Association of Physical Fitness With the Risk of Atrial Fibrillation: A Systematic Review and Meta-Analysis

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ABSTRACT

Several studies have investigated the role of physical fitness in atrial fibrillation (AF), but the results remain controversial. We aimed to estimate the association between physical fitness and risk of AF. We comprehensively retrieved data from the Cochrane Library, PubMed, and Embase databases until February 29, 2016, for studies evaluating the association of physical fitness with the risk of AF. Data were abstracted from included studies, and effect estimates were pooled using a random-effects model. Six studies with a total of 205 094 participants and 15 919 AF cases fulfilled the inclusion criteria. When physical fitness was assessed as a continuous variable, per incremental increase of physical fitness was associated with a 9% reduced risk of AF (risk ratio [RR]: 0.91, 95% confidence interval [CI]: 0.84-1.00, $P = 0.05$). When physical fitness was assessed as a categorical variable, the risk of AF was significantly reduced (RR: 0.51, 95% CI: 0.28-0.91, $P = 0.02$) in individuals with the highest level of physical fitness compared with those with the lowest level. The intermediate vs the lowest level of physical fitness was associated with a 28% reduced risk of AF (RR: 0.72, 95% CI: 0.56-0.93, $P = 0.01$). The sensitivity analysis indicated that these results were stable. Notably, there was evidence of statistical heterogeneity across studies; therefore, we should interpret the results cautiously. In conclusion, published literature supports that a higher level of physical fitness is associated with a lower risk of AF. Further studies should be performed to confirm these findings.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting approximately 33.5 million individuals worldwide.¹ Atrial fibrillation could increase the risk of morbidity and mortality, as well as clinical and public health expenses. Thus, the management and prevention of AF are vitally important and mainly include anticoagulation therapy, rhythm control, and rate control. In addition, comprehensive risk-factor modification, such as the management of modifiable cardiac risk factors, obstructive sleep apnea, obesity, and exercise, may also help prevent and treat

AF.²⁻⁴ The 2008 Physical Activity Guidelines Advisory Committee Report recommends 150 min/wk of moderate-intensity aerobic exercise or 75 min/wk of vigorous-intensity aerobic exercise for the general population.⁵ Guidelines from the American College of Cardiology and American Heart Association also include specific recommendations for diverse populations of cardiac patients, such as those with congenital heart disease, heart failure (HF), acute coronary syndrome, and stable ischemic heart disease.⁶⁻¹⁰ However, the effect of exercise on the risk of AF is still unclear.

To explore this effect, both physical activity and fitness should be examined, because they have different definitions¹¹ and may be different physiological markers of cardiovascular diseases.¹² Although several previous meta-analyses have indicated the inconsistent effects of physical activity on AF among different populations¹³⁻¹⁵ and have demonstrated an inverse association of physical fitness with all-cause mortality, coronary heart disease, and HF,^{16,17} little is known regarding the link between physical fitness and AF risk. Recently, epidemiological studies have explored the association between physical fitness and the risk of AF; however, they yielded conflicting findings. Specifically, higher exercise capacity estimated by

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the ergometer bicycle test seems to be associated with an increased risk of AF.¹⁸ In contrast, 5 previous studies have reported an inverse association between physical fitness and the risk of AF,^{19–23} and 2 of the 5 showed no statistically significant association.^{21,22} To date, the corresponding quantitative association has not been established; therefore, we conducted a meta-analysis to estimate the role of physical fitness on the risk of AF.

Methods

Inclusion and Exclusion Criteria

We included studies that (1) investigated the association of physical fitness with the risk of incident or recurrent AF, especially studies combining AF and atrial flutter as an outcome; (2) included population-based or hospital-based participants; (3) had a cohort study design; (4) used physical fitness as the exposure; (5) assessed physical fitness using an exercise tolerance test and expressed the maximal exercise capacity in units of metabolic equivalents (METs) or other measures; and (6) reported the risk ratios (RRs) and their corresponding 95% confidence intervals (CIs), or provided sufficient data to calculate them. Studies were excluded if (1) they reported individuals with postoperative AF; (2) the exposure of physical fitness was combined with another exposure; or (3) the studies were of certain publication types (eg, letters, case reports, and comments).

