

Risk of New-Onset Atrial Fibrillation in Relation to Body Mass Index

Sascha Dublin, MD, PhD; Benjamin French, MS; Nicole L. Glazer, MPH; Kerri L. Wiggins, MS, RD; Thomas Lumley, PhD; Bruce M. Psaty, MD, PhD; Nicholas L. Smith, PhD; Susan R. Heckbert, MD, PhD

Background: Obesity is associated with increased risk of atrial fibrillation (AF), but it is unknown whether the association differs by duration or persistence of AF. It is also unknown to what extent cardiovascular risk factors may mediate this association.

Methods: This population-based case-control study included 425 subjects with new-onset AF and 707 controls. The AF cases were identified through *International Classification of Diseases, Ninth Revision* codes for inpatient and outpatient visits and verified by medical record review. Medical records provided data on height, weight, and cardiovascular risk factors.

Results: On average, AF risk was 3% higher (95% confidence interval [CI], 1%-5%) per unit increment in body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared). For sustained AF (duration ≥ 6 months), risk was higher by 7% (95% CI, 3%-11%) per unit BMI increment; for intermittent AF (duration ≥ 8 days or recurrent), 4% (95% CI, 1%-6%);

and for transitory AF (duration < 8 days), 1% (95% CI, -1% to +4%). Compared with those with normal BMI, the odds ratios for overweight and obese subjects were as follows: overweight, 0.97 (95% CI, 0.68-1.38); obese class 1, 1.18 (95% CI, 0.80-1.73); obese class 2, 1.34 (95% CI, 0.82-2.18); and obese class 3, 2.31 (95% CI, 1.36-3.91) ($P = .002$ for trend). When diabetes mellitus, a possible mediator, was added to the model, the odds ratio per unit increment of BMI decreased from 1.034 to 1.028. Adjustment for other cardiovascular risk factors including hyperlipidemia and blood pressure did not attenuate the BMI-AF association.

Conclusions: The association with BMI was stronger for sustained AF than for transitory or intermittent AF. The obesity-AF association appears to be partially mediated by diabetes mellitus but minimally through other cardiovascular risk factors.

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ATRIAL FIBRILLATION (AF) IS common, affecting over 2 million people in the United States.¹ Lifetime risk after age 40 years is estimated to be 1 in 4.² Atrial fibrillation causes substantial morbidity, especially owing to the increased risk of ischemic stroke,³ and overall mortality is increased in the presence of AF.^{3,4}

Prior studies have reported increased AF risk associated with obesity,^{3,5-9} a common risk factor that is increasing in prevalence. It is unknown whether the obesity-AF relationship differs according to the duration or persistence of AF because prior studies have lacked information about these aspects of AF. In addition, the mechanism by which obesity may increase AF risk is unknown. Several mechanisms have been suggested, including increased left atrial (LA) size, chronic inflammation, and development of other cardiovascular risk factors or cardiovascular disease. While 2 prior studies have explored possible

mechanisms to a limited degree,^{5,7} no study has attempted to quantify the extent to which the association may be mediated by cardiovascular risk factors such as diabetes mellitus, hypertension, and hyperlipidemia. We studied these questions using data from a population-based case-control study of new-onset AF.

METHODS

SETTING AND DESIGN

This case-control study was conducted at Group Health Cooperative (GHC), a large, integrated health care delivery system in Washington State. Study procedures were approved by GHC's human subjects review committee.

STUDY POPULATION

We identified all GHC enrollees assigned an *International Classification of Diseases, Ninth Revision (ICD-9)* code for AF (427.31, atrial fi-

Author Affiliations: Veterans Affairs Puget Sound Health Care System (Dr Dublin) and Departments of Biostatistics (Mr French and Dr Lumley), Epidemiology (Ms Glazer and Drs Psaty, Smith, and Heckbert), Medicine (Ms Wiggins and Dr Psaty), and Health Services (Dr Psaty), University of Washington, Seattle.

brillation or 427.32, atrial flutter) during any inpatient or outpatient visit between October 1, 2001, and September 30, 2002, who had never before been assigned an ICD-9 code for AF during their enrollment at GHC. Trained abstractors reviewed medical records to verify the diagnosis and to confirm that the AF was of new onset; verified new-onset cases were retained as AF case subjects. Perioperative AF was included only if it persisted to the time of hospital discharge, and AF as part of a terminal hospitalized illness was excluded. In an unpublished pilot study conducted at GHC (February 2001) before the present study was initiated, we determined that the sensitivity of an ICD-9 code for AF was 95%, with 99% specificity.

