

Association between cardiorespiratory fitness, obesity, and incidence of atrial fibrillation [☆]



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ABSTRACT

Background: The interaction between cardiorespiratory fitness (CRF) and incidence of atrial fibrillation (AF) and the interaction between obesity and incidence of AF have been explored separately. Therefore, we evaluated the association between CRF, body mass index (BMI), and risk of developing AF in a cohort of middle-aged and older US Veterans.

Methods: Symptom limited exercise tests (ETT) were conducted among 16,397 Veterans (97% male) from January 9, 1987 to December 31, 2017. No history of AF was evident at the time of the ETTs. CRF was expressed as quartiles of peak metabolic equivalents (METs) achieved within each age decile. Weight status was classified as normal (BMI < 25 kg/m²), overweight (BMI 25–30 kg/m²), obese (BMI 30–35 kg/m²), or severely obese (BMI > 35 kg/m²). Multivariable Cox proportional hazards regression models were used to compare the association between BMI, CRF categories, and incidence of AF.

Results: Over a median follow-up of 10.7 years, 2,155 (13.1%) developed AF. Obese and severely obese subjects had 13% and 32% higher risks for incidence of AF, respectively, vs. normal weight subjects. Overweight and obese subjects in the most fit quartile had 50% decline in AF risk compared to the least-fit subjects. Severely obese subjects had marked increases in AF risk (~50–60%) regardless of fitness level. Risk of developing AF increases with higher BMI and lower CRF.

Conclusion: Improving CRF should be advocated when assessing those at risk for developing AF.

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1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in older adults, with a prevalence increasing from 0.1% among persons younger than 55 years to > 9.0% in adults aged 80 years or older [1]. Individuals with AF have a five-fold greater risk of developing stroke than the general population, and AF is associated with increased morbidity and mortality [1]. The prevalence of AF also increases with the presence of traditional cardiovascular disease

Abbreviations and Acronyms: AF, Atrial fibrillation; BMI, Body mass index; CPRS, Computerized patient record system; CRF, Cardiorespiratory fitness; CVD, Cardiovascular disease; DM, Diabetes mellitus; ETT, Exercise tolerance test; HR, Hazard ratio; HTN, Hypertension; MET, Metabolic equivalent; PA, Physical activity; VA, Veterans affairs.

^{*} This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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(CVD) risk factors including diabetes mellitus, obesity and hypertension (HTN) [2–4]. In recent years, cardiorespiratory fitness (CRF) has been advocated as a risk factor for CVD [5], given its strong inverse association with adverse outcomes particularly all-cause mortality and cardiovascular events [5–7]. Additionally, benefits of higher CRF consist of independent and inverse associations with the development of AF [2,8]. Among individuals with existing AF, better outcomes have been reported among comparatively fit subjects compared to those who are less fit [2]. Moreover, higher CRF is associated with a 13% lower risk of AF recurrence [2,9]. However, a controversy has recently arisen in this area given recent reports suggesting that participation in higher intensity exercise or competitive sports earlier in life are associated with a higher incidence of AF [8,10].

Studies have also shown that overweight and obesity increase the incidence of AF. AF incidence has been reported to increase by 5%–17% for every one unit (1 kg/m²) higher body mass index (BMI) [11,12]. In two recent meta-analyses, the risk of new-onset

and post-operative AF were 10% and 30% higher, respectively, for every 5 kg/m² increase in BMI [13]. In the Nord-Trøndelag Health Study (HUNT) Study, overweight and obesity were associated with higher risk of AF; however, higher levels of regular physical activity reduced the AF risk associated with obesity [14]. In addition, Pathak et al followed a group of overweight or obese participants with symptomatic AF for a mean of ≈4 years and observed that higher baseline CRF predicted long-term AF recurrence [15]. These findings, although limited, suggest that weight control along with moderate physical activity leading to improved CRF may reduce the risk of AF incidence. Given the debate regarding the interaction between obesity, CRF and incidence of AF, the aim of the current study was to evaluate the association between CRF, BMI, and risk of developing AF in a cohort of middle-aged and older US Veterans.

