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ORIGINAL PAPER

Body mass index and all-cause mortality in patients with atrial fibrillation: insights from the China atrial fibrillation registry study

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Abstract

Background Impact of body mass index (BMI) on all-cause mortality in atrial fibrillation (AF) patients remains controversial.
Methods A total of 10,942 AF patients were prospectively enrolled and categorized into four BMI groups: underweight (BMI < 18.5 kg/m^2), normal weight (BMI 18.5–24 kg/m^2), overweight (BMI 24–28 kg/m^2) and obesity (BMI ≥ 28 kg/m^2). The primary outcome was all-cause mortality. Different Cox proportional hazards models were performed to evaluate the association between BMI and all-cause mortality.
Results During a median follow-up of 30 months (IQR 18–48 months), 862 deaths events occurred. Compared to normal BMI, higher BMI was associated with a lower mortality risk (overweight: HR 0.70; 95% CI 0.61–0.81, $P < 0.0001$ and obesity: HR 0.54; 95% CI 0.44–0.67, $P < 0.0001$) and lower BMI was associated with a higher mortality risk (HR 2.23, 95% CI 1.67–2.97, $P < 0.0001$).
Conclusion A reversed relationship between BMI and all-cause mortality in AF patients was found. Higher risk of mortality was observed in underweight patients compared to patients with a normal BMI, while overweight and obese patients had a lower risk of all-cause mortality.
Clinical trial registration URL: http://www.chictr.org.cn/showproj.aspx?proj=5831. Unique identifier: ChiCTR-OCH-13003729.

Keywords Body mass index · Arial fibrillation · All-cause mortality

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Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice and is associated with significant mortality and morbidity [1–3]. Obesity, which leads to left atrial remodeling by various mechanisms [4, 5], has emerged as an important risk factor for new-onset AF and AF progression [6–9]. It directly accounts for 20% of the population-attributable risk for AF [10]. Every 5-unit increase in body mass index (BMI) is associated with a 10–29% increased risk of incident, post-operative, or post-ablation AF [11].

The impact of obesity on adverse outcomes in AF patients remains unclear. Some studies found that obese AF patients have a survival advantage over their normal-weight counterparts. This phenomenon is referred to as the "obesity paradox", meaning that obese AF patients have a lower risk of all-cause mortality, cardiovascular (CV) mortality and stroke/systemic embolic events [12–18]. However, the association of BMI with future health outcomes in certain populations is susceptible to reverse causation and confounders [19–21]. In addition, some studies demonstrated that there is no “obesity paradox” when specific groups of patients are excluded from the analyses or when adjustments are made for smoking status [22–24].

In this study, we used data from the China Atrial Fibrillation Registry (China-AF) to evaluate the association between BMI and the prognosis of Chinese AF patients. We adjusted for confounding factors and employed different statistical methods to minimize the effect of reverse causation.

Methods

Study population

The China-AF study is a prospective, multicenter, hospital-based, ongoing registry of patients diagnosed with AF. Details of the China-AF study have been described previously [25].The study was approved by the Human Research Ethics Committee of Beijing Anzhen Hospital and is in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all participants included in the study. The study was registered with the Chinese clinical trial registry, number ChiCTR-OCH-13003729.

From August 2011 to December 2016, 19,515 AF patients were recruited from outpatient clinics and inpatient wards of 31 hospitals located in Beijing, China. We collected the following information on patients' baseline characteristics: age, sex, height, weight, education level, insurance status, type of AF, smoking and drinking status, medical history including hypertension (HTN), diabetes mellitus (DM), hyperlipidemia, established coronary artery disease (CAD, including myocardial infarction or percutaneous coronary intervention or coronary artery bypass grafting), heart failure (HF), history of stroke/transient ischemic attack (TIA)/peripheral thromboembolism (PT) and major bleeding events, hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), peripheral artery disease (PAD), thyroid disease, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), CHA_2DS_2-VASc score (HF, HTN, age ≥ 75 years, DM, previous stroke/TIA/PT, vascular disease, age 65–74 years, female sex) as well as results of physical examination, laboratory and imaging tests and medication. All data were entered into a specific electronic data capture system. Data elements and definition of each variable were in accordance with the ACC/AHA recommendations on AF clinical data standards [26]. Each enrolled patient was followed up at 3 months, 6 months, and every 6 months thereafter at the outpatient clinics or via telephone interview by trained staff. Information on medical or interventional therapies, events of ischemic stroke/SE, hospitalizations, and deaths was collected at each follow-up.

For the present analysis, we excluded patients with a follow-up of less than 6 months ($n = 1374$) and patients with no available baseline weight or height ($n = 928$). We also excluded patients who underwent catheter ablation ($n = 6271$) to preclude any possible impact of the procedure on patients' prognosis. Finally, 10,942 participants were included in this analysis (Fig. 1).