Control subjects were drawn from 2 ongoing case-control studies of myocardial infarction (MI) at GHC among men and women with treated hypertension¹⁰ and among postmenopausal women.¹¹ Controls were randomly chosen from GHC enrollment lists, frequency matched to MI cases by sex, age (by decade), and treated hypertension status. Thus, AF cases and controls who either had treated hypertension or were postmenopausal women were eligible for this analysis and composed the study population.

We defined an index date for all subjects as the date the arrhythmia came to clinical attention for cases or a random date for controls. Eligible subjects were aged 30 to 84 years with at least 4 health care visits before the index date (to increase the likelihood that information would be available on health conditions). Subjects with a pacemaker were excluded as the pacemaker might interfere with the identification of AF. Subjects with missing data for body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) ($n=20$) were excluded, and those who were underweight (BMI < 18.5, $n=14$) were also excluded because of the small number of such subjects.

DATA COLLECTION

The GHC medical record includes notes from primary care and specialty physician visits, emergency department visit notes, discharge summaries, information from telephone contacts, problem lists, electrocardiograms, Holter monitor reports, and laboratory and diagnostic test reports. Trained abstractors reviewed the entire medical record for each subject, covering a median of 19 years of enrollment, to gather data on the following exposures and covariates, which were assessed prior to the index date: the most recent measured height and weight; presence and duration of diabetes mellitus, hypertension, and hyperlipidemia; presence of congestive heart failure or valvular heart disease; history of MI, coronary artery bypass grafting, angioplasty, or angina; and total and high-density lipoprotein (HDL) cholesterol levels and blood pressure. Information on medication use came from an automated pharmacy database. In past studies, 95% of members reported filling all or almost all prescriptions through GHC pharmacies.¹² In telephone interviews, subjects were asked about race, education, smoking status, and alcohol consumption prior to index date. For subjects who did not complete the telephone interview, these data were obtained from medical record review. The proportion of subjects lacking telephone interview data was similar in cases and controls.

For cases, information was collected regarding duration and persistence of AF in the 6 months after diagnosis and regarding the results of echocardiograms performed from 3 months before to 6 months after diagnosis, including degree of LA enlargement. Information on LA size was missing for 41% of cases.

EXPOSURE VARIABLES

Body mass index was categorized according to the National Institutes of Health/World Health Organization classification

scheme (18.5-24.9, normal; 25.0-29.9, overweight; and ≥ 30.0 , obese).¹³ The obese BMI category was subdivided into class 1 (30.0-34.9), class 2 (35.0-39.9), and class 3 (≥ 40.0).

COVARIATES: VARIABLE DEFINITIONS

We defined categories to describe the duration and persistence of AF (AF classification) using evidence available in the medical record. Cases of AF were classified into 3 mutually exclusive groups based on the pattern of AF: (1) transitory, (2) persistent or intermittent, or (3) sustained AF. Our classification scheme followed closely that of the American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) guidelines,¹⁴ but some modification was required because not all AF cases were initially evaluated by cardiologists, and thus information on the effectiveness of cardioversion was not uniformly available. *Transitory AF* was defined as a single episode of AF lasting 7 days or less without recurrence of AF during the next 6 months. *Persistent or intermittent AF* indicates that the initial AF episode lasted longer than 7 days or that AF recurred, but sinus rhythm was also present during the next 6 months (similar to the ACC/AHA/ESC category of *persistent*). We will refer to this group as *intermittent AF*, since subjects with intermittent AF made up most of this group. *Sustained AF* indicates that the patient was continuously in AF during the 6 months after AF onset (similar to the ACC/AHA/ESC category of *permanent*).

Diabetes mellitus and hyperlipidemia were considered present if there was a physician diagnosis in the medical record. For hypertension, we required a physician diagnosis and that the subject be receiving antihypertensive medication at the index date. *Coronary artery disease* was defined as any history of MI, coronary revascularization, or definite or probable angina. We calculated whether subjects were active users of medications at the index date based on the date of last medication fill and number of pills dispensed, assuming 80% compliance with prescribing instructions.¹⁵

STATISTICAL ANALYSIS

We performed descriptive analyses to examine characteristics associated with AF and with BMI category. Statistical significance was assessed by the χ^2 test for categorical variables and the t test or analysis of variance for continuous variables. Cholesterol and blood pressure values were log-transformed for these comparisons. Multivariate logistic regression was used to examine the risk of new-onset AF associated with category of BMI or BMI as a continuous variable. All models were adjusted for the stratification variables of age, sex, and treated hypertension. Because of the strong relationships of age with AF risk and BMI, we used a cubic spline for age to achieve more thorough adjustment than would be achieved with categorical or linear adjustment. Variables that did not substantially alter risk estimates for BMI were not retained in final models. In secondary analyses, we examined models containing height and weight in place of BMI.