Literature-Search Strategy

We comprehensively reviewed the Cochrane Library, PubMed, and Embase databases through February 29, 2016, for relevant studies evaluating the association between physical fitness and the risk of AF. We did not apply any language restrictions. Two groups of keywords were combined; the first keywords were linked to the exposure (“physical fitness” or “oxygen consumption” or “cardiorespiratory fitness” or “exercise test” or “exercise tolerance” or “exercise”). The second keywords were linked to the outcome (“atrial fibrillation” or “atrial flutter” or “atrial tachycardia” or “supraventricular tachycardia” or “arrhythmia”). Further searches were performed using reference lists, relevant journals, and conference abstracts.

Data Abstraction and Quality Assessment

Two reviewers (WZ and YS) independently abstracted data from the eligible studies and conducted the quality assessment. Discrepancies were resolved through discussion or consultation with a third reviewer (KH). We abstracted the following data from each study: name of the first author, year of publication, country of origin, study design, participants (sample size, sex, and age), follow-up duration, method of physical-fitness assessment, ascertainment of AF, adjusted covariates, and the RR values with 95% CIs. When several RRs were presented in 1 study, such as unadjusted and adjusted RRs, we abstracted the most completely adjusted RR. To judge the quality of the included studies, we used the validated Newcastle-Ottawa Scale (NOS) items, involving the selection of cohorts, the comparability of cohorts, and the assessment of outcome.²⁴ We defined studies with a NOS of ≥ 6 stars as moderate- to high-quality studies and studies with a NOS of < 6 stars as low-quality studies.

Figure 1. Flow diagram of literature search and study selection for the meta-analysis.

Statistical Analysis

When physical fitness was assessed as a continuous variable, we performed a dose-response analysis to examine how much risk reduction could be predicted per incremental increase of physical fitness. When physical fitness was assessed as a categorical variable, we compared the corresponding RR values between these groups as follows: (1) the highest vs the lowest category, and (2) the intermediate vs the lowest category. This method was based on a previous meta-analysis evaluating the association between physical fitness and cancer mortality.²¹ We defined the intermediate category as the median of all categories. In addition, the sensitivity analysis was performed where appropriate.

The effect measures were transformed to their natural logarithm (log RR), and the standard error (SE) was calculated from the corresponding CI. Statistical heterogeneity was calculated by a consistency test using the Cochrane Q test complemented with the I^2 statistic.²⁵ In this meta-analysis, given that the populations were variable across studies, we chose a random-effects model because it was better than the fixed-effects model for explaining between-study heterogeneity. All statistical analyses were performed using Review Manager version 5.3 software (the Nordic Cochrane Center, the Cochrane Collaboration, Copenhagen, Denmark). All tests were 2-sided, and statistical significance was defined as $P < 0.05$.

Results

Study Selection

We initially identified 9633 studies through electronic searches (Figure 1). We found no additional studies via

searching reference lists, relevant journals, and conference abstracts. After we screened the titles and abstracts, 1261 relevant studies remained. Then we screened the full text and excluded 1248 studies for not directly involving physical fitness and AF. The 13 remaining studies were reviewed in more detail, and we further excluded 7 studies with due to type of publication (1 letter, 1 review, and 5 comments). Finally, 6 studies^{18–23} comprising 205 094 participants and 15 919 AF cases were included in the meta-analysis (1 post-hoc analysis of a randomized controlled trial,²² 4 prospective cohort studies,^{18–23} and 1 retrospective cohort study²⁰).

Maximal exercise capacity was expressed in METs^{19–23} or watts (Table 1).¹⁸ Two studies assessed physical fitness using the cycle ergometer, both of which carried out a maximal exercise test.^{18,21} Two studies assessed physical fitness using a maximal treadmill exercise test according to the standard Bruce protocol.^{19,20} In the study of Alonso et al.,²² a graded exercise treadmill test was applied, including a maximal test administered at the baseline and a submaximal test administered at years 1 and 4. In addition, the details of the exercise tolerance test were unclear in 1 study.²³ All studies had a quality score ≥ 6 stars (Table 1).

