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ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Age-Specific Association Between Body Mass Index and the Incidence of Atrial Fibrillation in Japanese Men

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Background: Obesity is reportedly associated with the incidence of atrial fibrillation (AF), but the patterns of age-specific associations between body mass index (BMI) and the risk of AF are unknown.

Methods and Results: We analyzed 10,921 Japanese men without AF from a cohort of employees undergoing annual health examinations. During a follow-up period of 5.0±3.8 years, the incidence of AF was 118 (2.18/1,000 person-years). Using a multivariable Cox regression analysis, high BMI was associated with a risk of AF (hazard ratio; 1.07 by 1 unit change of BMI, 95% confidence interval [CI] 1.00–1.13, P=0.05) overall, and the effect of BMI on AF incidence changed with age (P for interaction=0.08); with subjects aged <65 years with BMI <25 as the reference, HR 0.74 (95% CI 0.47–1.17) in subjects aged <65 years with BMI ≥25, HR 2.98 (95% CI 1.36–6.54) in subjects aged ≥65 years with BMI <25, and HR 6.50 (95% CI 2.58–16.38) in subjects aged ≥65 years with BMI ≥25. The 5-year probability of AF incidence in subjects aged <65 years was 0.87% with BMI <25 and 0.64% in those with BMI ≥25, and in subjects aged ≥65 years it was 2.58% with BMI <25 and 5.53% with BMI ≥25.

Conclusions: Our results indicated that the effect of BMI on AF incidence changes with age among Japanese men. Both physicians and cardiologists need to integrate advice on lifestyle measures, particularly for elderly obese men, into their daily medical routine.

Key Words: Atrial fibrillation; Body mass index; Epidemiology; Men

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice and is increasingly being recognized as a major public health burden.[1] The worldwide prevalence of AF is already estimated at 33 million, and this is possibly a significant underestimate of the true figure, given the likelihood of study methodological limitations and under-diagnosis.[2,3]

The age-specific incidence of AF is increasing in addition to any further effects apart from an aging population.[4] It is likely that the epidemiologic transition worldwide towards increased longevity and unhealthy lifestyles is resulting in an increasing prevalence and multiplicative effect of AF risk factors.[5] A greater focus on and effort to reduce risk factors caused by unhealthy lifestyles, such as obesity, is thus required to prevent the initial development and subsequent burden of AF.[6]

A meta-analysis on the association between obesity and AF, including 51 studies, showed 29% (odds ratio [OR]: 1.29, 95% confidence interval [CI]: 1.23–1.36) and 19% (OR: 1.19, 95% CI: 1.13–1.26) greater excess risk of incident AF for every 5-Units of body mass index (BMI) increase in cohort and case-control studies, respectively.[7] Most of the studies, however, focused on the relationship between incremental increases in obesity and AF across different clinical settings, but did not assess the effect of age on the shape of the BMI-AF risk relationship. We aimed to investigate the age-specific association between BMI and the incidence of AF among Japanese men.

Methods

Study Subjects and Study Design

The Nishimura Health Survey is an ongoing cohort investigation of risk factors for chronic diseases, including hypertension, metabolic syndrome, and diabetes mellitus as well as AF.[8] The Nishimura Clinic (Kyoto, Japan) provides regular health check-ups for employees of various companies. In Japan, annual routine health examinations of employees are legally mandated, and the employers usually pay all or most of the health examination costs. We conducted a retrospective cohort study to assess the patterns of age-specific association between BMI and the incidence

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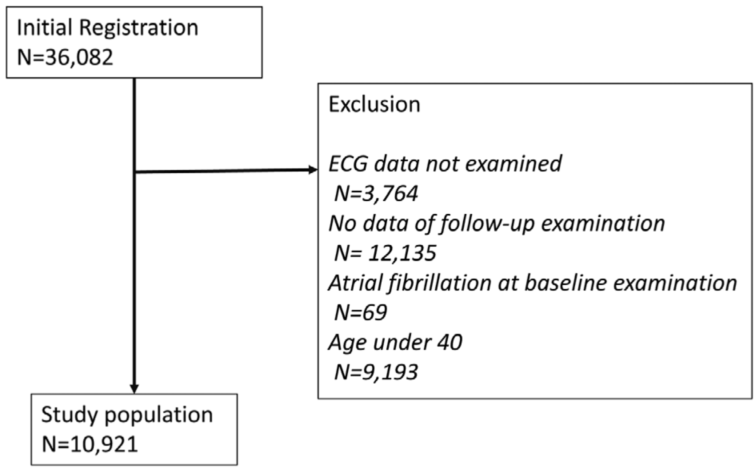


Figure 1. Flowchart of the inclusion and exclusion of study subjects.