2. Methods

2.1. Data source

Data were derived from large prospective databases from the Palo Alto, CA, and Washington, DC Veterans' Administration (VA) Medical Centers among subjects who were referred for an exercise tolerance test (ETT) for clinical reasons. The Veterans Exercise Testing Study (VETS) is an ongoing, prospective evaluation of Veteran subjects referred for exercise testing for clinical reasons (i.e. chest pain, ruling out coronary heart disease, risk factors, routine check-up, etc.), designed to address exercise test, clinical, and lifestyle factors and their association with health outcomes. The cohort included 21,474 Veterans who had undergone a maximal treadmill test for clinical reasons between January 9, 1987 and December 31, 2017. Patients were included if they had no history of AF prior to the ETT and no AF present at the time of the ETT. Subjects were excluded for the following reasons: 1) BMI < 18.5 kg/m²; 2) exercise capacity < 2 METs; 3) unstable or required emergent intervention or were unable to complete the test for orthopedic, neurologic, or other reasons; 4) patients not treated with beta-blockers but unable to achieve at least 85% of predicted maximal heart rate during the test; and 5) those with an implanted pacemaker, lost to follow-up or subjects with any missing data relevant to the outcome.

After these exclusions, the final cohort included 16,397 participants (97% male). A flow chart explaining the reason for exclusion and final number of patients is shown in Fig. 1. The study was approved by the respective Institutional Review Boards at each institution. Detailed information on relevant demographic, clinical and medication information, risk factors and co-morbidities as defined by ICD coding for all participants were obtained from the VA Computerized Patient Record System (CPRS) at the time of the exercise test. Historical information that was recorded included previous myocardial infarction by history or presence of Q waves, cardiac procedures, heart failure, hypertension (blood pressure $\geq 140/90$ mm Hg), hypercholesterolemia (>200 mg/dL, statin use, or both), claudication, chronic obstructive pulmonary disease, cancer, renal disease, type 2 diabetes (DM2), stroke, smoking status (current and past), and use of cardiac/antihypertensive medications. Weight, height and other clinical and demographic data were recorded at the time of the exercise test. Height and weight were used to calculate body mass index (BMI) and weight status was classified as normal weight (18.5–24.9 kg·m⁻²), overweight (25–29.9 kg·m⁻²), obese (30–34.9 kg·m⁻²), or severe obese (≥ 35 kg·m⁻²) [16].

2.2. Exercise testing

Patients underwent symptom-limited treadmill testing using the Bruce protocol (Washington DC) or an individualized ramp

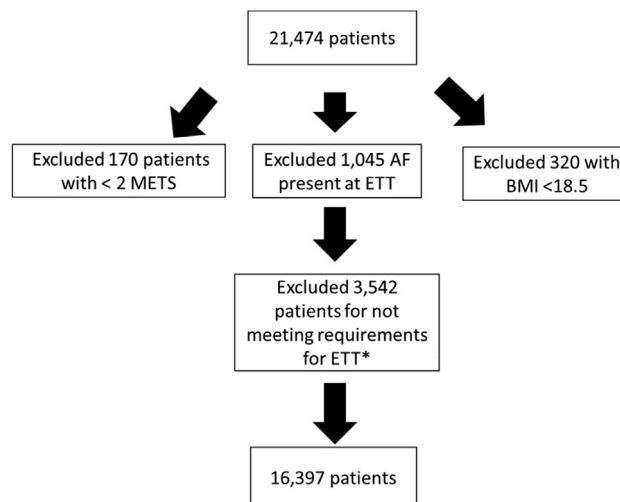


Fig. 1. Flow chart describing patient population. *Patients not able to perform an ETT because they were unstable or required emergent intervention or were unable to complete the test for orthopedic, neurologic, or other reasons; patients not treated with beta-blockers, but unable to achieve at least 85% of predicted maximal heart rate during the test; and those with an implanted pacemaker, lost to follow-up or subjects with any missing data relevant to the outcome. ETT = Exercise Tolerance Test.

treadmill protocol [17] (Palo Alto, CA). Standard criteria for termination were used, including moderately severe angina, >2.0 mm abnormal ST depression, a sustained decrease in systolic blood pressure, or serious rhythm disturbances. Subjects were encouraged to exercise until volitional fatigue in the absence of symptoms or other indications for stopping [18]. Exercise capacity (peak METs) for each participant was calculated by standardized equations based on treadmill speed and grade¹⁶. Blood pressure was taken manually [18]. Medications were not withheld and age-predicted maximal target heart rates were not used as end points.

