with data from other population-based cohort studies using a single measure of BMI (8,9,22–24), although the linear relationship observed here was not apparent in all the individual studies. In a meta-analysis of 5 population-based cohorts (10), baseline BMI was associated with a graded risk of AF, with estimated risk increases of 39% and 87% in the overweight and obese, respectively, compared with those of normal weight. A recent study of 6,903 Swedish men demonstrated that long-term weight gain from age 20 years to midlife was associated with an increased risk of AF, consistent with our findings on short-term risk (25).

Previous population-based studies did not report AF risk according to subgroups, and the reason for the interaction between age- and obesity-associated AF risk in our data is not clear. We observed a similar age interaction for the AF risk associated with habitual vigorous exercise among men in the Physicians Health Study (26), and it is possible that the influence of other AF risk factors may differ according to age. Women with a genetic or physiological predisposition to the development of obesity-associated AF may do so at a younger age and, therefore, these women would be excluded from analyses of older populations. This finding warrants further investigation because it raises potential alternative mechanisms for the rapid increase in the prevalence of new-onset AF not reliant on the aging of the U.S. population.

There are many reasons why dynamic changes in BMI might be expected to modify AF risk independent of obesity-associated comorbidities. Obesity is associated with

<table>
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<tr>
<th>BMI (kg/m²) Over 60 Months of Follow-Up</th>
<th>Age-adjusted (n = 32,309, 650 AF events)</th>
<th>Reduced &lt;30 (n = 599, 14 AF Events)</th>
<th>Stable ≥30 (n = 5,095, 187 AF Events)</th>
<th>Increased ≥30 (n = 2,411, 67 AF Events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable &lt;30</td>
<td>Referent</td>
<td>1.00 (0.57–1.76), p = 0.99</td>
<td>1.34 (0.97–1.86), p = 0.08</td>
<td>1.39 (1.03–1.87), p = 0.03</td>
</tr>
<tr>
<td>Reduced</td>
<td>(n = 32,016, 645 AF events)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduced &lt;30</td>
<td>Referent</td>
<td>1.01 (0.58–1.79), p = 0.96</td>
<td>1.32 (0.95–1.84), p = 0.096</td>
<td>1.41 (1.05–1.90), p = 0.02</td>
</tr>
</tbody>
</table>

Values are hazard ratio (95% confidence interval), p value. *Adjusted for age, BMI, vitamin E, beta carotene, and aspirin use. †Adjusted for age; BMI; race; vitamin E, beta carotene, and aspirin use; diabetes; hypertension; hyperlipidemia; alcohol use; smoking; and degree of physical activity.

Abbreviations as in Tables 1 and 2.
increased left atrial size and decreased left ventricular diastolic function, which by themselves lead to increased left atrial pressure (9,27). Weight reduction has also been linked to regression of left atrial enlargement (28). Dynamic changes in left atrial size and pressure likely affect both the atrial substrate and triggers for AF. Increased left atrial pressure may acutely lead to increases in atrial ectopy that triggers AF (11). Further, more prolonged BMI-mediated left atrial stretch may lead to the development of fibrosis and atrial enlargement on a structural basis (29). Some of these obesity-associated atrial changes could be reversible or modifiable with weight loss, whereas other changes may be irreversible.

If the observed dynamic associations between BMI and AF are causal, the public health impact of the current obesity epidemic on the growing AF burden could be quite substantial with respect to clinical outcomes, quality of life, and health care costs associated with AF. In our study, the prevalence of obesity increased over the course of the study from 18.0% to 24.2%, and 12.2% of incident AF cases were estimated to be attributable to obesity independent of other measured risk factors. When one also takes into account the modestly but significantly increased risks observed in more than one-third of the women who were overweight, the percentage of AF cases attributable to an elevated BMI increases to 18.3%. Given the even higher prevalence of obesity and overweight in most Western populations, with current estimates for obesity approaching one-third of the population (7), the attributable risk proportion associated with obesity and overweight in the general population is likely even higher.

The strengths of the present study include its prospective design, large sample size, updated measures of BMI, and long-term follow-up with a large number of confirmed events.

Study limitations. First, cases of AF were identified by self-report, and electrocardiographic screening was not performed in this cohort. Therefore, asymptomatic cases of AF would have been missed if not detected through the participant’s usual medical care. Although the percentage of AF

### Figure 3: Overweight and Obesity and Risk of Incident AF, Stratified by Various Baseline Characteristics

Shown are hazard ratios for incident AF stratified by various baseline characteristics. The number of patients in each category is indicated in the first column. Hazard ratios and 95% confidence intervals are shown on a logarithmic scale with overweight in black and obese in green. All hazard ratios are adjusted for age, race, vitamin E, beta carotene, and aspirin use; diabetes; hypertension (defined as self-reported systolic blood pressure of ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or report of diagnosis of hypertension by a physician); history of hypercholesterolemia (self-reported cholesterol of at least 240 mg/dl [6.22 mmol/l]); diabetes; alcohol consumption (rarely/never, <1 drink/week, 1 to 6 drinks/week, ≥1 drink/day); smoking (never, past, current); and physical activity (<1,000 kcal/week, ≥1,000 kcal/week). Abbreviation as in Figure 1.
cases that were asymptomatic in this health professional cohort with access to health care was similar to that in cohorts using screening electrocardiograms (30,31), it is likely that a more rigorous electrocardiographic screening method such as ambulatory electrocardiographic monitoring may have detected more asymptomatic episodes (32). Additionally, due to the sometimes subtle nature of symptoms, AF onset can be difficult to ascertain exactly.

Second, body weight and height, as well as data on all potential confounders, were self-reported, potentially leading to some misclassification, which, if nondifferential, would bias our results toward the null. However, high correlations have been demonstrated between self-reported and directly measured weight ($r = 0.96$) in a comparable cohort of female health professionals (33). BMI as a measure of adiposity in general may also misclassify those with high muscle mass, although BMI is highly correlated with absolute fat mass in women (34).

Third, the selective nature of the cohort, initially healthy, middle-aged female health professionals primarily of Caucasian origin, may limit the generalizability of the findings, specifically to men or other non-Caucasian female populations in whom risk factors for AF may differ. Last, we were not able to include echocardiographic measures in our multivariable analysis because these were not measured systematically in the entire cohort.

Conclusions

BMI is linearly associated with risk of incident AF in this large cohort of women, and the association is stronger among younger women. Only a portion of the obesity-associated AF risk is mediated by inflammation and traditional risk factors. With updated measurements of BMI, significant short-term increases in AF risk persisted in both the overweight and obese ranges after controlling for these potential mediators. An estimated 18.3% of the incident AF in this cohort was attributable directly to short-term increases in BMI above the normal range. Taken together, these data suggest that weight control may be a reasonable strategy for reducing the increasing population burden of AF.

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Key Words: atrial fibrillation • obesity • prevention.