To determine whether the BMI-AF association varied by classification of AF (transitory, intermittent, or sustained), we used polytomous logistic regression, with statistical significance assessed using the Wald test. In an analysis limited to the AF cases, we examined the relationship between obesity and LA size.

To examine what proportion of the effect of BMI may be mediated through cardiovascular risk factors or coronary artery disease, we compared the regression coefficient for BMI in the baseline model adjusted only for sex, age, and treated hypertension (β_B) with the coefficient derived from more fully adjusted models (β_A). Characteristics considered as potential mediators included hyperlipidemia, diabetes mellitus, duration of diabetes

Table 1. Characteristics of Study Subjects*

Characteristic	Controls (n = 707)	All AF Subjects (n = 425)	P Value	AF Classification†			P Value
				Transitory (n = 163)	Intermittent (n = 180)	Sustained (n = 78)	
Age, y	69 (59-76)	73 (64-79)	NA	71 (62-78)	73 (64-79)	76 (69-81)	<.001
Female sex	390 (55.2)	264 (62.1)	NA	115 (70.6)	112 (62.2)	35 (44.9)	.001
White	613 (87.2)	386 (91.3)	.04	143 (88.3)	166 (92.7)	73 (93.6)	.25
GHC enrollment, y	19 (11-29)	19 (11-29)	.45	18 (10-28)	21 (12-29)	19 (11-29)	.42
Treated hypertension	561 (79.4)	308 (72.5)	NA	106 (65.0)	131 (72.8)	69 (88.5)	.001
Diabetes mellitus‡	120 (17.0)	101 (23.8)	.005	38 (23.3)	40 (22.2)	23 (29.5)	.44
Hyperlipidemia‡	153 (21.6)	110 (25.9)	.10	39 (23.9)	46 (25.6)	23 (29.5)	.65
Total cholesterol ≥240 mg/dL	259 (37.7)	137 (33.9)	.21	43 (28.1)	60 (34.7)	32 (43.2)	.07
Valvular heart disease	12 (1.7)	27 (6.4)	<.001	7 (4.3)	13 (7.2)	7 (9.0)	.32
MI§	52 (7.4)	47 (11.1)	.03	22 (13.5)	17 (9.4)	7 (9.0)	.40
Coronary artery disease	129 (18.3)	107 (25.2)	.005	42 (25.8)	45 (25.0)	19 (24.4)	.97
Congestive heart failure	20 (2.8)	47 (11.1)	<.001	14 (8.6)	22 (12.2)	11 (14.1)	.37
Claudication	16 (2.3)	30 (7.1)	<.001	15 (9.2)	11 (6.1)	4 (5.1)	.40
Current smoker	73 (10.3)	37 (8.7)	.37	16 (9.8)	14 (7.8)	7 (9.0)	.80
Alcohol use			.15				.26
Nondrinker	259 (38.3)	182 (44.0)		70 (43.5)	76 (43.4)	35 (47.3)	
Occasional	333 (49.3)	180 (43.5)		74 (46.0)	79 (45.1)	25 (33.8)	
Frequent or alcoholic	84 (12.4)	52 (12.6)		17 (10.6)	20 (11.4)	14 (18.9)	
Total cholesterol, mg/dL	224 (196-253)	223 (196-253)	.53	218 (191-246)	224 (199-255)	230 (204-269)	.01
HDL cholesterol, mg/dL	52 (41-64)	54 (43-65)	.24	54 (44-66)	54 (43-67)	51 (42-62)	.18
Systolic BP, mm Hg	138 (126-150)	140 (125-152)	.12	138 (124-152)	140 (128-152)	140 (128-152)	.99
Diastolic BP, mm Hg	80 (70-84)	80 (70-84)	.33	78 (70-84)	80 (70-84)	78 (70-84)	.19

Abbreviations: AF, atrial fibrillation; BP, blood pressure; GHC, Group Health Cooperative; HDL, high-density lipoprotein; MI, myocardial infarction; NA, not applicable (stratification variables used in selection of controls).