We stratified the cohort by age decades as < 50, 50 to 59, 60 to 69, and ≥ 70 years and defined CRF categories according to quartiles of peak MET levels achieved within each age stratum. We then combined the CRF categories from each age and formed the CRF categories; least fit (4.41 ± 1.23), moderately fit (6.57 ± 1.31), fit (8.06 ± 1.40), and highly fit (11.28 ± 2.47) [19]. For binary comparisons, the least and moderately fit groups comprised the Unfit group (mean ≤ 6.6 METs) and the fit and the highly fit groups comprised the Fit group (mean > 6.6 METs).

2.3. Follow-up and end point

The primary outcome was incidence of AF, determined through review of CPRS using any AF diagnosis through ICD coding. Follow-up was completed through December 31, 2017.

2.4. Statistical analyses

Follow-up time is presented as median (interquartile range). Rate of atrial fibrillation incidence was calculated as the ratio of AF occurrence to the person-years of follow-up. Continuous variables are presented as mean and standard deviation. Categorical variables are presented as frequency (percentage). Baseline associations between categorical variables were compared using chi-square tests. A one-way analysis of variance was used to evaluate differences between fitness categories and continuous variables. Age and BMI were used as covariates in the analyses for resting heart rate, systolic blood pressure, diastolic blood pressure, hyperlipidemia, diabetes, and exercise capacity. Cox proportional haz-

ards regression models were used to evaluate the association between the development of AF and peak METs (continuous variable) and between the development of AF and fitness categories. Hazard ratios (HRs) were calculated along with 95% CIs. The least fit category was the reference group for all Cox proportional hazards regression models. We adjusted analyses for age, resting blood pressure, BMI, ethnicity, sex, risk factors (hypertension, type 2 diabetes, dyslipidemia, and smoking status), and alcohol/drug abuse present at the time of the exercise test. An interaction between BMI and CRF was tested in the fully adjusted Cox Regression model. The proportionality assumption was met for each model using the Schoenfeld residuals test. All hypotheses were 2-sided, and p values < 0.05 were considered statistically significant. All statistical analyses were performed using SPSS software version 25.0.

3. Results

Follow-up time ranged from 0.5 to 31 years (median 10.7 years; 5.6 and 14.9 years for the 25th and 75th percentiles, respectively), comprising a total of 178,352 person-years. A total of 2,155 subjects (13.1%) developed AF during the follow-up. Demographic and clinical characteristics for the four BMI categories are presented in Table 1. The prevalence of comorbidities was generally higher with greater body mass, and CRF was higher in normal weight subjects vs. subjects with obesity and severe obesity.

Compared to normal weight subjects (reference group), subject with obesity and severe obesity had 13% (95%CI: 0.99–1.28) and 32% (95%CI: 1.13–1.55) higher risks for incidence of AF (Fig. 2). Fig. 3 shows AF risk for CRF groups within each BMI category comparing to least fit individuals. A graded and inverse association between CRF and incidence of AF was observed across all BMI categories. Patients in the normal BMI and highly fit group had an incidence of 9.6/1000 years of follow up; for the obese and least fit, there was an incidence of 16.9/1000 years of follow up. The gradient for reduced AF risk with higher CRF was similar for each BMI category. For normal weight and overweight subjects in the highest CRF category, AF risk was approximately 50% lower compared to the least-fit subjects in their respective BMI categories. For severely obese but highly-fit subjects, the risk was approximately 40% (95%CI: 0.38–0.89) lower compared to the least fit subjects.

Table 1
Demographic and Clinical Characteristics of the Sample Based on BMI Categories.