Meta-Analyses

When physical fitness was assessed as a continuous variable, the analysis comprised a total of 5 risk estimates. According to the dose-response analysis, per incremental increase of physical fitness was associated with a 9% reduction in the risk of AF (RR: 0.91, 95% CI: 0.84–1.00, $P = 0.05$; Figure 2). When physical fitness was assessed as a categorical variable, the analysis comprised a total of 6 risk estimates. There were 4 physical fitness categories in 3 studies^{20,21,23}; therefore, we used the pooled RRs of the second and third categories as the intermediate category. As shown in Figure 3, the risk of AF was significantly reduced (RR: 0.51, 95% CI: 0.28–0.91, $P = 0.02$) in individuals with the highest level of physical fitness compared with those with the lowest level. The intermediate vs the lowest level of physical fitness was associated with a 28% reduced risk of AF (RR: 0.72, 95% CI: 0.56–0.93, $P = 0.01$). The sensitivity analysis indicated that these results were stable after we removed the included RR values one at a time. Notably, there was evidence of statistical heterogeneity across studies; therefore, the results should be interpreted cautiously.

Specifically, Pathak et al.¹⁹ divided obese individuals with symptomatic AF into low ($n = 95$), adequate ($n = 134$), and high ($n = 79$) cardiorespiratory fitness groups based on their baseline exercise performance. At an average of a 4-year follow-up, the rate of AF recurrence was 88%, 65%, and 34% in the low, adequate, and high fitness groups, respectively. Each increase in METs of baseline cardiorespiratory fitness was associated with a 13% reduced risk of AF recurrence (RR: 0.87, 95% CI: 0.80–0.94, $P < 0.001$). Therefore, baseline fitness could predict the risk of AF recurrence. In addition, increasing fitness via the study intervention was also associated with a reduced risk of AF recurrence. For every increase in METs, there was a 9% reduction in the risk of

AF recurrence (RR: 0.90, 95% CI: 0.83–1.00, $P = 0.036$). The rate of AF recurrence was 82% in the < 2 METs gain group but only 39% in the > 2 METs gain group.

Discussion

To the best of our knowledge, our meta-analysis is the first to quantify the association between physical fitness and the risk of AF. According to the dose-response analysis, per incremental increase of physical fitness was associated with a 9% reduced risk of AF. In the categorical analysis, when compared with the low level of physical fitness, both the intermediate and higher levels of physical fitness were associated with a lower risk of AF. The sensitivity analysis indicated that these results were stable. Specifically, a higher level of physical fitness was also associated with lower risk of AF recurrence.

Previously, several meta-analytic studies have quantified the association between physical activity and the risk of AF.^{13–15} Long-term vigorous physical training is associated with an increased risk of AF in athletes,^{13,15} but this association does not exist in nonathletes.^{13,14} Interestingly, there is a sex difference in the aforementioned association; in brief, an increased level of physical activity is most likely associated with an increased risk of AF in men and a reduction of AF incidence in women.²⁶ These inconsistent results may be due to the imprecision of physical activity assessment via self-reported rather than direct measurement. Although physical-activity habits are considered the main determinant of physical fitness,²⁷ we should not equate physical fitness with habitual physical activity. Physical activity and fitness may be different physiological markers of cardiovascular diseases,¹² and physical fitness can be readily assessed by an exercise tolerance test. Higher level of physical fitness have been previously shown to reduce the risk of all-cause mortality, coronary heart disease, and HF,^{16,17} and our current meta-analysis also indicated an inverse association between physical fitness and the risk of AF.

Because AF has multiple cardiovascular and noncardiovascular risk factors, the reduction in the risk of AF at a higher level of physical fitness may be partly mediated through the improvement of preexisting risk factors. A previous study showed that higher physical fitness is associated with a lower level of inflammatory markers (eg, C-reactive protein).^{28,29} Thus, it is likely that the reduction in the risk of AF at a higher level of physical fitness is partly mediated through reducing the incidence of inflammation. Overweight and obesity are also the important risk factors for AF^{30,31} and may induce AF by increasing left atrial size and volume.^{32,33} Whether the inverse association between physical fitness and AF is mediated through the regulation of body mass index (BMI, a measure of obesity) is not well established. In a cohort of healthy middle-age men, a BMI > 28 kg/m² and weight gain > 10 kg were associated with an increased risk of incident AF, but increasing fitness via the study intervention could attenuate this association.³⁴ In the Henry Ford Exercise Testing (FIT) Project,²⁰ there was an inverse association between cardiorespiratory fitness and the risk of AF, and the magnitude of this association was greater in obese individuals than