SI conversion factor: To convert total and HDL cholesterol to millimoles per liter, multiply by 0.0259.

*Unless otherwise indicated, data are reported as median (25th-75th percentile) for continuous variables and number (percentage) of subjects for all others. Subtotals might not sum to total subjects owing to missing values, but fewer than 5% of subjects had missing data for each characteristic (except HDL cholesterol: data missing for 3% of controls and 6% of cases).

†Four subjects with AF lacked information about duration or persistence of AF and thus could not be classified.

‡Defined as physician diagnosis of the condition in the medical record.

§Defined as prior hospitalization with a diagnosis of MI.

||Defined as history of MI, coronary revascularization, or definite or probable angina.

mellitus, duration of hypertension; and systolic blood pressure, diastolic blood pressure, and total and HDL cholesterol levels (modeled with cubic splines). We used the formula $1 - (\beta_A/\beta_B)$ to calculate the amount by which the AF-BMI relationship was attenuated by adjustment for these variables. We interpreted this as the proportion of the effect of BMI potentially mediated through these risk factors.¹⁶ The bootstrap method was used to generate 95% confidence intervals (CIs).¹⁷

Likelihood ratio tests were used to determine statistical significance except as noted above. Analyses of potential mediators of the relationship between BMI and AF were performed in R 2.2 (R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria). All other analyses were carried out in Stata 8.2 (StataCorp LP, College Station, Tex).

RESULTS

There were 425 eligible cases of new-onset AF among GHC members during the study year. Thirty-nine percent had transitory AF, 43% intermittent, and only 19% sustained. Information on duration and/or persistence of AF was not available for 4 cases, and thus 421 subjects were available for the portion of the analysis examining AF classification. There was only 1 case with new perioperative AF that persisted until hospital discharge. A total of 707 eligible control subjects were identified.

CHARACTERISTICS OF CASES AND CONTROLS

Diabetes mellitus and hyperlipidemia were more common among AF cases than controls (**Table 1**), as were valvular heart disease, history of MI, coronary artery disease, congestive heart failure, and claudication. The distribution of alcohol use was similar between cases and controls. Compared with subjects with transitory or intermittent AF, those with sustained AF were older and more likely to have underlying conditions including hypertension, diabetes mellitus, hyperlipidemia, valvular heart disease, and congestive heart failure, although not all of these differences were statistically significant.

CHARACTERISTICS ASSOCIATED WITH OBESITY AMONG CONTROL SUBJECTS

Controls with normal weight were more likely to be female and older compared with those who were overweight or obese (**Table 2**). The prevalence of hypertension, diabetes mellitus, and hyperlipidemia was higher in subjects with higher BMI. Higher BMI was also associated with a slightly higher systolic blood pressure and with a lower HDL cholesterol level. These patterns did not change after adjustment for age and sex.

Table 2. Characteristics of Control Subjects by BMI Category*

Characteristic*	BMI Category				P Value
	Normal (18.5-24.9) (n = 147)	Overweight (25.0-29.9) (n = 252)	Obese		
			Class 1 (30.0-34.9) (n = 171)	Classes 2 and 3 (≥35.0) (n = 137)	
BMI, median	23	27	32	39	NA
Female sex	75	50	44	57	<.001
Age at index date, median, y	73	71	67	61	<.001
Education, any college or professional school	53	57	56	59	.80
White	86	88	89	85	.58
Treated hypertension	61	82	84	88	<.001
Diabetes mellitus†	11	12	22	26	<.001
Hyperlipidemia‡	15	19	29	24	.01
Total cholesterol ≥240 mg/dL	38	42	36	32	.26
Coronary artery disease‡	16	17	23	17	.34
Current smoker	10	10	11	10	.98
Frequent alcohol use§	13	14	13	8	.72
Systolic BP, median, mm Hg	132	138	139	138	.009
Diastolic BP, median, mm Hg	78	80	80	80	<.001
Total cholesterol, median, mg/dL	220	230	222	220	.02
HDL cholesterol, median, mg/dL	62	55	47	45	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; HDL, high-density lipoprotein; NA, not applicable.

SI conversion factor: To convert total and HDL cholesterol to millimoles per liter, multiply by 0.0259.