BMI Categories (kg*m ⁻²)	Entire Cohort (n = 16,397)	<25.0 (n = 3,694)	25.0–29.9 (n = 6,862)	30.0–34.9 (n = 3,943)	≥35.0 (n = 1,898)	P value*
Age (years)	58.7 ± 11.16	59.7 ± 11.2	58.15 ± 10.9	59.13 ± 11.2	57.90 ± 11.3	<0.001
Sex						<0.001
Male	15,695 (95.7)	3523 (95.3)	6640 (96.8)	3764 (95.5)	1768 (93.2)	
Female	697 (4.3)	172 (4.7)	217 (3.2)	170 (4.5)	129 (6.8)	
Ethnicity						
White	3287 (20.1)	723 (19.6)	1416 (20.7)	781 (19.9)	367 (19.3)	<0.001
Black	11,216 (68.4)	2411 (65.3)	4614 (67.3)	2807 (71.2)	1384 (73.0)	
Hispanic	1889 (11.5)	561 (15.2)	827 (12.1)	355 (9.0)	146 (7.7)	
Resting heart rate (bpm)	73.6 ± 12.7	76.0 ± 13.1	73.9 ± 12.4	72.08 ± 12.3	72.42 ± 12.6	<0.001
Resting systolic BP (mmHg)	130.6 ± 19.7	130.6 ± 21.6	133.4 ± 19.8	129.0 ± 19.0	130.05 ± 18.5	<0.001
Resting Diastolic BP (mmHg)	80.0 ± 11.3	80.5 ± 11.9	79.6 ± 11.3	79.3 ± 10.9	80.9 ± 10.9	<0.001
Peak heart rate (bpm)	142.7 ± 24.8	129.6 ± 27.9	141.56 ± 22.9	144.9 ± 24.5	150.6 ± 20.6	<0.001
Peak Systolic BP (mmHg)	181.2 ± 36.5	173.0 ± 32.8	182.3 ± 53.0	181.9 ± 26.0	185.1 ± 24.3	<0.001
Peak Diastolic BP (mmHg)	86.0 ± 16.4	86.2 ± 15.2	86.7 ± 17.0	85.6 ± 19.6	85.5 ± 13.4	0.006
Exercise Capacity (METs)	7.6 ± 2.3	7.9 ± 3.3	7.8 ± 3.1	7.4 ± 2.6	6.7 ± 2.3	<0.001
Incidence of AF**	2155 (13.1)	463 (12.5)	917 (13.4)	500 (12.7)	275 (14.5)	<0.001
Hypertension	7840(47.8)	1355(36.7)	3110(45.3)	2221(56.3)	1154 (60.8)	<0.001
Diabetes	4348 (26.5)	510 (13.8)	1697 (24.7)	1330 (33.7)	811 (42.7)	<0.001
Smoking	8227 (50.2)	1997 (54.0)	3418 (49.8)	1945 (49.3)	867 (45.7)	<0.001
Dyslipidemia	6075 (37.0)	1128 (30.5)	2549 (37.1)	1647 (41.7)	751 (39.5)	<0.001
Chronic kidney disease	494 (3.0)	96 (2.6)	218 (3.2)	132 (3.3)	48 (2.5)	<0.001
Alcohol or drug abuse	977 (6.0)	237 (6.4)	403 (5.9)	251 (6.4)	86 (4.5)	<0.001

Values express in n(%), or mean ± standard deviation. BPM, Beats per minute; Blood Pressure BP; Metabolic equivalents (METs).

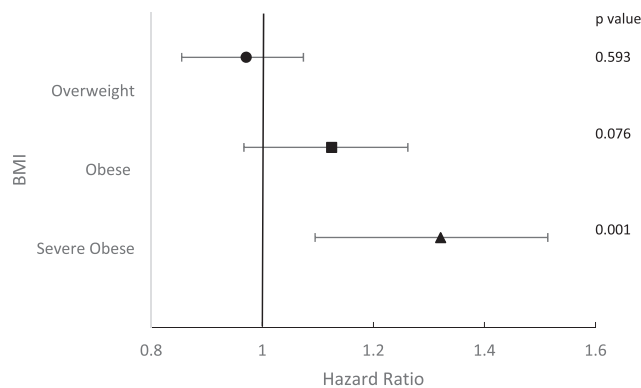


Fig. 2. Hazard ratios for incidence of atrial Fibrillation by obesity status with 95% confidence intervals. Normal BMI is the reference group. BMI: Body Mass Index; Normal : 18.5–24. 9 kg/m²; Overweight: 25–29.9 kg/m²; Obese: 30–34.5 kg/m²; Severe Obese: ≥35 kg/m².

