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Review

Incidence of atrial fibrillation is associated with age and gender in subjects practicing physical exercise: A meta-analysis and meta-regression analysis

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ABSTRACT

The link between physical activity and the risk of atrial fibrillation (AF) remains controversial. We therefore sought to further assess by a meta-analysis whether increased levels of physical activity may increase the risk of AF.

In October 2015, a PubMed research was conducted for studies that investigated this topic. We identified 11 relevant studies with a total of 81,787 participants. The pooled analysis did not show an increased risk of AF in subjects practicing physical activity (odds ratio (OR) = 0.92, 95% C.I. = 0.84–1.01, $p = 0.077$, $I^2 = 90\%$).

However, given the observed large heterogeneity among studies, a subgroup analysis was performed in order to identify possible variables influencing the risk of AF. Significantly higher risk of AF in subjects with reported physical activity was found in studies enrolling exclusively male participants (OR = 7.49, 95% C.I. = 3.12–19.01, $p < 0.001$, $I^2 = 0\%$) and subjects younger than 54 years (OR 5.30, 95% C.I. = 3.43–8.20, $p < 0.001$, $I^2 = 1.7\%$), while results were opposite in studies enrolling male and/or female participants OR = 0.89 (95% C.I. = 0.81–0.97, $p = 0.01$) and subjects older than 54 years (OR = 0.84, 95% C.I. = 0.76–0.92, $p < 0.001$). A reverse correlation was also found at meta-regression analysis between age and OR of AF ($p = 0.047$).

In conclusion, in our meta-analysis, there is a non-significant trend toward lower risk of AF in subjects practicing physical activity. The risk seems higher in male subjects. A reverse correlation between age and risk of AF seems to be evident.

1. Introduction

Observational studies report an association between physical exercise and a lower incidence of cardiovascular disease [1]; the hypothesized mechanism responsible for such positive effect is thought to be the modulation of physical exercise on principal cardiovascular risk factors and markers of inflammation [2,3]. Nevertheless, some studies raised the doubt that physical exercise may be linked with higher rates of incidence of atrial fibrillation (AF) [4]. In a study by Karjalainen et al., intense sport activity was associated with a 5-fold increased risk of AF [5]. In another study by Molina et al., endurance sport practice (marathon running) was associated with an 8.8-fold risk of incident AF in the multivariate age- and blood pressure-adjusted Cox regression analysis [6].

Meta-analysis studies yielded contrasting results. A first meta-analysis by Abdulla and Nielsen showed a higher risk of AF in athletes compared with controls (odds ratio (OR) = 5.3) [7]. On the other hand, more recent meta-analyses did not confirm such results and found comparable incidence of AF in larger populations of subjects practicing physical exercise, regardless of the intensity of such exercise [8,9].

On the base of such data, we therefore aimed to further investigate in a more comprehensive meta-analysis study the link between physical

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exercise and AF, seeking to identify possible bias responsible for such contrasting evidence.

2. Methods

2.1. Eligibility criteria

Studies assessing the risk of developing AF in subjects practicing physical exercise or sport activity were selected for the meta-analysis. There was no strict definition of physical activity and also studies including athletes and subjects practicing sport activity were not excluded. Moreover, studies including subjects practicing exercise which had a comparator group with less physical activity which would allow risk estimates to be calculated were also included in the study. Studies were required to assess or follow-up participants for AF. There was no restriction based on study design (e.g., retrospective, prospective), study cohort and language of study report.

2.2. Search strategy

We searched PubMed with no date or language restriction in October 2015 using the search terms “atrial fibrillation” AND “physical exercise” OR “physical activity” OR sport OR athlete AND “0001/01/01”[PDat]: “2015/09/01”[PDat] AND “0001/01/01”[PDat]: “2015/09/01”[PDat]. We also checked the bibliographies of potentially relevant studies and reviews for additional studies.

2.3. Study selection and data extraction

Two reviewers (NDB and GC) screened all titles and abstracts for studies that met the inclusion criteria and excluded any articles that did not clearly fulfill the selection criteria. Full reports of potentially relevant studies were retrieved and studied and final decisions on inclusion or exclusion were made. We then independently double extracted data from included studies on study design, study date, sample size, participant age, gender, physical activity groups, follow-up, and results. We aimed to contact authors for clarification if there were any uncertainties.

