Regular Physical Activity and Risk of Atrial Fibrillation
A Systematic Review and Meta-analysis

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Background—Although previous studies have suggested that competitive athletes have a higher risk of atrial fibrillation than the general population, limited and inconsistent data are available on the association between regular physical activity and the risk of atrial fibrillation.

Methods and Results—A systematic, comprehensive literature search was performed using MEDLINE, EMBASE, and COCHRANE until 2011. Extracted data from the eligible studies were meta-analyzed using fixed effects model. Four studies, which included 95,526 subjects, were eligible for meta-analysis. For all of the studies included, the extreme groups (ie, maximum versus minimal amount of physical activity) were used for the current analyses. The total number of participants belonging to the extreme groups was 43,672. The pooled odds ratio (95% confidence interval) for atrial fibrillation among regular exercisers was 1.08 (0.97–1.21).

Conclusions—Our data do not support a statistically significant association between regular physical activity and increased incidence of atrial fibrillation. (Circ Arrhythm Electrophysiol. 2013;6:252-256.)

Key Words: atrial fibrillation ■ epidemiology ■ physical exercise ■ risk factors

Atrial fibrillation (AF) is a very common medical problem with estimated prevalence in the general population of 0.4% to 1.0%.1 AF prevalence increases with advancing age.2 It is associated with increased morbidity and mortality.3,4 Major risk factors for AF in addition to age include hypertension, structural heart disease, diabetes mellitus, and thyroid disease.5 Several studies have reported higher rates of AF among athletes.5-10 A meta-analysis11 showed a higher incidence rate of AF in athletes compared with the general population (pooled odds ratio [OR; 95% confidence interval], 5.29 [3.57–7.85]). At the same time, only limited and inconsistent data are available on a potential association between regular physical activity (PA) and the risk of AF in the general population. Although some studies (both traditional case-control6,10 and prospective cohort12) reported an increased risk of AF with regular PA, others studies found no association13,14 or nonstatistically significant lower risk of AF.15 To test the hypothesis that regular PA does not increase the risk of AF, we conducted a systematic review and meta-analysis.

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Methods

Search Strategy
Two authors (P.O., O.K.) independently conducted search of large electronic databases. The following databases were searched: MEDLINE (from 1948 to November 31, 2011), EMBASE from 1988 to 2011, week 48), COCHRANE (from inception until the third quarter of 2011) for all available studies reporting cases of AF based on the amount of exercise. The search was without language limitation. The following keywords were used: atrial fibrillation, exercise, athlete, and sports. We used advanced search engines to ensure that in each article at least 2 of the keywords are present: atrial fibrillation and either exercise, athlete or sports. References of the retrieved articles and the review articles were also screened for eligible studies.

Study Eligibility
Both prospective cohort studies and nested case–control studies examining the relation of regular PA and AF risk were eligible for inclusion. Studies on professional athletes, studies not reporting AF in controls, and traditional case–control studies, where it is difficult to establish temporality between exposure and outcome, were excluded. Two authors (P.O. and O.K.) graded the quality of the selected studies using the criteria developed by the United States Preventive Services Task Force16 as good, fair, or poor.
### Table. Characteristics of the Included Studies