Further subgroup analysis including smokers vs. non-smokers and diabetics vs. non-diabetics yielded similar results. Overall, there was a 6% reduction in AF risk per MET achieved.

Fig. 4 shows incidence of AF between fit and unfit groups within each BMI category, dichotomized by high and low exercise capacity in which unfit subjects were defined as ≤ 6.6 METs and fit subjects were defined as > 6.6 METs. Normal weight, fit individuals comprised the reference group. While risk of AF increased with higher BMI, there was a marked impact of CRF. Unfit individuals had markedly higher rates of AF during the follow-up period versus fit individuals regardless of weight category. Severely obese, unfit subjects had more than twice the risk of AF compared to normal weight, fit subjects. Notably, unfit normal weight subjects had a risk of AF that was similar to severely obese subjects who were fit.

4. Discussion

The current findings support two main concepts. First, they demonstrate that body mass is inversely related to AF incidence; AF risk was approximately 30% higher among subjects with severe

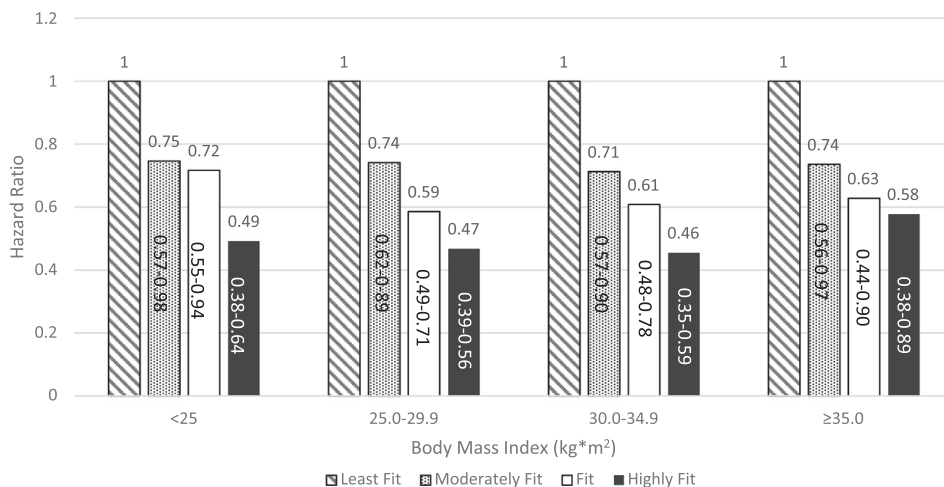


Fig. 3. Risk of atrial fibrillation (HR and 95% CI) within each BMI category according to quartiles of cardiorespiratory fitness, with the least fit group as the referent. *P* < 0.001 for each CRF category within all BMI categories. Numbers within each bar indicate 95% confidence intervals.