Definition of BMI

Body weight was stratified by BMI. At the initial visit of the study, trained research staff measured and recorded height (to the nearest 0.1 cm) and weight (to the nearest 0.1 kg) for each patient. BMI was calculated by dividing in kilograms by the square of height in meters. Patients were categorized into four different BMI groups: underweight (< 18.5 kg/m [2]), normal weight (18.5–24.0 kg/m^2), overweight (24.0–28.0 kg/m^2) and obesity (≥ 28.0 kg/m^2) based on the Criteria of Weight for Adults released by the Ministry of Health of China [27]. The analyses were also performed using BMI as a continuous variable (per 1 kg/m^2) and using BMI quartiles. BMI quartiles were categorized as: Q1 (< 22.91 kg/m^2), Q2 (22.91–25.14 kg/m^2), Q3 (25.14–27.43 kg/m^2) and Q4 (≥ 27.43 kg/m^2).

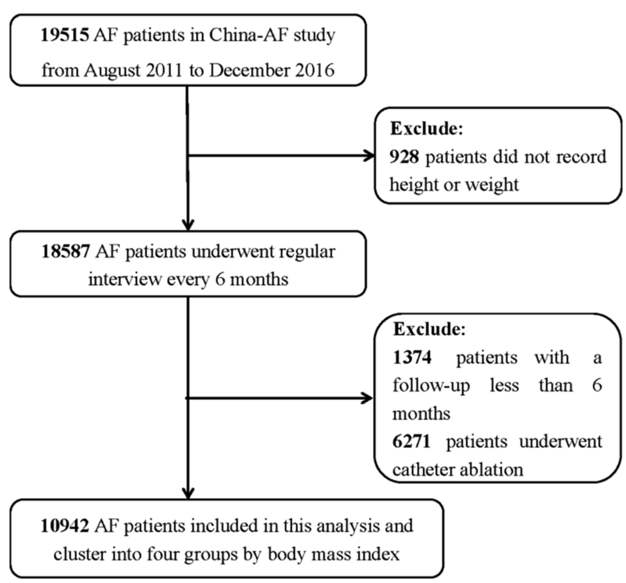

Fig. 1 Flowchart of patients included

Follow-up and outcomes

The primary outcome for the current analysis was time to death from any cause. Causes of death were collected and the outcome of CV mortality was analyzed. In this study, CV mortality includes death resulting from myocardial infarction, HF, sudden cardiac death, and death due to other CV causes. Patients who did not experience the outcome and who could not be reached by investigators were censored at their last follow-up contact.

Statistical analysis

Baseline characteristics were summarized for patients in each BMI category. Continuous variables were presented as the mean and standard deviation or median and interquartile range (IQR) and compared with one-way analysis of variance (ANOVA) or Mann–Whitney *U* test. Categorical variables were expressed as numbers and percentages (%) and analyzed by Pearson's Chi square test.

Cumulative event-free survival rate of all-cause mortality in different BMI categories was analyzed using the Kaplan–Meier method and evaluated with the use of log-rank test. The incidence rate of all-cause mortality was reported as the number of events per 100 person-years of follow-up in each of the BMI groups. The causes of death were analyzed and were compared between BMI groups as well as between underweight and overweight groups. A histogram was used to illustrate a frequency distribution of all-cause mortality in relation to BMI (per 2 kg/m^2).

Hazard ratios (HRs) with their 95% confidence intervals (95% CIs) for all-cause mortality were estimated with the use of Cox proportional hazards regression models with adjustment for age, type of AF, smoking and drinking status, comorbid diseases and medications (all covariates with $P < 0.2$ in the univariable models were entered into multivariable models). The normal weight (BMI 18.5–24.0 kg/m^2) group was used as the reference group for BMI categories; the lower quartile (BMI < 22.91 kg/m^2) was used as the reference group for BMI quartiles. Box plots of hazard ratios were constructed to show the mortality risk tendency of BMI per 2 kg/m^2 (with BMI 24–26 kg/m^2 as reference). Regression methods were used to test for the trend, to find whether an association existed between BMI and all-cause mortality. The same analyses were performed with patients stratified by age (< 65 years, 65–75 years and ≥ 75 years), by sex (male, female), by AF type (paroxysmal, non-Paroxysmal) and by the presence of common comorbidities (HF, Stroke/TIA, CAD, HTN, DM, Hyperlipidemia) to test the consistency of the results. Similarly, HRs and 95% CI of the primary outcome were estimated and their interactions were tested. All analyses performed for the outcome of all-cause mortality were also conducted for the outcome of CV mortality.

We conducted sensitivity analyses in the following patients sets to minimize the effect of reverse causation: First, we excluded patients who smoked (former and current smokers) and those who experienced the primary outcome in the first 12 months of follow-up; Second, we excluded patients with comorbidities including history of HF, CAD, HCM, DCM, HTN, DM, hyperlipidemia, PAD, stroke/TIA/PT, CKD, COPD and thyroid disease. Cox proportional hazards regression models were also used in sensitivity analyses.