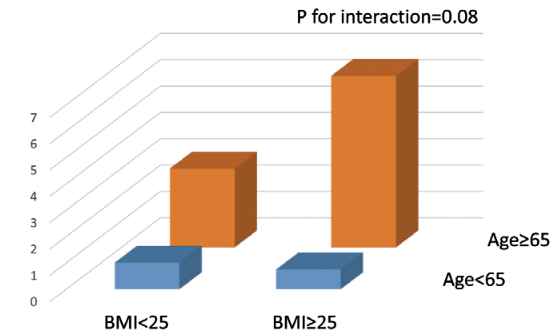
Table. Clinical Characteristics of the Study Participants

	Total (n=10,921)	BMI <25 (n=7,668)	BMI ≥25 (n=3,253)	P value
Age (years)	49.6±7.4	49.7±7.5	49.3±7.1	0.02
BMI	23.6±3.2	22.0±1.9	27.4±2.5	<0.001
Waist circumference, cm	84.8±8.9	80.7±6.2[a]	93.8±7.3[b]	<0.001
SBP, mmHg	126.5±16.4	124.0±15.8[c]	132.4±16.3[d]	<0.001
DBP, mmHg	79.6±11.3	78.0±10.9[c]	83.6±11.1[d]	<0.001
Total cholesterol, mg/dL	206±33	204±32[e]	210±34[f]	<0.001
LDL cholesterol, mg/dL	125±31	122±30[g]	132±32[h]	<0.001
HDL cholesterol, mg/dL	63±17	66±17[i]	55±13[j]	<0.001
Triglycerides, mg/dL	129±103	115±89[i]	163±124[j]	<0.001
Fasting glucose, mg/dL	100.2±19.8	98.3±17.2[k]	104.8±24.2[l]	<0.001
Drinking				
Never	394 (9.4)	278 (9.7)	116 (8.8)	<0.001
Seldom	878 (20.9)	552 (19.2)	326 (24.7)	
Sometimes	1,341 (32.0)	875 (30.4)	466 (35.3)	
Daily	1,584 (37.7)	1,172 (40.7)	412 (31.2)	
Unknown	6,724	4,791	1,933	
Smoking				
Never	1,632 (39.0)	1,131 (39.4)	501 (38.0)	0.67
Ex-smoker	1,207 (28.8)	822 (28.7)	385 (29.2)	
Smoker	1,349 (32.2)	916 (31.9)	433 (32.8)	
Unknown	6,733	4,799	1,934	
ECG findings				
PR extension	86 (0.8)	53 (0.7)	33 (1.0)	0.08
Supraventricular beat	54 (0.44)	37 (0.5)	17 (0.5)	0.78
Atrial enlargement and/or hypertrophy	51 (0.5)	43 (0.6)	8 (0.2)	0.03

Mean ± SD for the continuous variables and n (%) for the categorical variables. P-value is for the comparison between groups by χ^2 or t-test. Number of missing values: n[a]=1,726; n[b]=598; n[c]=1; n[d]=3; n[e]=1,013; n[f]=490; n[g]=1,706; n[h]=590; n[i]=30; n[j]=16; n[k]=62; n[l]=32; otherwise no missing values. Drinking and smoking status were only available for those who had their first visit after April 2013. BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

of AF during a follow-up period of 5.0±3.8 years. Among 36,082 men who underwent health examinations from January 1, 2005 to March 27, 2019, we excluded 12,135 subjects who underwent only 1 health examination. We also excluded a further 3,764 subjects with ECG data that had not been examined and 69 subjects with ECG data indicating AF at recruitment. From the remaining 20,114 subjects, we omitted 9,193 subjects aged under 40 years at baseline. Finally, 10,921 subjects were selected as eligible according to the study criteria (**Figure 1**).

The subjects were divided into groups according to age: <65 and ≥65 years. All procedures of the study were



	BMI<25			BMI≥25		
Age	AF cases/ person years	Hazard ratio	95%CI	AF cases / person years	Hazard ratio	95%CI
<65	77 / 37545	1.00 (reference)		29 / 15248	0.74	0.47-1.17
≥65	7 / 1119	2.98	1.36-6.54	5 / 310	6.50	2.58-16.38

Figure 2. Hazard ratio for atrial fibrillation (AF) incidence by age and body mass index (BMI) categories. Adjusted for SBP, HDL, TG, fasting glucose. CI, confidence interval; HDL, high-density lipoprotein; SBP, systolic blood pressure; TG, triglycerides.

approved by the local research ethics committee and were conducted in accordance with the Declaration of Helsinki. Informed consent was given by all subjects.