2.4. Data analysis

We used Stata statistical software to conduct a fixed effects meta-analysis using inverse variance method for pooled OR. Where possible, we chose to pool adjusted risk estimates from the primary studies; otherwise, we used raw outcome data to yield unadjusted risk estimates. Furthermore, where multiple groups were reported, we chose to pool the extreme (high intensity) or the lower exercise (low intensity) groups (i.e., the highest intensity or highest frequency of exercise compared to controls) because this would be likely to improve the chance of detecting any potential association. We planned to perform subgroup analysis based on mean age and gender of populations enrolled in the studies.

2.5. Statistical heterogeneity

Statistical heterogeneity was assessed using I^2 statistic, with I^2 values of 30%–60% representing a moderate level of heterogeneity. If I^2 was above 60% for the pooled analysis, we sought to explore sources of heterogeneity in subgroups of studies.

We also assessed publication bias by plotting the OR against its standard error in a funnel plot diagram and by the Egger regression asymmetry test.

2.6. Meta-regression analysis

A final meta-regression analysis was performed with OR for developing AF as dependent variable and mean age of patients enrolled in the studies as predictor.

3. Results

3.1. Study design and participant characteristics

A total of 11 studies were included in this meta-analysis, which included 1 post hoc analysis of randomized controlled trials [10], 5 cohort studies [5,11–13], and 5 case–control studies [4,6,14–17] with 81,787 subjects considered for the final pooled analysis. The number of study participants ranged from 57 to 57,000, and their mean ages ranged from 43 years to 73 years. The process of study selection is shown in Fig. 1.

The results of the meta-analysis using fixed effects model are shown in Fig. 2. The overall risk of AF using a fixed effects model was not significantly lower in subjects practicing physical exercise than in controls: OR = 0.92 (95% C.I. = 0.84–1.01, $p = 0.077$).

For heterogeneity, $p < 0.0001$ and $I^2 = 89.6\%$ were significant, indicating fairly non-homogenous studies with significant variation in between studies, Egger's linear regression test was significant (Egger bias = 1.50 (95% CI = 0.29–2.80, $p = 0.0193$), and funnel plot showed (Fig. 3) a large asymmetry and therefore a publication bias.

Subgroup analysis was therefore performed considering main data retrievable from studies. When considering 4 studies enrolling exclusively male gender participants [5,6,14,17], the OR of AF associated with physical exercise was significantly higher (OR = 7.49, 95% C.I. = 3.12–19.01, $p < 0.001$, $I^2 = 0\%$) (Fig. 2). Results were different when considering studies enrolling also female gender participants

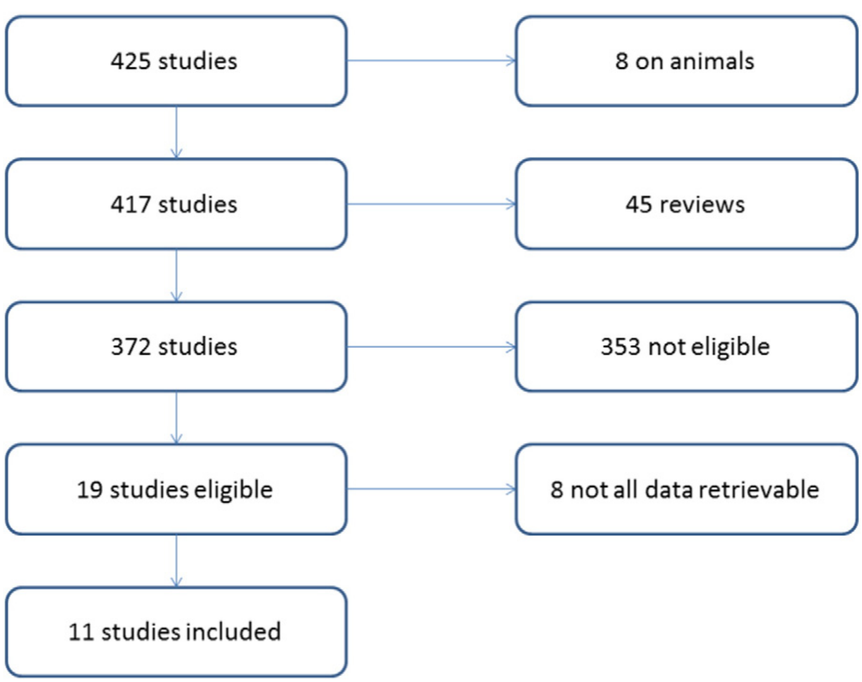

Fig. 1. Studies selection flow-chart.