A 2-sided *p* value < 0.05 was considered to be statistically significant. All analyses were performed using R (The R Foundation; http://www.r-project.org).

Results

A total of 10,942 patients (57.6% men; mean age, 66.7 years) were included in this analysis, with 251 (2.29%), 3650 (33.36%), 4856 (44.38%) and 2185 (19.97%) patients being categorized as underweight, normal weight, overweight, and obesity, respectively.

Characteristics of the study population

Baseline characteristics according to categories of BMI are detailed in Table 1. Specifically, patients with overweight and obesity were younger, more likely to be men, current smoker and drinker, to have non-paroxysmal AF and a higher prevalence of HTN, DM, and hyperlipidemia. They also had higher levels of total cholesterol, triglyceride, fasting blood glucose, a larger left atrial size, and a thicker interventricular septum. The use of warfarin, statin, and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEIs/ARB) was also more common among those patients. In contrast, underweighted patients were older, had a higher prevalence of HF and stroke/TIA/PT, as well as higher level of natriuretic peptides (B-type natriuretic peptide, N-terminal pro B-type natriuretic peptide).

Association of BMI with all-cause mortality

During a median follow-up of 30 months (IQR, 18–48 months), a total of 862 deaths occurred. A significant association was observed between BMI groups and all-cause mortality ($P < 0.001$) (Fig. 2a). All-cause mortality was highest in underweight patients (9.11 per 100 patient-years), followed by normal weight (4.08 per 100 patient-years), overweight (2.88 per 100 patient-years) and obesity (2.22 per 100 patient-years) (Table 2). There was no significant difference in the cause of death for the different BMI categories (Online Resource 1) or when the underweight and overweight groups were compared (Online Resource 2).

Table 1 Baseline characteristics according to categories of body mass index (BMI) among all patients