Data Collection and Measurements

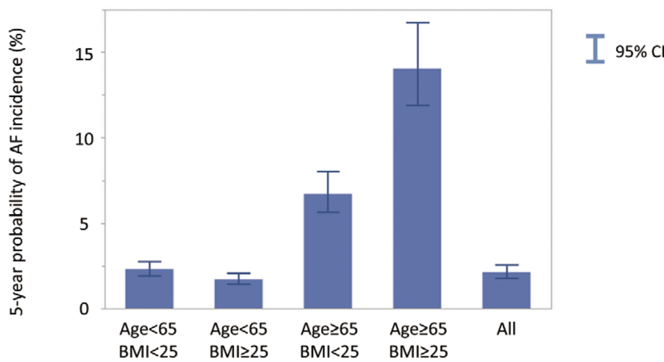
All subjects provided demographic details. BMI was calculated as weight in kilograms divided by height in meters squared. After an overnight fast, venous blood was collected for the measurement of various factors, including fasting plasma glucose, high-density lipoprotein (HDL) cholesterol, and triglycerides (TG). Well-trained nurses measured each participant's blood pressure (BP) twice using an automatic monitor, and the BP value was taken as the average of the 2 measurements. Physicians and nurses administered questionnaires covering personal habits and present illness. Smoking habit was classified as current smoker, ex-smoker, never smoker and unknown, and drinking habit was daily, sometimes, seldom, never drinking and unknown. Participants were diagnosed with AF when AF was present (Minnesota Codes 8-3-1 and 8-3-3) on the ECG (n=44) or when indicated in a patient interview (n=74). The endpoint of the follow-up period for each participant was whichever of the following options occurred first: (1) date of the first AF event, (2) date of the last health examination, or (3) March 27, 2019 (censored).

Statistical Analysis

Clinical characteristics of the study participants, including patient background, laboratory data and ECG data, are listed in the **Table**, presented as mean±1 standard deviation and categorical variables as numbers (percentage). The hazard ratios (HRs) for incident AF were calculated using multivariable Cox regression analyses, first treating age and BMI as continuous variables without interaction, and then treating both age and BMI as binary variables (65 years of age as the binary threshold for age and 25 kg/m^2 for BMI) including an interaction term between age and BMI. To account for the limitation of the frequency of AF diagnosis (i.e., usually once a year due to the study design), we conducted Cox regression analyses accounting for interval censoring with a cubic spline model as the baseline hazard.[9] Total cholesterol and low-density cholesterol, drinking and smoking habits were not included in those multivariable Cox regression analyses because the sample size obtained with those data was small. Diastolic BP (DBP) was also not included in those multivariable Cox regression analyses because it was highly correlated (r=0.86) with systolic BP (SBP). The following variables were treated as potential modifiable covariates: SBP, high-density lipoprotein cholesterol (HDL), TG, and fasting glucose. Proportional-hazard assumption was verified by martingale residuals. Also, the age-specific 5-year probabilities of the incidence of AF were estimated, using the latter multivariable Cox regression model. A P-value of <0.05 was considered statistically significant. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA) and JMP Pro 15 (SAS Institute Inc.).

Results

Baseline characteristics of the 10,921 subjects in this study are shown in the **Table**. Overall, the mean age of the subjects was 49.6±7.4 years, and 29.8% were obese (BMI ≥25). In subjects with BMI ≥25, the mean waist circumference, SBP and DBP, total cholesterol, LDL cholesterol, TG, and fasting glucose were all higher than in those with BMI <25 (all P-values <0.05). During a mean follow-up of 5.0±3.8 years, AF developed in 118 subjects (incidence: 2.18 per 1,000 person-years). In the multivariable Cox proportional-hazard models with age and BMI as continuous variables, increasing age (HR, 2.40 per 10-years; 95% confidence interval [CI], 1.92–2.98; P<0.001) and BMI (HR, 1.07; 95% CI, 1.00–1.13; P=0.05) were associated with the incidence of AF (data not shown). As shown in **Figure 2**, when adding the interaction term between age and BMI, the effect of BMI on AF incidence changed with age (P for interaction= 0.08); the number of cases of incident AF was 77 in subjects aged <65 years with BMI <25 as reference, 29 with HR 0.74 (95% CI 0.47–1.17) in subjects aged <65 years with BMI ≥25, 7 with HR 2.98 (95% CI 1.36–6.54) in subjects



	BMI			
	<25		≥25	
	5-year probability of AF incidence (%)			
Age	Median	Interquartile range	Median	Interquartile range
<65	0.87	0.73-1.05	0.64	0.54-0.78
≥65	2.58	2.16-3.11	5.53	4.65-6.66
ALL	0.80	0.68-0.97		

Figure 3. 5-year probability of atrial fibrillation (AF) incidence by age and body mass index (BMI) categories. CI, confidence interval.

aged ≥65 years with BMI <25, and 5 with HR 6.50 (95% CI 2.58–16.38) in subjects aged ≥65 years with BMI ≥25. The 5-year probability of AF incidence in subjects aged <65 years was 0.87% with BMI <25 and 0.64% with BMI ≥25, and in subjects aged ≥65 years it was 2.58% with BMI <25 and 5.53% with BMI ≥25 group (**Figure 3**).