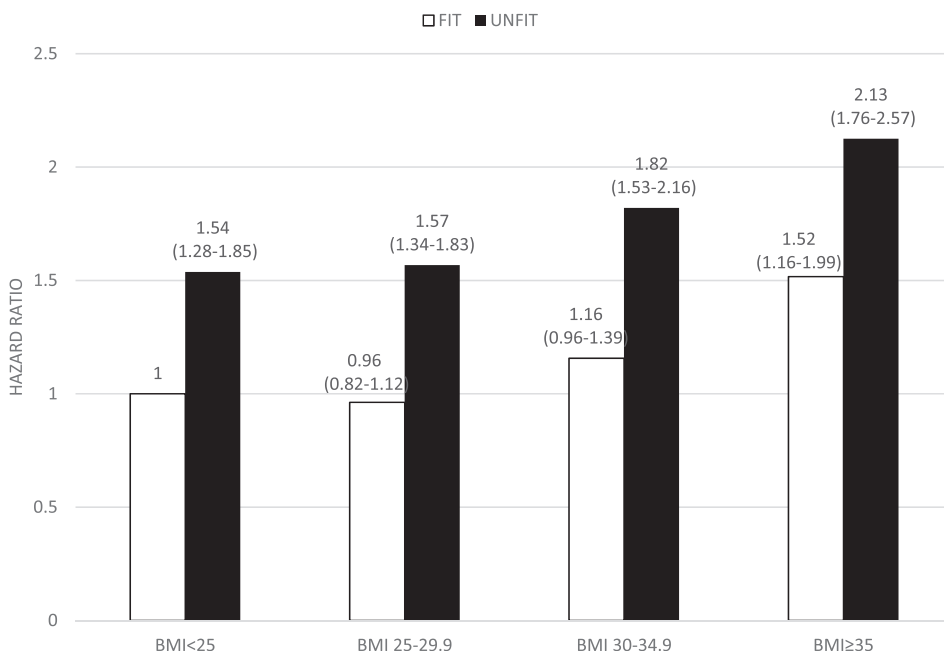


Fig. 4. Risk of atrial fibrillation (hazard ratio and 95% confidence intervals) for fit and unfit subjects within each BMI category using normal weight (kg/m²). Fit and normal BMI subjects as the referent group. *P* < 0.001.

obesity vs. normal weight subjects. Second, CRF was inversely associated with incidence of AF throughout the spectrum of body mass. AF risk declined progressively with higher CRF within each BMI category (Figs. 3 and 4). The impact of CRF was also evident when AF risk was assessed considering the BMI-CRF interaction. For this analysis we stratified the cohort into binary Fit and Unfit categories and used normal weight, Fit individuals as the referent (Fig. 4). For fit individuals, we observed a significant increase (52%) in AF risk only in those with BMI ≥ 35 kg/m² while a non-significant increase (16%) was observed among fit individuals with a BMI 30–34.9 kg/m². However, AF risk among Unfit individuals was 57% higher in overweight subjects, 82% higher among obese subjects and > 2-fold higher among severely obese subjects. These findings strongly suggest that the deleterious impact of increased body mass on AF risk is reduced by higher CRF.

Findings on the association between physical activity patterns and AF incidence have been conflicting. Some studies have

reported that the overall risk of AF is higher in current and former athletes or those involved in high intensity training compared to non-athletes [8,20,21]. However, in a meta-analysis comparing 1,550 athletes and non-athletes, Abdulla et al. observed that AF was lower with advancing age among athletes when compared to non-athletes [20]. Mozaffarian et al reported that light to moderate physical activity was associated with a lower risk of AF in older adults [22]. In a large follow-up study from the Women’s Health Initiative (WHI), there was an inverse association between current physical activity patterns and incidence of AF. In addition, they observed that higher physical activity patterns mediated some of the AF risk associated with obesity, reporting that increased physical activity could be a benefit in those who are obese [23]. In terms of CRF, Faselis et al. observed that higher CRF was inversely and independently associated with reduced AF incidence; in fact, even modest increases in exercise capacity were associated with marked reductions in risk [2]. Similar to our find-

ings, the Henry Ford Exercise Testing Study reported a strong inverse association between CRF and incident AF, particularly among obese subjects [24]. They observed that for each higher MET, a 7% decrease in risk for developing AF occurred [24], similar to the 6% decrease in risk of AF with each higher MET in the current study. The current results expand on these observations not only by the strong inverse gradient between CRF and AF incidence, but also by the fact that higher CRF moderated the higher incidence of AF with higher body mass. We observed that although the largest risk of AF was observed in subjects with severe obesity (Figures 2 and 5), there were roughly 50% declines in risk among highly-fit subjects in the overweight and obese groups compared to the least-fit subjects (Fig. 3).