Characteristics	Underweight (BMI < 18.5 kg/m^2) (*n* = 251)	Normal weight (BMI 18.5–24.0 kg/m^2) (*n* = 3650)	Overweight (BMI 24.0–28.0 kg/m^2) (*n* = 4856)	Obesity (BMI ≥ 28.0 kg/m^2) (*n* = 2185)	*P* value
Age (years), mean (SD)	73.7 ± 10.89	68.6 ± 11.89	66.1 ± 11.32	64.09 ± 11.88	< 0.0001
Male, *n* (%)	108/251 (43.0)	2001/3650 (54.8)	3002/4856 (61.8)	1194/2185 (54.6)	< 0.0001
BMI (kg/m^2), mean (SD)	17.4 ± 0.92	21.9 ± 1.43	25.86 ± 1.14	30.6 ± 2.86	< 0.0001
Education level, *n* (%)					
Middle school or below	161/232 (69.4)	2265/3394 (66.7)	3013/4465 (67.5)	1499/2010 (74.6)	< 0.0001
High school or above	71/232 (30.6)	1129/3394 (33.3)	1452/4465 (32.5)	511/2010 (25.4)	
Patients insurance status, *n* (%)					
All	40/251 (15.9)	502/3650 (13.7)	569/4856 (11.7)	187/2185 (8.6)	< 0.0001
Partially	189/251 (75.3)	2864/3650 (78.5)	3920/4856 (80.7)	1824/2185 (83.5)	
None/other	22/251 (8.8)	284/3650 (7.8)	367/4856 (7.6)	174/2185 (7.9)	
Atrial fibrillation type, *n* (%)					
Paroxysmal	156/251 (62.2)	2194/3646 (60.2)	2793/4851 (57.6)	1200/2184 (54.9)	**0.002**
Non-paroxysmal	95/251 (37.8)	1452/3646 (39.8)	2058/4851 (42.4)	984/2184 (45.1)	
Smoking, *n* (%)					
Never	189/251 (75.3)	2575/3626 (71.0)	3165/4816 (65.7)	1455/2169 (67.0)	< 0.0001
Former	37/251 (14.7)	536/3626 (14.8)	893/4816 (18.5)	368/2169 (17.0)	
Current	25/251 (10.0)	515/3626 (14.2)	758/4816 (15.8)	346/2169 (16.0)	
Drinking, *n* (%)					
Never	202/251 (80.5)	2674/3623 (73.8)	3169/4814 (65.8)	1430/2172 (65.8)	< 0.0001
Former	16/251 (6.4)	414/3623 (11.4)	684/4814 (14.2)	275/2172 (12.7)	
Current	33/251 (13.1)	535/3623 (14.8)	961/4814 (20.0)	467/2171 (21.5)	
CHA_2DS_2-VASc score					
≤ 1	36 (14.3)	819 (22.4)	1228 (25.3)	526 (24.1)	**0.001**
≥ 2	215 (85.7)	2831 (77.6)	3628 (74.7)	1659 (75.9)	
Comorbidity, *n* (%)					
Established CAD	45/251 (17.9)	628/3650 (17.2)	934/4856 (19.2)	393/2185 (18.0)	0.117
Heart failure	78/251 (31.1)	750/3650 (20.6)	914/4856 (18.8)	466/2185 (21.3)	< 0.0001
Hypertension	138/251 (55.0)	2203/3650 (60.4)	3348/4856 (68.9)	1700/2185 (77.8)	< 0.0001
DM	44/251 (17.5)	792/3650 (21.7)	1258/4856 (25.9)	667/2185 (30.5)	< 0.0001
Hyperlipidemia	97/251 (38.6)	1612/3650 (44.2)	2456/4856 (50.6)	1215/2185 (55.6)	< 0.0001
History of stroke/TIA/PT	56/251 (22.3)	672/3650 (18.4)	900/4856 (18.5)	377/2185 (17.3)	0.212
PAD	9/251 (3.6)	105/3650 (2.9)	136/4856 (2.8)	62/2185 (2.8)	0.909
History of bleeding	27/251 (10.7)	217/3650 (5.95)	240/4856 (4.94)	99/2185 (4.5)	0.0001
Hypertrophic cardiomyopathy	3/250 (1.20)	39/3645 (1.07)	48/4848 (0.99)	23/2178 (1.06)	0.975
Dilated cardiomyopathy	0	35/3649 (0.96)	50/4853 (1.03)	27/2182 (1.24)	0.292
CKD	19/180 (10.56)	192/2475 (7.76)	190/3299 (6.76)	92/1530 (6.01)	0.003
Thyroid disease	7/122 (5.7)	96/2013 (4.7)	102/2777 (3.7)	41/1256 (3.3)	0.342
COPD	7/251 (2.8)	55/3642 (1.5)	56/4841 (1.2)	41/2179 (1.9)	0.03
Examinations					
Heart rate (bpm)	81.8 ± 20.7	80.9 ± 20.6	80.8 ± 19.7	81.6 ± 20.0	0.504
SBP (mmHg)	126.2 ± 19.4	127.0 ± 17.3	129.2 ± 16.7	130.8 ± 17.0	< 0.0001
DBP (mmHg)	73.7 ± 10.8	76.0 ± 10.8	78.4 ± 11.1	79.9 ± 11.4	< 0.0001
LVEF (%)	58.7 ± 12.5	61.3 ± 10.3	61.2 ± 10.1	61.3 ± 9.7	0.259
Left atrial size (mm)	40.21 ± 8.55	40.39 ± 8.46	41.55 ± 7.62	43.42 ± 7.58	< 0.0001
Interventricular septum (mm)	9.10 ± 1.75	9.58 ± 3.55	9.89 ± 2.58	10.17 ± 2.11	< 0.0001
Laboratory test					
eGFR (mL/min/1.73 m^2)	99.8 ± 45.5	103.3 ± 40.1	105.2 ± 45.4	104.8 ± 39.0	0.174
BNP (pg/mL)	482.0[206.8–2628.7]	364.0[127.2–963.6]	280.0[123.0–758.1]	218.5[103.5–569.4]	< 0.0001

Table 1 (continued)

Characteristics	Underweight (BMI < 18.5 kg/m^2) (*n* = 251)	Normal weight (BMI 18.5–24.0 kg/m^2) (*n* = 3650)	Overweight (BMI 24.0–28.0 kg/m^2) (*n* = 4856)	Obesity (BMI ≥ 28.0 kg/m^2) (*n* = 2185)	*P* value
NT-proBNP (pg/mL)	2781.5[1140.0–7234.3]	1090.0[432.5–2725.5]	980.0[360.0–2249.0]	921.9[348.3–2109.0]	< 0.0001
Total cholesterol (mmol/L)	4.21 ± 1.14	4.29 ± 1.06	4.33 ± 1.06	4.39 ± 1.06	< 0.0001
Total triglyceride (mmol/L)	1.03 ± 0.75	1.30 ± 0.85	1.50 ± 1.09	1.72 ± 1.16	0.024
Fasting blood glucose (mmol/L)	5.50 ± 1.57	5.95 ± 1.78	6.14 ± 1.85	6.42 ± 2.14	< 0.0001
Baseline medications, *n* (%)					
Warfarin	89/251 (35.5)	1315/3641 (36.1)	1846/4852 (38.05)	910/2180 (41.7)	0.0003
NOACs	7/124 (5.65)	131/2046 (6.40)	212/2851 (7.44)	89/1295 (6.87)	0.507
Aspirin	99/251 (39.4)	1487/3641 (40.8)	2028/4851 (41.8)	875/2180 (40.1)	0.528
Clopidogrel	11/124 (8.87)	159/2046 (7.77)	227/2850 (7.96)	107/1295 (8.26)	0.941
Statin	82/251 (32.7)	1330/3641 (36.5)	2023/4852 (41.7)	978/2180 (44.9)	< 0.0001
ACEI/ARB	85/251 (33.9)	1186/3641 (32.6)	1890/4851 (39.0)	1014/2180 (46.5)	< 0.0001
AADs	54/250 (21.5)	713/3641 (19.5)	874/4852 (18.0)	388/2181 (17.8)	0.119
Propafenone	16/250 (6.40)	251/3641 (6.89)	290/4852 (5.98)	115/2181 (5.27)	0.083
Amiodarone	17/250 (6.80)	240/3641 (6.59)	307/4852 (6.33)	148/2181 (6.79)	0.894
Sotalol	5/250 (2.00)	52/3641 (1.43)	81/4852 (1.67)	46/2181 (2.11)	0.264
β-blocker	135/251 (53.75)	1971/3641 (54.1)	2681/4852 (55.3)	1260/2181 (57.8)	0.055
CCB	8/251 (3.18)	208/3641 (5.71)	307/4852 (6.33)	162/2181 (7.43)	0.053
Digoxin	48/251 (19.1)	430/3641 (11.8)	467/4852 (9.62)	220/2181 (10.09)	0.011