<table>
<thead>
<tr>
<th>Study first author, year</th>
<th>Total No. of Study Participants (% of Men)</th>
<th>No. of Study Participants Used in the Current Meta-analysis</th>
<th>Mean Age, y (SD)</th>
<th>Study Type</th>
<th>Exercise Ascertainment</th>
<th>Follow-up Duration, y</th>
<th>Atrial Fibrillation Ascertainment</th>
<th>Incident Atrial Fibrillation vs None</th>
<th>Variables Adjusted for</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frost et al (2004)*</td>
<td>38400 (55%)</td>
<td>20343 (4)</td>
<td>56 (4)</td>
<td>Prospective cohort</td>
<td>Work-related physical activity; (1) sedentary (predominantly sitting position)*; (2) sedentary (predominantly standing position); (3) light workload; and (4) heavy workload</td>
<td>Questionnaire</td>
<td>5.7 (mean)</td>
<td>Danish National Registry of Patients validated by manual reviews of the charts and ECGs</td>
<td>240/20343</td>
<td>Denmark</td>
</tr>
<tr>
<td>Mozaffarian et al (2008)*</td>
<td>5446 (42%)</td>
<td>982 (6)</td>
<td>73 (6)</td>
<td>Prospective cohort</td>
<td>(1) no leisure-type physical activity*; (2) leisure-time activity (low intensity); (3) leisure-time activity (medium intensity); and (4) leisure-time activity (high intensity)</td>
<td>Leisure-time activity and exercise: at baseline, and at the end of third and seventh annual visits using questionnaire. Walking habits: by self-report at baseline and annually</td>
<td>12 (mean)</td>
<td>Annual resting 12-lead ECG Hospital records discharge diagnosis for all hospitalizations</td>
<td>192/982</td>
<td>US</td>
</tr>
<tr>
<td>Aizer et al (2010)*</td>
<td>16921 (100%)</td>
<td>8448 (n/a)</td>
<td>51 (n/a)</td>
<td>Prospective cohort</td>
<td>(1) no exercise*; (2) exercise to break sweat &lt;1 d/wk; (3) exercise to break sweat 1–2 d/wk; (4) exercise to break sweat 3–4 d/wk; and (5) exercise to break sweat 5–7 d/wk</td>
<td>Questionnaires 3 and 9 y after enrollment</td>
<td>12 (mean)</td>
<td>Data not provided</td>
<td>Age, sex, race, enrollment site, education, smoking status, pack-year of smoking, coronary heart disease, chronic pulmonary disease, DM, alcohol use, and β-blocker use</td>
<td>US</td>
</tr>
<tr>
<td>Everett et al (2011)*</td>
<td>34759 (0%)</td>
<td>13899 (7)</td>
<td>54.6 (7)</td>
<td>Prospective cohort</td>
<td>Cumulative average physical activity: (1) &lt;2 METS-h/wk; (2) 2 to &lt;5.9 METS-h/wk; (3) 5.9 to &lt;12 METS-h/wk; (4) 12 to &lt;23 METS-h/wk; and (5) ≥23 METS-h/wk</td>
<td>Questionnaires at baseline, at 36, 72, and 96 mo, at the end of randomized portion of the study and at the end of the 2 y of the observational study</td>
<td>14.4 (median)</td>
<td>Questionnaire at the time of enrollment, at 48 mo and then annually thereafter Medical charts and ECG reviews of those who self-reported AF to confirm the diagnosis</td>
<td>411/13899</td>
<td>US</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; CVD, cardiovascular disease; CHF, congestive heart failure; DM, diabetes mellitus; ECG, electrocardiogram; h/o, history of; HTN, hypertension; LVH, left ventricular hypertrophy; MET, metabolic equivalent task; MI, myocardial infarction; No, number; SBP, systolic blood pressure; and y, years.

*Reference group.
Data Extraction
Demographic data and the number of patients with AF in regular exercisers and controls were extracted from each study. Two authors (P.O. and O.K.) performed the searching, study evaluation, and data extraction independently, and any disagreement was resolved by a senior author (L.D.)

Exposure Assessment
All of the studies used for the meta-analysis divided subjects into 4 or 5 groups on the basis of cumulative PA per week, amount and intensity of work-related PA, leisure-type PA, or amount of exercise per week. For all of the studies included, the extreme groups (ie, maximum versus minimal amount of PA) were used for the current analyses. The total number of participants belonging to the extreme groups was 43,672.

Exclusion criteria for each individual study used in the meta-analysis were not uniform. Some studies, such as the study of Frost et al, excluded subjects with ischemic heart disease, stroke, and diabetes at baseline, whereas others did not. Each study, however, excluded subjects with AF at baseline and complete information about PA or AF. All the studies adjusted for incident comorbidities during follow-up (Table).

Regular PA was defined differently at each study (Table). Aizer et al divided the patients into several groups on the basis of frequency of sweat-breaking exercise per week. The study of Everett et al used metabolic equivalent task for each PA performed and divided the patient into several groups on the basis of metabolic equivalent task range. The study of Frost et al evaluated the amount of PA performed at work and divided the patients into several groups. The study of Mozaffarian et al categorized patients into several groups on the basis of amount and intensity of leisure-time activity (walking).

Data Synthesis
The meta-analysis was performed by computing unadjusted OR using fixed-effects model. OR for new onset incident AF was calculated by comparing the most physically active groups to the least active groups along with the 95% confidence intervals. For studies that included men and women provided sex-specific relative risks, we treated relative risk for each sex as an independent study. Heterogeneity was tested using $I^2$ statistics. The $I^2$ (measured as 0%–100%) indicates the percentage of variation in the study results attributed to between-study heterogeneity rather than sampling error. All analyses were performed with RevMan Analyses Version 5.0.20 (Nordic Cochrane Center, Rikshospitalet 2008).

