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QUARTERLY FOCUS ISSUE: HEART RHYTHM DISORDERS

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/m^2. 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.

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As we have witnessed this rapid increase in AF, the prevalence of obesity and overweight has steadily increased as well, and recent estimates suggest that 32.2% of adults are obese (body mass index [BMI] >30 kg/m^2) and 6.9%

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Abbreviations and Acronyms

AF = atrial fibrillation
BMI = body mass index
CI = confidence interval
CVD = cardiovascular disease
HR = hazard ratio
hsCRP = high-sensitivity C-reactive protein
ICAM = intercellular adhesion molecule
WHO = World Health Organization

of women are extremely obese (BMI >40 kg/m^2) (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 out of the observational follow-up and 7 were excluded due to presence of CVD at baseline, leaving 35,545 women potentially eligible for inclusion in this analysis. The investigation of AF was not pre-specified as part of the original WHS; however, the present and other analyses on AF were pre-specified in 2006 before confirmation of the end point.

For this analysis, we excluded 787 women with a history of AF at baseline and 449 women with missing information on BMI at baseline. Thus, the study population for the present analysis consisted of 34,309 women with a mean follow-up of 12.9 ± 1.9 person-years. All participants gave written informed consent. The study was approved by the institutional review board of Brigham and Women's Hospital in Boston, Massachusetts.

Assessment of BMI. BMI, self-reported weight in kilograms divided by the square of self-reported height in meters (kg/m^2), was the primary measure of total body adiposity in this study. Participants reported their height on the baseline questionnaire, the 72- and 108-month questionnaires, and at the beginning of the observational phase of the study. Participants were asked to report their weight on the 24-, 36-, 60-, 72-, and 108-month questionnaires during the randomized period and at the beginning of the observational phase and yearly thereafter. We analyzed BMI as a continuous variable and divided into the World Health Organization (WHO) categories for overweight and obesity (normal, <25 kg/m^2; overweight, 25.0 to 29.9 kg/m^2; obese, ≥30 kg/m^2) (15).

Study variables. Information on baseline variables was collected using questionnaires. Follow-up questionnaires asking participants about study outcomes and other information were sent every 6 months during the first year and every 12 months thereafter. Covariates of interest assessed at study entry and at varying time points during follow-up included diabetes, hypertension, hyperlipidemia, smoking, alcohol use, and physical activity (16). Plasma levels of high-sensitivity C-reactive protein (hsCRP) (17), intercellular adhesion molecule (ICAM)-1 (18), and fibrinogen (19) were measured at baseline in 24,621 of the women included in this analysis. 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.