BNP and NT-proBNP were represented using the median and [interquartile range]

BMI body mass index, *CAD* coronary artery disease, *DM* diabetes mellitus, *TIA* transient ischemic attack, *PT* peripheral thromboembolism, *PAD* peripheral artery disease, *CKD* chronic kidney disease: eGFR < 60 mL/min/1.73 m^2, *Thyroid disease* hyperthyroidism and hypothyroidism, *COPD* chronic obstructive pulmonary disease, *OSAHS* obstructive sleep apnea–hypopnea syndrome, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *LVEF* left ventricular eject fraction, *NOACs* novel oral anticoagulants, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *AADs* antiarrhythmic drugs, *CCB* calcium channel blocker, *eGFR* estimated glomerular filtration rate, *BNP* brain natriuretic peptide, *NT-proBNP* N-terminal pro b-type natriuretic peptide

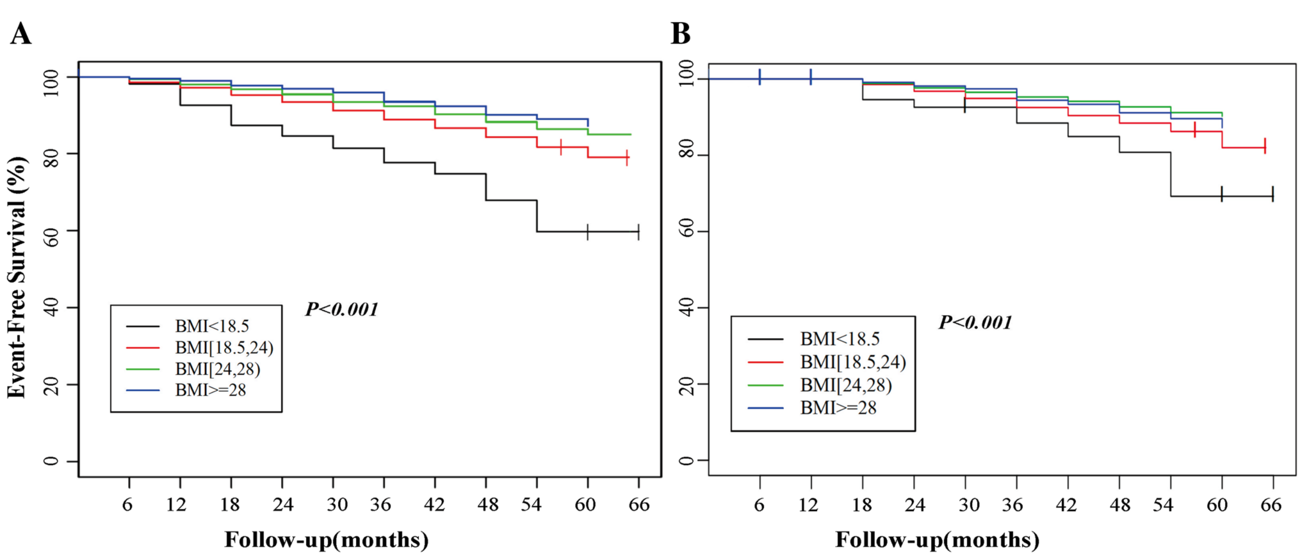

Fig. 2 Kaplan–Meier estimates of all-cause mortality, **a** all patients (*N* = 10,942); **b** exclusion of smokers (former and current) and patients with death happened in the first year (*N* = 7202)