*Unless otherwise indicated, data are reported as percentage of nonmissing values. Fewer than 5% of subjects were missing data for each characteristic except education and alcohol consumption. For normal, overweight, class 1 obese, and class 2 and 3 obese, education data were missing for 20%, 17%, 16%, and 19%, respectively; alcohol use data were missing for 5%, 4%, 4%, and 5%, respectively.

†Defined as physician diagnosis of the condition in the medical record.

‡Defined as history of myocardial infarction, coronary revascularization, or definite or probable angina.

§Defined as 10 or more drinks per week or active diagnosis of alcoholism.

Table 3. Risk of New-Onset Atrial Fibrillation According to BMI*

BMI Measure	Cases, No. (n = 425)	Controls, No. (n = 707)	OR (95% CI)	P Value
Categorical				.002 For trend
Normal (18.5-24.9)	100	147	1.00	
Overweight (25.0-29.9)	138	252	0.97 (0.68-1.38)	
Obese class 1 (30.0-34.9)	99	171	1.18 (0.80-1.73)	
Obese class 2 (35.0-39.9)	44	82	1.34 (0.82-2.18)	
Obese class 3 (≥40.0)	44	55	2.31 (1.36-3.91)	
Per-unit incremental	425	707	1.03 (1.01-1.05)	.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; OR, odds ratio.

*Models are adjusted for sex, treated hypertension, and age (cubic spline). Adjustment for additional potential confounding factors did not alter risk estimates substantially.

RELATIONSHIP OF BMI TO RISK OF NEW-ONSET AF

Risk of new-onset AF was greater for subjects with a higher BMI (**Table 3**) ($P = .002$ for trend across categories). For obese subjects (BMI ≥ 30), the overall odds ratio (OR) compared with subjects with normal BMI was 1.37 (95% CI, 0.97-1.94), adjusted for sex, age, and treated hypertension. On average, each unit BMI increment was associated with a 3% greater risk of AF (95% CI, 1%-5%) ($P < .001$). The addition of quadratic and square root terms or linear splines for BMI did not significantly improve the model. Further adjustment for potential confounders, including use of

β -blockers at the index date, did not alter these risk estimates.

Height and weight both had strong positive associations with AF risk ($P < .01$ for trend across sex-specific quartiles), and each remained significant after adjustment for the other. For height, the adjusted OR for AF comparing the fourth quartile with the first was 1.87 (95% CI, 1.25-2.81), and for weight, the OR was 1.38 (95% CI, 0.94-2.03).

RELATIONSHIP OF BMI AND AF BY AF CLASSIFICATION AND IN SUBJECT SUBGROUPS

There was a stronger relationship between BMI and risk of sustained AF than intermittent or transitory AF

Table 4. Association of BMI With AF Risk by AF Classification and in Subject Subgroups*

Subgroup	Per Unit BMI Increment	BMI Category				P Value†
		Normal (18.5-24.9)	Overweight (25.0-29.9)	Obese		
				Class 1 (30.0-34.9)	Classes 2 and 3 (≥35.0)	
All subjects (n = 425)	1.03 (1.01-1.05)	Referent	0.97 (0.69-1.38)	1.18 (0.80-1.73)	1.69 (1.12-2.56)	.04‡
Classification of AF						
Transitory (n = 163)	1.01 (0.99-1.04)	Referent	0.87 (0.53-1.41)	1.13 (0.67-1.91)	1.20 (0.67-2.14)	
Intermittent (n = 180)	1.04 (1.01-1.06)	Referent	1.00 (0.63-1.60)	1.16 (0.69-1.95)	1.75 (1.01-3.02)	.61
Sustained (n = 78)	1.07 (1.03-1.11)	Referent	1.13 (0.56-2.31)	1.42 (0.64-3.15)	2.92 (1.30-6.57)	
Men§ (n = 161)	1.04 (1.01-1.08)	Referent	1.40 (0.71-2.77)	1.91 (0.91-4.01)	2.66 (1.20-5.93)	
Women§ (n = 147)	1.05 (1.01-1.08)	Referent	1.03 (0.57-1.87)	1.34 (0.70-2.55)	1.86 (0.95-3.64)	.58
Age <70 y (n = 167)	1.05 (1.02-1.07)	Referent	0.86 (0.46-1.62)	0.97 (0.51-1.83)	1.78 (0.96-3.30)	
Age ≥70 y (n = 258)	1.02 (0.99-1.05)	Referent	0.99 (0.65-1.51)	1.36 (0.83-2.23)	1.42 (0.76-2.64)	
Hypertensive women (n = 147)	1.05 (1.01-1.08)	Referent	1.03 (0.57-1.87)	1.34 (0.70-2.55)	1.86 (0.95-3.64)	.86
Nonhypertensive women (n = 117)	1.01 (0.97-1.05)	Referent	0.69 (0.37-1.29)	0.66 (0.31-1.42)	1.19 (0.51-2.79)	
Diabetes¶ (n = 101)	1.07 (1.02-1.13)	Referent	1.80 (0.63-5.18)	2.24 (0.77-6.53)	4.08 (1.36-12.3)	
No diabetes mellitus (n = 324)	1.02 (1.00-1.04)	Referent	0.89 (0.61-1.30)	1.01 (0.66-1.56)	1.28 (0.79-2.06)	.17
Hyperlipidemia¶ (n = 110)	1.02 (0.98-1.07)	Referent	0.88 (0.38-2.02)	0.96 (0.41-2.25)	1.34 (0.52-3.43)	
No hyperlipidemia (n = 315)	1.04 (1.01-1.06)	Referent	0.95 (0.65-1.41)	1.14 (0.73-1.79)	1.73 (1.08-2.77)	
Coronary disease# (n = 107)	1.03 (0.97-1.08)	Referent	1.20 (0.55-2.61)	1.19 (0.51-2.78)	2.21 (0.82-5.97)	.91
No coronary disease (n = 318)	1.04 (1.01-1.06)	Referent	0.92 (0.62-1.37)	1.18 (0.76-1.83)	1.58 (1.00-2.50)	