Studies such as the Atherosclerosis Risk in Communities (ARIC) study [25] and the Women's Health Study [26] reported that with as little as a $1 \text{ kg} \cdot \text{m}^{-2}$ increase in BMI, there were 17% and 12% higher risks of AF, respectively. In a meta-analysis of 51 studies and > 600,000 participants, every $5 \text{ kg} \cdot \text{m}^{-2}$ increase in BMI was associated with a 30% higher risk for developing AF [11]. Measures of body mass other than BMI have also been suggested to increase the incidence of AF; for example, a higher proportion of body fat measured using bioelectrical impedance markedly increased the incidence of AF in a 13 year follow-up among Danish men and women [27]. In addition, using data from the Framingham Heart Study, Wang et al (2004) observed that the risk of AF was 52% higher among obese subjects compared to normal weight subjects [28]. However, when echocardiographic adjustments were made for left atrial diameter and clinical risk factors in obese individuals, BMI was no longer associated with risk of AF [28]. Conversely, recent observations suggest that lean body mass might be also be an indicator for increased risk of AF. These studies used different methods of anthropometric measures and observed that obesity might be partially mediated by the effects of lean body mass [23,29].

Several mechanisms may combine to explain the association between body mass and AF risk. Physiologically, obesity has been shown to impact left atrial remodeling in such a way as to produce conditions that underlie AF [30]. Remodeling appears to be most pronounced in severely obese patients, but may occur to a lesser extent in those with mild to moderate obesity [30,31]. In individuals with obesity, pericardial fat volume increases and epicardial fat thickness are associated with AF. An increase in epicardial fat leads to electrical and sympathovagal imbalances in the atria [13]. Modulation of the autonomic nervous system may serve as a trigger for the development of AF and contribute to its severity. Additionally, in individuals with obesity, there is an increase in inflammation of adipocytes, and inflammation plays a prominent role in the development of AF [32].

Both higher CRF and reduced BMI are associated with more favorable cardiometabolic risk profiles, which may contribute to reducing AF risk [33]. Higher CRF and weight loss have been shown to have favorable changes in cardiac structure and function [30,31]. While studies have evaluated these matters separately, there are no studies to our knowledge that have assessed the interaction between CRF, BMI, and the development of AF. While we do not have data on adulthood physical activity patterns in our cohort, the current results rebut the concept that fitter individuals (and by extension, more active individuals) have a higher incidence of AF. Our results provide further evidence that developing CRF through regular physical activity is associated with better health outcomes; in the current case, a potential lessening of the burden of AF.

4.1. Strengths

This study has several strengths. The database was relatively large, with over 16,000 individuals without evidence of existing

AF at baseline. In addition, CRF was determined objectively with a maximal exercise test. Incidence of AF was established over an approximate 30-year follow-up period (median 10.7 years). Access to the longitudinal data allowed us to adjust for important covariates including medications and CVD risk factors. The Veterans Health Administration offers equal access to care regardless of a patient's financial status, minimizing the effects of economic disparities. Finally, the computerized patient record system available in the VA health care system helped to reduce the likelihood of reverse causality².

4.2. Limitations

This study also has several limitations. CRF was measured only at baseline and we did not have information regarding changes in CRF or physical activity patterns of the participants during the follow-up. Further, the study included mostly men, and because all participants in the cohort were referred for an exercise test for a clinical reason, a bias could exist that would limit the generalizability of the findings. Therefore, our results may not necessarily apply to females or healthier populations. Although BMI is a strong prognosticator for clinical outcomes, it is limited in that it does not take into consideration body composition, including fat mass, fat free mass, lean mass, and skeletal muscle mass, and their distribution [34]. We did not have information on alcohol intake, which can contribute to the incidence of AF. Additionally, were unable to control for inflammation, which plays a prominent role in the development of AF. Treatment of AF has evolved over the period of observation, and this may have impacted the incidence of AF. Finally, some AF cases could have been missed if participants did not seek medical care; thus, it is possible that the incidence of AF may have been underreported.

4.3. Summary

The present findings suggest that the risk of developing AF is reduced by higher CRF levels in patients who are overweight or obese. In addition, these findings support the concept that risk of AF associated with body weight is masked if fitness status of the individuals is not considered [35]. Health professionals should consider fitness and BMI levels when assessing those who are at risk for development of AF and advise patients accordingly.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcha.2020.100663>.

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