Table 2 Numbers and rates (per 100 person-years) and multivariable-adjusted Cox regression of all-cause mortality according to categories of BMI among all patients

Categories of BMI	No. (per 100 p-y)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Underweight (BMI < 18.5 kg/m^2) (*n* = 251)	61 (9.11)	2.69 (2.05–3.52)	2.23 (1.67–2.97)
Normal weight (BMI 18.5–24.0 kg/m^2) (*n* = 3650)	358 (4.08)	1.00 (reference)	1.00 (reference)
Overweight (BMI 24.0–28.0 kg/m^2) (*n* = 4856)	341 (2.88)	0.71 (0.61–0.82)	0.70 (0.61–0.81)
Obesity (BMI ≥ 28.0 kg/m^2) (*n* = 2185)	102 (2.22)	0.48 (0.38–0.59)	0.54 (0.44–0.67)

BMI body mass index, *HR* hazard ratio, *CI* confidence interval

All-cause mortality multivariable model adjusted for age, heart failure, coronary artery disease, stroke/transient ischemic attack/peripheral thromboembolism, hypertension, diabetes mellitus, hyperlipidemia, history of bleeding, chronic kidney disease: eGFR < 60 mL/min/1.73 m^2, chronic obstructive pulmonary disease, the usage of warfarin, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, antiarrhythmic drugs and statin

All-cause mortality across the range of BMI (per 2 kg/m^2) is illustrated in Fig. 3a.

Multivariate Cox regression analysis showed that, when compared with a normal BMI, a lower BMI was significantly associated with a higher risk of all-cause mortality (underweight: HR 2.23, 95% CI 1.67–2.97, $P < 0.0001$), while a higher BMI was associated with a lower risk of all-cause mortality (overweight: HR 0.70, 95% CI 0.61–0.81 and obesity: HR 0.54, 95% CI 0.44–0.67, both $P < 0.0001$) (Table 2). The same findings were observed in the analyses using BMI as a continuous variable (HR 0.93, 95% CI 0.91–0.95, $P < 0.0001$) and using BMI quartiles. Compared with the lowest quartile (BMI Q1, reference group), patients in the higher quartiles had a significantly reduced risk of all-cause mortality (BMI Q2: HR 0.69, 95% CI 0.57–0.83, $P = 0.002$; BMI Q3: HR 0.67, 95% CI 0.55–0.82, $P < 0.0001$; and BMI Q4: HR 0.51, 95% CI 0.41–0.64, $P = 0.0003$), illustrating a protective effect of a higher BMI (Online Resource 3). The results were consistent across different age groups (< 65 years, 65–75 years and ≥ 75 years) (Online Resource 4) and sex (Male, Female) (Online Resource 5). A similar association between BMI and the risk of all-cause mortality was observed across different AF type and comorbidities groups (Online Resource 6). Adjusted HRs of all-cause mortality across the ranges of BMI (per 2 kg/m^2) are shown in Fig. 3b. The test for trend demonstrated that a higher BMI was associated with a lower risk of all-cause mortality (P trend < 0.0001).

Sensitivity analysis

After excluding patients who smoked (former and current smokers) and those who died in the first 12 months of follow-up, a lower BMI was still associated with a significantly higher risk of all-cause mortality and a higher BMI was still associated with a significantly lower risk of mortality (Fig. 2b). Overweight status also remained significantly associated with a lower mortality risk. Although the association between obesity and a lower mortality risk was not significant, a similar trend was observed (Table 3). When only patients with lone AF (i.e. without any comorbidity) were analyzed, the association between a lower BMI and a higher risk of all-cause mortality remained significant.

Association of BMI with CV mortality

A significant association was also observed between BMI and CV mortality (HR 0.93, 95% CI 0.90–0.96, $P < 0.0001$). When compared with a normal BMI, a lower BMI was significantly associated with a higher risk of CV mortality (underweight: HR 1.65, 95% CI 1.01–2.71, $P = 0.049$), while a higher BMI was associated with a lower risk of CV mortality (overweight: HR 0.60, 95% CI 0.46–0.79, $P = 0.0002$ and obesity: HR 0.67, 95% CI 0.48–0.94, $P = 0.019$) (Online resource 7).

Discussion

In this study of Chinese AF patients, we observed a significant association between BMI and all-cause mortality. Compared with normal BMI, underweight status was associated with a higher risk of all-cause mortality, while overweight and obesity status were associated with a lower risk of all-cause mortality. This association remained consistent across different age, sex and different comorbidities groups, and after excluding both former/current smokers and patients who died in the first year of follow-up, as well as exclusion of patients with comorbidities.