Abbreviations: AF, atrial fibrillation; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; OR, odds ratio.

*Unless otherwise indicated, data are reported as OR (95% CI), and models adjusted for age (cubic spline), sex, and presence of treated hypertension; all reported numbers of subjects refer only to numbers of AF cases, not the total number of subjects in the analysis.

†Except where otherwise indicated, P value is for interaction between BMI unit increment (continuous) and the characteristic on which subjects were stratified.

‡From the Wald test comparing the regression coefficient for BMI across the 3 case types in the polytomous regression models.

§Estimates adjusted only for age. Only subjects treated for hypertension are included in this comparison because men without hypertension were not included in the study.

||Estimates adjusted only for age. Only women are included in this comparison because men without hypertension were not included in the study.

¶Defined as physician diagnosis of the condition in the medical record.

#Defined as history of myocardial infarction, definite or probable angina, or coronary revascularization.

($P = .04$ comparing the 3 classes) (Table 4). This finding was not affected by adjustment for use of β -blockers or antiarrhythmic medications during the first 6 months after AF onset.

The relationship between BMI and AF was stronger in subjects with diabetes mellitus than in those without and somewhat stronger in subjects with hypertension and those younger than 70 years compared with subjects without these characteristics, but these differences were not statistically significant.

POSSIBLE MEDIATORS OF THE ASSOCIATION OF BMI WITH RISK OF NEW-ONSET AF

Adding diabetes mellitus to the baseline model (adjusted for age, sex, and treated hypertension) attenuated the association between BMI and risk of AF: the regression coefficient for BMI decreased by 16%, and correspondingly, the OR per unit increment in BMI decreased from 1.034 (95% CI, 1.014-1.054) to 1.028 (95% CI, 1.008-1.049). Addition of other potential mediators, including duration of diabetes mellitus, duration of hypertension, presence of treated hyperlipidemia, systolic and diastolic blood pressure, total and HDL cholesterol levels, and coronary artery disease, did not significantly weaken the association between BMI and AF risk.

BMI AND LA SIZE AMONG AF CASES

Among AF cases, a higher BMI was associated with LA enlargement. Among AF cases with normal BMI, 49% had normal LA size compared with 23% of those who were overweight or obese ($P = .001$). The OR for the association between elevated BMI and LA enlargement was 3.1 (95% CI, 1.5-6.1).

COMMENT

In this population-based case-control study, each unit BMI increment was associated with a 3% higher risk of new-onset AF (95% CI, 1%-5%). This is comparable to prior studies, which found the risk to be 3% to 8% higher for each unit BMI increment.^{5,7,8,18} When BMI was categorized according to the National Institutes of Health/World Health Organization scheme, our results were consistent with those of most prior studies. For obese subjects, our summary OR is very close to that of Wang et al⁷ but lower than that of Frost et al.⁵ Because Frost et al excluded subjects with cardiovascular risk factors or disease at baseline, their population may not be comparable to ours or that of other studies. Given the broad CIs, however, all of these risk estimates are generally consistent.

