Regular Physical Activity and Risk of Atrial Fibrillation: A Systematic Review and Meta-Analysis.

Running title: Ofman et al.; Exercise and Atrial Fibrillation

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Journal Subject Codes: [5] arrhythmia, clinical electrophysiology, drugs; [8] epidemiology
Abstract:

Background - While 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 (PA) and the risk of AF.

Methods and Results - A systematic, comprehensive literature search 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 (i.e. maximum vs. minimal amount of PA) 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 AF among regular exercisers was 1.08 (0.97-1.21).

Conclusions - Our data do not support a statistically significant association between regular PA and increased incidence of AF.

Key words: atrial fibrillation, physical exercise, risk factors, epidemiology
Introduction

Atrial fibrillation (AF) is a very common medical problem with estimated prevalence in the general population of 0.4-1.0% \(^1\). 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 \(^3\). Several studies have reported higher rates of AF among athletes \(^5\)\textsuperscript{–}\(^10\). A meta-analysis \(^11\) showed a higher incidence rate of AF in athletes compared with the general population [pooled odds ratio (OR) (95% confidence interval (CI)), 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-control \(^6,10\) as well as prospective cohort \(^12\)) reported an increased risk of AF with regular PA, others studies found no association \(^13,14\) or non-statistically 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.

Methods

Search Strategy

Two authors (PO, OK) 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 in order to ensure that in each article at...
least the two 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, as well as traditional case-control studies, where it is difficult to establish temporality between exposure and outcome, were excluded. Two authors (PO and OK) graded the quality of the selected studies by using the criteria developed by the United States Preventive Services Task Force (USPSTF)16 as good, fair, or poor.

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-analysis12-15, divided subjects into four or five groups based on the cumulative PA per week13, amount and intensity of work-related PA14, leisure-type PA15 or amount of exercise per week12. For all of the studies included, the extreme groups (i.e. maximum vs. 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 papers, such as the paper of Frost at al14, excluded subjects with ischaemic heart disease, stroke and diabetes at baseline, while others (15) did not. Each study, however, excluded subjects
with AF at baseline, as well as incomplete information about PA or AF. All the papers adjusted for incident comorbidities during follow-up (Table 1).

Regular PA was defined differently at each study (Table 1). Aizer et al. 12 divided the patients into several groups based on the frequency of sweat-breaking exercise per week. The study of Everett et al. 13 used metabolic equivalent task (MET) for each PA performed and divided the patient into several groups based on the MET range. The study of Frost et al. 14 evaluated the amount of PA performed at work and divided the patients into several groups. The study of Mozaffarian et al. 15 categorized patients into several groups based on the 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 those in the least active groups along with the 95% CIs. For studies that included men and women and 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 Centre, Ringhopitalet 2008).

Results

Figure 1 illustrates our review and exclusion/inclusion process. Ultimately, four longitudinal prospective cohort studies 12-15 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 (USPSTF) \(^\text{16}\). Studies and subject’s characteristics are reported in table 1. Three of the studies \(^\text{12,13,15}\) were conducted in the US and one in Europe \(^\text{14}\).

Using a fixed effects model, the pooled OR of AF comparing the most physically active vs. the least physically active groups was 1.08 (95% CI 0.97-1.21), \(p=0.17\) (Fig 2). There was no evidence of heterogeneity between studies (\(I^2 = 0\%\)).

In a sensitivity analysis excluding the non-US study \(^\text{14}\), (which was also the only study evaluating work-related PA), the pooled OR of AF comparing the most vs. the least physically active groups was 1.05 (95% CI 0.88-1.26), \(p=0.6\). In addition, pooling ORs of AF for men and women from the study of Frost et al.\(^\text{14}\) 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 life style. To the best of our knowledge this is the first meta-analysis to 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 \(^\text{17,18}\), at the same time does not appear to increase the risk of AF \(^\text{19}\). PA guidelines recommend 150 min of moderate PA /week or 75 minutes of vigorous exercise per week \(^\text{19}\).

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 \(^{20}\) (“vagal AF”, initially described in 1994 by Coumel \(^{21}\)), leading to shortening of the effective refractory period (ERP) in the atria and increased ERP dispersion, resulting in AF. The second potential mechanism is increase in the left atrial size leading to atrial fibrosis \(^{20}\). Our data suggest that in non-athletes such mechanisms may not play a major role for the development of AF. Alternatively, PA in non-athletes might reduce weight, blood pressure and incident diabetes, 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 sub-categorized the amount of PA differently. Even the type of PA differed across studies, with three studies comparing the amount of exercise, while one compared those the amount of PA at work. However, the study evaluating work-related PA \(^{14}\) also evaluated for the amount of exercise of the subjects, which “was used in statistical analysis” (page 50). 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 sub-analyses, such as stratification by gender or type of exercise. The ascertainment of AF differed from study to study (Table 1). In one of the studies \(^{12}\) 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 due to asymptomatic or undiagnosed AF. Despite these differences, there was little heterogeneity between studies (\(I^2\) of 0). Lastly, we were not able to examine the effect of cause-specific mortality on our findings since we did not have study-specific points for analysis.