The association between obesity and better outcomes has been reported in patients with HF, CAD, DM, and AF [28–32]. It is referred to as the "obesity paradox". However, this phenomenon nowadays is criticized as being confounded by unadjusted factors [33, 34]. Association between obesity and mortality is vulnerable to two major biases: smoking status and reverse causation. After adjusting for smoking, the paradoxical phenomenon vanished in some studies which aimed to explore the influence of obesity on the outcomes of

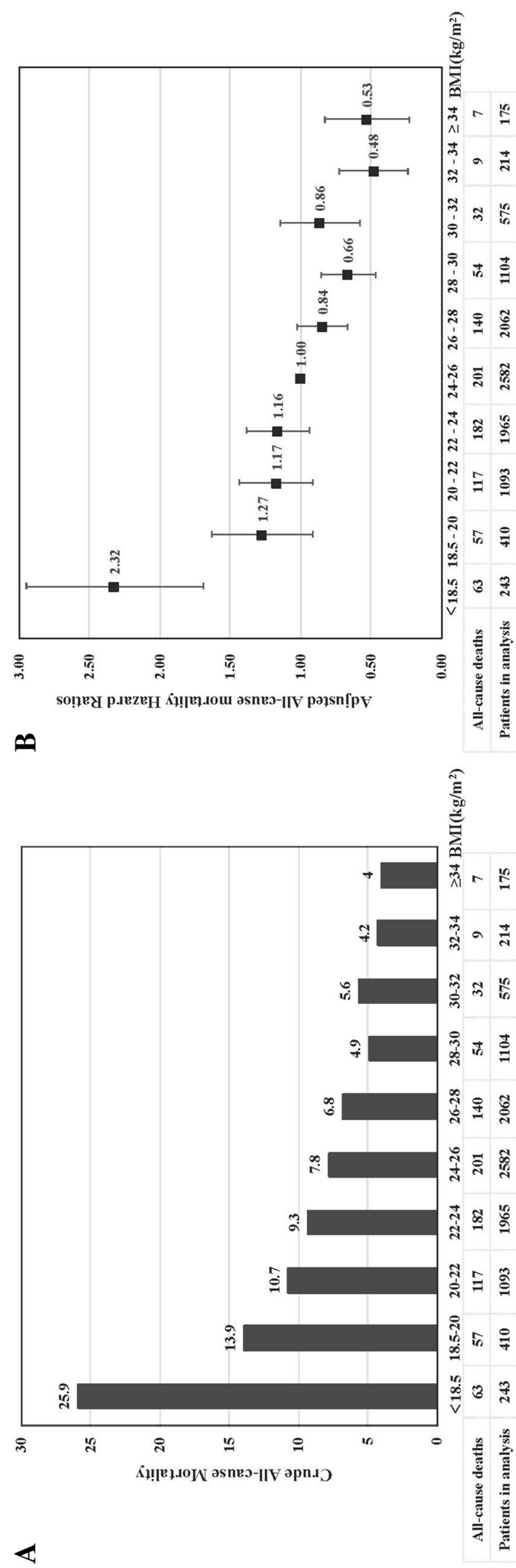

Fig. 3 **a** The crude all-cause mortality in the subdivided BMI groups (per 2 kg/m^2). **b** Adjusted hazard ratios and 95% CI of subdivided BMI groups (per 2 kg/m^2) with Cox proportional hazard models, BMI 24–26 kg/m^2 as reference

Table 3 Sensitivity analyses: Cox regression of all-cause mortality according to categories of BMI (compared with normal BMI patients)

BMI categories	Exclusion of smokers (former and current) and patients with death happened in the first year ($N=7202$)			Inclusion of lone AF patients only ($N=1370$)		
	n/*N* (%)	Unadjusted HR (95% CI)	Adjusted[a] HR (95% CI)	*n*/*N* (%)	Unadjusted HR (95% CI)	Adjusted[b] HR (95% CI)
Underweight (BMI < 18.5 kg/m^2)	24/169 (14.2)	2.50 (1.62–3.86)	1.79 (1.05–3.03)	5/36 (13.9)	4.25 (1.58–11.45)	3.33 (1.23–9.03)
Normal weight (BMI 18.5–24.0 kg/m^2)	141/2497 (5.65)	1.00 (reference)	1.00 (reference)	18/585 (3.08)	1.00 (reference)	1.00 (reference)
Overweight (BMI 24.0–28.0 kg/m^2)	133/3097 (4.29)	0.75 (0.59–0.95)	0.68 (0.50–0.92)	4/559 (0.72)	0.22 (0.08–0.66)	0.28 (0.10–0.85)
Obesity (BMI ≥ 28.0 kg/m^2)	51/1439 (3.54)	0.63 (0.45–0.86)	0.60 (0.41–0.89)	2/190 (1.05)	0.35 (0.08–1.52)	0.61 (0.14–2.68)