This is the first study we know of to explore whether AF risk differs by AF classification, defined according to persistence and/or duration of AF. Our study reveals that the association between BMI and AF risk was stronger for sustained than for intermittent or transitory AF. On average, each unit increment in BMI was associated with a 7% greater risk of sustained AF but only 4% greater risk for intermittent AF and 1% for transitory AF. This result requires confirmation. A possible explanation for this result is that obesity may contribute to maintaining AF once it has been initiated. Support for this idea comes from studies showing that increased C-reactive protein (CRP) levels, which are positively associated with obesity,¹⁹⁻²¹ are more strongly associated with persistent than with paroxysmal AF,²² and that elevated CRP levels are associated with decreased success of cardioversion in patients with AF.²³

This is also the first study that we know of to explore the extent to which the association between obesity and AF risk may be mediated by cardiovascular risk factors. We found that diabetes mellitus may play a modest role in mediating the relationship between BMI and AF risk. The mechanism through which diabetes mellitus may lead to increased AF risk is not well understood, although several possible mechanisms exist. Diabetes mellitus is associated with increased inflammation as measured by CRP,²⁴⁻²⁶ and increased CRP level is associated with an increased risk of AF.^{19,22} In addition, diabetes mellitus leads to myocardial fibrosis and diastolic dysfunction, which may lead to increased LA volume and thereby to increased AF risk, as LA size is known to be associated with risk of new-onset AF.²⁷ In our study, there was a suggestion of a stronger association between BMI and AF risk among subjects with diabetes mellitus than among those without diabetes mellitus, although this difference was not statistically significant.

The association between BMI and AF risk was not weakened when other cardiovascular risk factors, including hyperlipidemia and lipid and blood pressure measurements, were added to the model. This suggests that these cardiovascular risk factors likely do not play a major role in mediating the relationship between obesity and AF risk. Our findings are consistent with prior studies in which the association between BMI and AF risk persisted after adjustment for these characteristics.^{5,7}

Another possible mediator—one that we did not have the ability to explore—is increased LA size, allowing the development and propagation of re-entrant electrical circuits. Wang et al⁷ found that the association between BMI and AF risk became insignificant after adjustment for LA size and concluded that LA enlargement accounted for the entire observed association between BMI and AF risk. Consistent with these observations, in our study, increased BMI was associated with LA enlargement among AF cases. Further research is needed regarding the mechanism by which obesity may lead to increased risk of AF, and in particular, the relative contributions of LA enlargement and systemic inflammation.

Strengths of our study include its population-based design and the use of detailed medical record review to validate the diagnosis of incident AF and to exclude prevalent cases. Data on covariates were obtained from medi-

cal record review and telephone interview, which are more sensitive than administrative data for capturing this information. Unlike prior studies, we had information on duration and persistence of AF.

This study also has several limitations. First, we were able to identify only AF cases that came to clinical attention. Thus there may have been additional asymptomatic or transitory cases that were not identified. Second, confounding by an unmeasured characteristic could be responsible for the relationship we observed between BMI and AF risk. Third, our ability to examine possible mechanisms for the relationship between BMI and AF risk was limited because we lacked echocardiographic data on many subjects and had no data on CRP level. In addition, because echocardiograph results for cases could have been obtained before or after AF onset, LA enlargement could have been a consequence rather than a precursor of AF. Fourth, the method we used to examine potential mediators is limited in that if there is misclassification in the measurement of potential mediators, their importance may be underestimated.

Taken together, study findings to date suggest that a heightened suspicion for AF is appropriate in obese individuals, particularly those who are extremely obese. If future studies confirm that obese individuals are at increased risk for sustained rather than transitory AF, then more aggressive approaches to anticoagulation may be appropriate in these individuals. In addition, nonpharmacologic interventions such as exercise and dietary change may be beneficial if it is shown that weight loss can decrease the risk of developing AF, a question that has not yet been examined.

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Correspondence: Sascha Dublin, MD, PhD, Health Services Research and Development, Veterans Affairs Puget Sound Health Care System, Metropolitan Park West, 1100 Olive Way, Suite 1400, Seattle, WA 98101 (Sascha.Dublin@va.gov).

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