Table 1. Basic Characteristics of Studies Included in the Meta-Analysis

Study, by First Author and Year	Region	Design	Sex, Age	Participants (Sample Size, n)	New-Onset or Recurrent AF (n)	Follow-up Duration	Categorization of Physical Fitness	Method for Physical Fitness Assessment	Ascertainment of AF	Adjusted Covariates	NOS Items
Andersen 2015 ¹⁸	Sweden	Prospective cohort	Males, median 18.2 years	Population-based (1126 899)	New-onset (9668)	Median 23.6 years	5 fitness categories (measured in watts): first, second, third, fourth, and fifth	Ergometer	AF hospitalization: ICD-10 (I48.9), ICD-9 (427D), ICD-8 (427.92)	Age, conception date, region, education level, height, muscle strength, SBP and DBP, weight, and ischemic heart disease	8 stars
Pathak 2015 ¹⁹	Australia	Prospective cohort	Both, mean 60 years	Hospital-based (308)	Recurrent (198)	Mean 2.0 years	3 fitness categories (baseline): low (<85%), adequate (86% to 100%), and high (>100%)	Treadmill	ECG, Holter monitoring, and clinical review	Weight loss, baseline cardiorespiratory fitness	8 stars
Qureshi 2015 ²⁰	United States	Retrospective cohort	Both, mean 54.5 years	Hospital-based (64 561)	New-onset (4616)	Median 5.4 years	4 fitness categories: <6 METs, 6 to 9 METs, 10 to 11 METs, and >11 METs	Treadmill	AF hospitalization: ICD-9 427.31	Age, sex, race, history of HTN, DM, sedentary habits, obesity, family history of CHD, smoking, hyperlipidemia, hypertensive response, chronotropic incompetence, thyroid medications, digoxin, treated lung disease, β -blocker use, ACEI use, ARB use, CCB use, and all lipid-lowering medications including statins	8 stars
Khan 2015 ²¹	Finland	Prospective cohort	Males, mean 52.6 years	Population-based (1950)	New-onset (305)	Mean 19.5 years	4 fitness categories: 20.3, 27.7, 32.6, and 40.6 mL/kg/min	Ergometer	Hospital discharge diagnoses, inpatient physician claims data, and study ECG	Age, SBP, BMI, history of CVD, history of DM, and resting heart rate, smoking status, HTN, fasting glucose, and LDL-C	9 stars

Table 1. Continued

Study, by First Author and Year	Region	Design	Sex, Age	Participants (Sample Size, n)	New-Onset or Recurrent AF (n)	Follow-up Duration	Categorization of Physical Fitness	Method for Physical Fitness Assessment	Ascertainment of AF	Adjusted Covariates	NOS Items
Alonso 2015 ²²	United States	Post-hoc analysis of RCT	Both, 45–76 years	Hospital-based (5067)	New-onset (294)	Mean 9 years	5 fitness categories (% improved fitness): –52.9 to –6.9, –6.8 to 0.0, 0.1 to 13.5, 13.6 to 31.7, and 31.8 to 185.7	Treadmill	ECG and hospitalization discharge diagnosis: ICD-9 427.31/9 427.32	Clinic, age, sex, race, intervention group, education, family income, smoking, BMI, height, SBP, DBP, use of antihypertensive medication, HbA _{1c} , prevalent CHD, and prevalent HF	8 stars
Pittaras 2015 ²³	United States	Prospective cohort	Unclear	Population-based (6309)	New-onset (838)	Median 8.0 years	4 fitness categories: least fit (4.9 ± 1.13 METs), low fit (6.7 ± 1.0 METs), moderate fit (7.9 ± 1.0 METs), and high fit (9.3 ± 1.2 METs)	Unclear	Unclear	Unclear ^a	7 stars

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CHD, coronary heart disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; ECG, electrocardiogram; HbA_{1c}, glycated hemoglobin; HF, heart failure; HTN, hypertension; ICD, *International Classification of Diseases*; LDL-C, low-density lipoprotein cholesterol; METs, metabolic equivalents of oxygen consumption; NOS, Newcastle-Ottawa Scale; PAD, peripheral arterial disease; RCT, randomized controlled trial; SBP, systolic blood pressure.