Our systematic review has several strengths including the novelty of examining regular PA in non-athletes. 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.

**Conclusion**

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

**Conflict of Interest Disclosures:** None.

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Table 1. Characteristics of the included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Total number of study participants</th>
<th>Number of study participants used in the current meta-analysis</th>
<th>Mean age (SD) yrs</th>
<th>Study type</th>
<th>Groups</th>
<th>Exercise ascertainment</th>
<th>Follow-up duration</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>38,400 (55%)</td>
<td>20,343 (56)</td>
<td>4 (4)</td>
<td>Prospective cohort</td>
<td>Work-related physical activity: 1) Sedentary (predominantly sitting position)* 2) Sedentary (predominantly standing position) 3) light workload 4) heavy workload</td>
<td>questionnaire</td>
<td>5.7 years (mean)</td>
<td>Danish National Registry of Patients validated by manual reviews of the charts and ECGs</td>
<td>240/20,343</td>
<td>Age, body height, BMI, smoking, consumption of alcohol, SBP, treatment for HTN, total serum cholesterol, duration of sporting activities, and level of education</td>
<td>Denmark</td>
</tr>
<tr>
<td>Mozaffarian et al. 2008</td>
<td>5,446 (42%)</td>
<td>982 (73)</td>
<td>6 (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 4) leisure-time activity - high intensity</td>
<td>-Leisure-time activity and exercise. At baseline, and at the end of 3rd and 7th annual visits using questionnaire. -Walking habits: by self-report at baseline and annually</td>
<td>12 years (mean)</td>
<td>-Annual resting 12 lead ECG -Hospital records discharge diagnosis for all hospitalizations</td>
<td>192/982</td>
<td>Age, gender, race, enrollment site, education, smoking status, pack-year of smoking, coronary heart disease, chronic pulmonary disease, DM, alcohol use, beta-blocker use</td>
<td>US</td>
</tr>
<tr>
<td>Aizer et al. 2010</td>
<td>16,921 (100%)</td>
<td>8448 (51)</td>
<td>n/a</td>
<td>Prospective cohort</td>
<td>1) no exercise* 2) exercise to break sweat &lt;1 day/week 3) exercise to break sweat 1-2 days/week 4) exercise to break sweat 3-4 days/week 5) exercise to</td>
<td>Questionnaires 3 years and 9 years after enrollment</td>
<td>12 years (mean)</td>
<td>-Annual questionnaire to report any new medical condition -Questionnaire including specific question about atrial</td>
<td>Data not provided</td>
<td>Age, treatment assignment (aspirin or placebo, beta carotene or placebo), BMI, h/o: DM, HTN, hyperlipidemia; parental h/o premature MI, alcohol intake,</td>
<td>US</td>
</tr>
<tr>
<td>Everett et al. 2011 13</td>
<td>34,759 (0%)</td>
<td>13,899</td>
<td>54.6 (7)</td>
<td>Prospective cohort</td>
<td>Cumulative average physical activity: 1) &lt;2 METS-h/week * 2) 2 to &lt;5.9 METS-h/week 3) 5.9 to &lt;12 METS-h/week 4) 12 to &lt;23 METS-h/week 5) &gt;=23 METS-h/week.</td>
<td>Questionnaires at baseline, at 36,72 and 96 months, at the end of randomized portion of the study and at the end of the observational study</td>
<td>Questionnaire at the time of enrollment, at 48 months and then annually thereafter. Medical charts and ECG reviews of those who self-reported AF in order to confirm the diagnosis.</td>
<td>411/13,899</td>
<td>* = Reference group</td>
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<td></td>
<td></td>
<td></td>
<td>Age, randomized treatment, cholesterol, current smoking, past smoking, alcohol, diabetes, race, HTN, BMI</td>
<td>US</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Figure Legends:

**Figure 1:** Summary of search strategy results

**Figure 2:** Meta-analysis results
1729 identified

1593 articles excluded by title

136

117 excluded by abstract

19

15 without control, not reporting AF, not fitness-type PA, or traditional case-control

4 included in meta-analysis
<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>0.083</td>
<td>49.7%</td>
<td>1.20 [1.02, 1.41]</td>
<td></td>
</tr>
<tr>
<td>Everett et al.</td>
<td>0</td>
<td>0.111</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></td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**

100.0% 1.08 [0.97, 1.21]

Heterogeneity: $\chi^2 = 3.96$, df = 4 ($P = 0.41$); $I^2 = 0$

Test for overall effect: $Z = 1.36$ ($P = 0.17$)
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