Results
Figure 1 illustrates our review and exclusion/inclusion process. Ultimately, 4 longitudinal prospective cohort studies with follow-up periods of 5.7, 14.4, 12, and 12 years, respectively, published in peer-review journals were eligible for meta-analysis (N=95,526). Of these, we used 43,672 subjects belonging to extreme exercise categories for current analysis. All of the selected studies were graded as good by the criteria developed by the United States Preventive Services Task Force. Studies and subject’s characteristics are reported in Table. Three of the studies were conducted in the United States and 1 in Europe.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[OR]</th>
<th>SE</th>
<th>Weight</th>
<th>IV, Fixed, 95% CI</th>
<th>IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aizer et al.</td>
<td>0.182</td>
<td>0.023</td>
<td>49.7%</td>
<td>1.20 [1.02, 1.41]</td>
<td></td>
</tr>
<tr>
<td>Everett et al.</td>
<td>0.011</td>
<td>0.011</td>
<td>27.8%</td>
<td>1.00 [0.80, 1.24]</td>
<td></td>
</tr>
<tr>
<td>Frost et al. (men)</td>
<td>0.086</td>
<td>0.21</td>
<td>7.8%</td>
<td>1.09 [0.72, 1.64]</td>
<td></td>
</tr>
<tr>
<td>Frost et al. (women)</td>
<td>0.14</td>
<td>0.594</td>
<td>1.0%</td>
<td>1.15 [0.36, 3.68]</td>
<td></td>
</tr>
<tr>
<td>Mozaffarian et al.</td>
<td>-0.139</td>
<td>0.158</td>
<td>13.7%</td>
<td>0.87 [0.64, 1.19]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>1.08 [0.97, 1.21]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 3.96, df = 4 (P = 0.41); P = 0%</td>
<td>Test for overall effect: Z = 1.36 (P = 0.17)</td>
<td></td>
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</tbody>
</table>

Using a fixed effects model, the pooled OR of AF comparing the most physically active versus the least physically active groups was 1.08 (95% confidence interval, 0.97–1.21; $P=0.17$; Figure 2). There was no evidence of heterogeneity between studies ($I^2=0%$).

In a sensitivity analysis excluding the non-US study (which was also the only study evaluating work-related PA), the pooled OR of AF comparing the most versus the least physically active groups was 1.05 (95% confidence interval, 0.88–1.26; $P=0.6$). In addition, pooling ORs of AF for men and women from the study of Frost et al into a single study did not change the results.

Discussion
Overall, we found that the regular PA is not associated with significantly higher risk of AF compared with sedentary lifestyle. To the best of our knowledge, this is the first meta-analysis to

Figure 1. Summary of search strategy results. AF indicates atrial fibrillation; and PA, physical activity.

Figure 2. Meta-analysis results. CI indicates confidence interval; and OR, odds ratio.
evaluate the relation between regular PA and AF among non-athletes. The results are important because they demonstrate that regular exercise, which has been long established to have beneficial effects on cardiovascular risks, at the same time does not seem to increase the risk of AF. PA guidelines recommend 150 minutes of moderate PA per week or 75 minutes of vigorous exercise per week. Many physiological mechanisms by which PA may influence AF risk have been suggested, albeit speculative for the most of them.

The potential mechanisms, by which PA may be associated with a higher risk of AF, are those that are thought to be responsible for a higher risk of AF among elite endurance athletes. They include altering the balance between sympathetic and parasympathetic nervous systems, which results in increased vagal tone (vagal AF, initially described in 1994 by Coumel), leading to shortening of the effective refractory period in the atria and increased effective refractory period dispersion, resulting in AF. The second potential mechanism is increase in the left atrial size leading to atrial fibrosis. Our data suggest that in nonathletes such mechanisms may not play a major role for the development of AF. Alternatively, PA in nonathletes might reduce weight, blood pressure, and incident diabetes mellitus, all of which are established risk factors for AF.

Strengths and Limitations
Our study has several limitations. Each of the studies used for the meta-analysis subcategorized the amount of PA differently. Even the type of PA differed across studies, with 3 studies comparing the amount of exercise, whereas 1 compared those the amount of PA at work. However, the study evaluating work-related PA also evaluated for the amount of exercise of the subjects, which was used in statistical analysis (see page 50 of reference 14). The study evaluating occupational activity was the only non-US study in our meta-analysis, which could have created confounding errors. There was also a difference in sample sizes. Because of a small number of studies included to the meta-analysis, we were limited in conducting subanalyses, such as stratification by sex or type of exercise. The ascertainment of AF differed from study to study (Table). In one of the studies, the participants were physicians, who were more likely to recognize AF. Incidence of the outcome may have been under-reported in all of the studies because of asymptomatic or undiagnosed AF. Despite these differences, there was little heterogeneity between studies (P of 0). Lastly, we were not able to examine the effect of cause-specific mortality on our findings because we did not have study-specific points for analysis.

Our systematic review has several strengths, including the novelty of examining regular PA in nonathletes. The studies include both men and women of a wide age range and from different geographic regions. We have large sample size, which improves the statistical power to detect smaller effects.

Conclusions
Overall, our data do not support a statistically significant association between regular PA and higher incidence of AF in nonathletes.

Disclosures
None.

References
CLINICAL PERSPECTIVE

Although previous studies have suggested that competitive athletes have a higher risk of atrial fibrillation (AF) than the general population, limited and inconsistent data are available on the association between regular physical activity and the risk of AF. To investigate whether regular physical activity is associated with an increased risk of AF, we analyzed data published between 1948 and 2011 and found that regular physical activity was not associated with increased risk of AF. These findings suggest that exercise recommendations from the Institute of Medicine should be followed for heart health benefits without concern about elevated risk of AF.
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