^aMultivariable Cox models were performed, but the adjustments could not be reached.

Figure 2. Meta-analysis of the risk of AF per incremental increase of physical fitness. Abbreviations: AF, atrial fibrillation; CI, confidence interval; df, degrees of freedom; IV, inverse of the variance; SE, standard error.

Figure 3. Meta-analysis of the risk of AF for individuals with the highest vs the lowest physical fitness or the intermediate vs the lowest physical fitness. Abbreviations: AF, atrial fibrillation; CI, confidence interval; df, degrees of freedom; IV, inverse of the variance; SE, standard error.

in nonobese individuals. However, Khan and colleagues²¹ indicated that BMI did not play an important role in determining the association between cardiorespiratory fitness and the risk of AF. Overall, to examine the effect modification of the association between physical fitness and AF, further meta-analysis should be conducted by strata of BMI and other possible confounders of AF, such as smoking, diabetes mellitus, and cardiovascular disease status at baseline.

Recently, clinicians have recommended their patients perform moderate-intensity exercise training for significant cardiovascular improvements.^{35,36} Although the etiologies of AF are not fully understood, multiple modifiable and nonmodifiable risk factors for AF have been discovered. There is growing evidence that potential lifestyle modifications, such as the management of exercise, may help prevent and treat AF.⁴ The Aggressive Risk Factor Reduction Study for Atrial Fibrillation and Implications for the Outcome of Ablation (ARREST-AF) cohort study demonstrated that aggressive risk-factor modifications, mainly including the management of blood pressure and glycemic control, weight management, and obstructive sleep apnea, could improve the long-term success of AF ablation.³⁷

Regular exercise for ≥ 20 min/d in conjunction with other lifestyle modifications could reduce the risk of AF by 50%.³ However, no study has evaluated the effects of physical-fitness improvement, in conjunction with other risk modifications, on the prevention and treatment of AF. From a clinical viewpoint, the observations of our study may be valuable, because the predictive ability of AF risk could be improved when we comprehensively combined physical fitness with other risk-factor modifications.

Notably, physical activity has a U-shaped relationship with the risk of AF in both athletes and nonathletes,^{38–40} and a nonlinear relationship is observed between physical fitness and the risk of AF.²¹ Andersen and co-workers¹⁸ investigated 1.1 million Swedish young men at a median follow-up of 26.3 years and found that exercise capacity had a U-shaped relationship with the risk of arrhythmia, driven by a direct association with risk of AF. Importantly, this study examined the association between exercise capacity and risk of arrhythmia in the young participants, which would minimize the risk of reverse causation caused by preexisting cardiac diseases. Therefore, it would not be surprising if there were adverse effects of physical fitness on AF in people with sustained exercise training. Before

the upper limit of benefit is well established, we should not overinterpret the results and intensify the exercise prescription for our patients.

Study Limitations

Our study has several potential limitations. First, the populations were variable across studies, and the pooled RRs would be expected to represent a weighted average of association between physical fitness and the risk of AF. Although the random-effects model could explain between-study heterogeneity to a certain degree, we should interpret the results carefully and further confirm the causal association. Second, the physical-fitness categories were variable across studies, and we may have misclassified them in our analysis. Third, although most studies additionally adjusted for potential risk factors of AF, it was possible that some unknown or residual confounding was not fully ruled out. Fourth, the methods of AF ascertainment were highly variable, and we did not differentiate the subtypes of AF. Additionally, a number of individuals with undiagnosed AF as well as those with asymptomatic paroxysmal AF may be missed. Finally, we did not determine the magnitude of the association between physical fitness and AF modulated by age, sex, ethnicity, study type, or other study characteristics.

Conclusion

Overall, a higher level of physical fitness was associated with a lower risk of AF. We suggest that physical fitness could be useful for predicting the risk of AF. Further study should confirm the causal association between physical fitness and the risk of AF.

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