Discussion

To the best of our knowledge, this is the first large cohort study to show that the effect of BMI on AF incidence changes with age among Japanese men.

Obesity and the Incidence of AF

Obesity is an important contributor to the burden of AF, with obese patients comprising one-fifth of all AF cases.[10] It has also been estimated that obesity may account for approximately 60% of the rising age- and sex-adjusted incidence of AF.[1] A recent meta-analysis[7] pooled data from 51 studies and more than 600,000 individuals in a range of clinical settings. For every 5-Units increase in BMI, there is 10–29% greater excess risk of incident, postoperative, and post-ablation AF. As in those previous studies, there was an 7% excess risk of AF associated with every 1-U increase in BMI in the study population. The consistency of obesity-related risk across different settings lends further weight to the reliability of obesity as an AF risk factor.

Although there have been several studies examining the relationship of BMI with AF, the effect of BMI on AF incidence by age remains largely unknown. Our results suggested that the effect of BMI on incident AF was higher in elderly men (HR 6.50 in those with BMI ≥25 vs. HR 2.98 in those with BMI <25) than in non-elderly men (HR 0.74 in those with BMI ≥25 vs. HR 1.00 in those with BMI <25). Years of unhealthy lifestyle and subsequent weight gain, especially at older ages, might be risk factors for developing AF in middle-aged men. Adiposity may have a direct influence on myocardial structure, perhaps via increased oxidative stress.[11] Body composition-related changes often occur after age 60, such as a decrease in bone mineral density and muscle mass and fat mass increase and redistribution with increased central adiposity, which might be associated with increasing effects of obesity on the AF risk with aging.

Probability of AF Incidence and Future Perspective

Our results also showed a 5-year probability of AF incidence by age and BMI categories, indicating 5.53% of men aged ≥65 years with BMI ≥25 would develop AF, 2.58% of men aged ≥65 years with BMI <25, 0.64% of men aged <65 years with BMI ≥25, and 0.87% of men aged <65 years with BMI <25. In particular, the effect of high BMI on AF risk in elderly obese men aged over 65 years was 6-fold greater than for non-elderly non-obesity men over 5 years. East Asians, including Japanese, tend to have lower BMI than Westerners, albeit the higher the BMI, the higher the risk of developing AF. Thus, our future prediction regarding age-specific AF risk by BMI is particularly significant, given the rising prevalence of both AF and obesity in Asian countries.[12]

From a public health perspective, obesity is a modifiable risk factor that could be beneficially targeted. Moreover, dietary and lifestyle improvements addressing obesity would also favorably affect other AF risk factors such as hypertension and diabetes, further reducing the AF burden more than that attributable to obesity alone. Lifestyle interventions, even if adopted in moderation, can help significantly. For those patients who are unable to completely reverse AF with lifestyle modification, the changes will likely enhance the efficacy of AF treatment. Thus, both physicians and cardiologists need to become more aware and proactive in initiating early adoption of lifestyle modifications to prevent and manage AF.

Study Limitations

First, there were missing data on lifestyle factors (e.g., smoking and drinking habits), and serum total and LDL cholesterol, and therefore we could not allow for these factors as possible confounding factors in the analyses. Second, the manner and frequency of evaluation of AF during the follow-up period may have led to underestimation of incident AF, and the incidence of AF appears lower in this study than in Western countries.[1,13] Lastly, we analyzed the data of subjects who visited the health promotion center as part of their mandatory annual health check-up as employees of various companies, and this group might not be representative of the general population.

Conclusions

Our results indicated that the effect of BMI on incident AF changes with age. Both physicians and cardiologists need to integrate advice for lifestyle measures, particularly for elderly obese men, into their daily medical routine.

Disclosure of Conflicts of Interest

K.S. is affiliated with an endowed department sponsored by Japan lifeline and Biotronik. All other authors declare no conflicts of interest.

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Ethics Approval and Consent to Participate

All subjects were informed about the study and informed consent was given by all the subjects. The study adhered to the Declaration of Helsinki and ethics approval was given by the Institutional Review Board of Kyoto Prefectural University of Medicine.

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Authors' Contributions

K.S. contributed to the data research and analyses, and wrote the manuscript. M.N. and S.T. contributed to the data research and analyses. T.Y. and H.N. researched data and reviewed and edited the manuscript. S.M. contributed to the manuscript organization and reviewed and edited the manuscript. All authors were involved in the writing of the manuscript. All authors read and approved the final manuscript.

IRB Information

The present study was approved by the institutional Clinical Research Review Board of Kyoto Prefectural University of Medicine (reference no. ERB-C-1512).

Data Availability

The deidentified participant data will not be shared.

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