Lone AF means AF patients without pre-comorbidities including: heart failure, coronary artery disease, hypertrophic cardiomyopathy, dilated cardiomyopathy, hypertension, diabetes mellitus, peripheral artery disease, stroke/transient ischemic attack/peripheral thromboembolism, chronic kidney disease: eGFR < 60 mL/min/1.73 m^2 and thyroid disease

BMI body mass index, *HR* hazard ratio, *CI* confidence interval, *AF* atrial fibrillation

[a]Cox regression model adjusted for age, drinking status, heart failure, hypertension, diabetes mellitus, history of stroke/TIA/PT, CKD, chronic obstructive pulmonary disease, left atrial diameter, the usage of warfarin, ACEI/ARB, statin, digoxin

[b]Cox regression model adjusted for age and smoking status

CV diseases [20]. Reverse causation refers to examples in which lower weight might be a result rather than a cause of illness. Some reports observed that when the patients experiencing adverse events in the first years of follow-up were excluded from the analyses, the obesity paradox disappeared [23, 24, 35]. In previous studies evaluating the relationship between obesity and prognosis in patients with AF, few efforts have been taken to reduce these potential biases.

In the present study, we did sensitivity analyses by excluding smokers (former and current) and patients who died in the first 12 months of follow-up and found that the association between BMI and all-cause mortality remained significant. The presence of comorbidity might also have an impact on the association between obesity and all-cause mortality. However, in the second sensitivity analysis excluding patients with comorbidities to exclude possible confounding effect, the relationship between overweight and all-cause mortality remained consistent (i.e. "overweight paradox"), but the paradox relationship between obesity and all-cause mortality disappeared. Of note, a study found that the obesity paradox only existed in female AF patients [36], or in elderly AF patients [37]. We also analyzed the association between BMI and all-cause mortality in different sex, age and comorbidities groups and found that this association was consistent.

Although there is no plausible explanation for the "obesity paradox", several factors may contribute to this observed phenomenon. First, patients with overweight or obesity may get earlier and more intensive medical attention due to a higher prevalence of metabolic diseases such as HTN or DM, compared with patients with a normal body weight. In our study, we did observe a higher proportion usage of anticoagulant treatment, statins or ACEIs/ARB in patients with obesity. Besides, AF is independently associated with higher natriuretic peptide (NP) levels which could further increase the risk of stroke and mortality [38]. Obese and overweight patients have considerably lower plasma NP levels than individuals with normal BMI and this may contribute to the protective mechanism [39]. The reverse association between BMI and NP levels was also observed in the present study. The balances between body fat and the lean mass (i.e. muscle) may also be relevant. Higher body fat is reported to be an independent predictor of lower mortality in patients with coronary heart disease regardless of their lean mass index being low or high [40]. Overweight or obesity could represent either more body fat or a higher lean mass index, the later representing a condition of better metabolic reserve, less frailty or malnutrition [41]. The reverse is true for patients with underweight. In our study, since the underweight patients were older and suffered more from comorbidities such as history of stroke and HF, this could have resulted in a worst prognosis.

Limitations

Some limitations deserve mentioning in the present study. We used BMI as a measure of adiposity to explain the relationship between obesity and CV diseases. Although BMI is conventionally accepted as a measure of obesity all over the world, waist circumference (WC) and waist-hip ratio could have provided additional information. However, in a recent study including AF patients, WC results were in accordance with the BMI analyses [14]. Our analysis considered the baseline BMI without information on weight changes during the follow-up; therefore, changes in adiposity over the course of the study and adverse outcomes could not be assessed. As mentioned above, the significant difference in age at baseline between BMI categories might also involve a potential bias. Although the results of a subgroup analysis with stratification by age were consistent across different groups (< 65 years, 65–75 years and ≥ 75 years), a reverse causation effect regarding low BMI and higher mortality may not be fully eliminated. Patients who underwent catheter ablation were excluded from our analyses. This may have led to a potential selection bias and whether our findings also apply to patient undergoing catheter ablation for AF is unknown. Finally, we did not analyze the patients' cardiorespiratory fitness, which might be a significant factor involved in the mechanism of the "obesity paradox" in CV diseases [42]. Despite these limitations, our study provides important 'real-world' data on the relationship between BMI and clinical outcomes in AF patients.

Conclusions

In this observational study, we found a reversed relationship between BMI and all-cause mortality in AF patients. A higher mortality rate was observed in underweight patients compared to patients with a normal BMI, whereas patients with overweight and obesity had a lower risk of all-cause mortality.

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Compliance with ethical standards

Conflict of interest Dr. Jian-Zeng Dong received honoraria from Johnson & Johnson for giving lectures. Dr. Chang-Sheng Ma received honoraria from Bristol-Myers Squibb (BMS), Pfizer, Johnson & Johnson, Boehringer-Ingelheim (BI), and Bayer for giving lectures. The other authors report no conflicts of interest.

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