Physical activity and incidence of Atrial Fibrillation: a systematic review and meta-analysis

Short running title: Physical activity and AF

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Abstract

Background: Whether physical activity increases or decreases the risk of atrial fibrillation (AF) remains controversial. We conducted a systematic review and meta-analysis to evaluate the relationship between AF and extent of physical activity.

Methods: We searched Medline and EMBASE in June 2014 for studies that reported on the associated risk of AF according to history of physical activity. Pooled risk ratios for AF were calculated using inverse variance random effects model, and heterogeneity assessed using I^2. Subgroup analysis was performed according to the nature of the physical activity, and the quality of the studies.

Results: We identified 19 relevant studies with a total of over half a million participants (n=511,503). The pooled analysis showed no association between intensive physical activityand AF (RR 1.00 95%CI 0.82-1.22, I^2=73%, 8 studies, 152,925 participants) with no difference considering low and moderate to high risk of bias studies. Pooled analysis of studies reporting on increasing amount of time spent on physical activities did not show a significant association with AF (RR 0.95 95% CI 0.72-1.26, I^2=84%, 4 studies, 112,784 participants). Studies of athletes or participants with a history of sports activity which were of poor methodology quality showed a borderline significant association with AF, pooled RR 1.98 95% CI 1.00-3.94, I^2=59%, 6 studies, 1,973 participants).

Conclusions: In conclusion, we found no significant increase in AF with a higher level of physical activity. These findings support clinical guidelines encouraging patients to exercise as there is no evidence for harm associated with increased physical activity.

Introduction

Physical activity is associated with reduced risk of coronary heart disease[1] and modulates key cardiovascular risk factors including blood pressure, body mass index, lipids and fibrinogen levels.[2,3] As a result, regular physical activity is recommended for the general population by the United States Government,[4] Department of Health in the United Kingdom[5] and World Health Organization.[6] However, several studies have reported increased risk of atrial fibrillation (AF) amongst athletes[7-9] and participants with increased level of physical activity[10,11] compared to controls.

The mechanism for increased AF with physical activity is not fully understood but the potential mechanisms include increased parasympathetic tone, left atrial enlargement, left ventricular hypertrophy and left ventricular dilatation.[12] Regular exercise alters the sympathetic and parasympathetic stimulation to the heart and results in reduced sympathetic activity at rest.[13] The resultant increase in vagal tone is known to shorten the atrial refractory period, which can induce AF as long as the increased vagal tone is maintained.[14] This is also supported by an animal study that revealed that administration of intravenous cholinergic drugs is associated with auricular fibrillation in dogs.[15] In addition, dynamic exercise can trigger increase in dimension of the heart cavity and static exercise promotes hypertrophy.[16] It has further been suggested that interstitial fibrosis may play a role in the pathogenesis of AF with chronic sports practice.[17]

Previous systematic reviews have shown the inconsistent findings between physical activity and the risk of AF.[18-20] The review of four studies by Ofman et al[19] reported no association between AF and regular physical activity, but a more recent review by Nielsen et al[20] including ten studies concluded that long-term vigorous physical training is associated with increased risk of AF. A third review highlighted that the overall quality of the evidence indicating increases in risk of AF is low and that risk appears to be overestimated substantially.[21]

Since these reviews several new studies have been published. Drca et al recently evaluated the risk of AF with different levels of physical activity using the Swedish National Inpatient Register and found that leisure-time exercise at younger age is associated with increased risk of AF.[21] Knuiman et al examined the risk factors for AF using the Busselton Health Study and found that some vigorous exercise each week is associated with non-significant trend towards reduced risk of AF.[22] Thelle et al used the Norwegian Prescription Database and found that increasing levels of self-reported physical activity in men is associated with flecainide treatment, which was used as surrogate marker for lone AF.[23]

In view of the new studies and divergent findings of previous systematic reviews, we aimed to conduct a more comprehensive systematic review and meta-analysis of the risk of AF with physical activity.

Methods

Eligibility criteria

We selected studies that evaluated the link between the history of physical activity and the subsequent risk of AF. For physical activity there was no strict definition and we also included studies that evaluated outcomes in athletes. In addition, studies had to have a comparator group with less physical activity which would allow risk estimates to be calculated. Studies had to monitor or follow up participants for AF or a surrogate marker of AF (e.g. flecainide use).There was no restriction based on study design (e.g. retrospective, prospective), study cohort and language of study report.

Search strategy

We searched MEDLINE and EMBASE using Ovid SP with no date or language restriction in June 2014 using the broad search terms (AF).mp AND (exercise OR (physical activity)).mp. We also checked the bibliographies of potentially relevant studies and reviews for additional studies.

Study selection and data extraction

Two reviews (CSK and SGA) screened all titles and abstracts for studies that met the inclusion criteria and excluded any articles that did not clearly fulfil the selection criteria. Full reports of potentially relevant studies were retrieved and studies and final decisions on inclusion or exclusion was made by the other 2 reviewers (MAM and YKL). We then independently double extracted data from included studies on study design, study date, country of origin, sample size, participant age, gender and inclusion criteria, risk of bias, physical activity groups, follow up and results. We aimed to contactauthors for clarification if there were any uncertainties.

Risk of bias assessment

Risk of bias was evaluated by considering 5 categories: study design allowed for assessment of recent physical activity, reliable ascertainment of physical activity, control group was from same population of exercise/case group, reliable ascertainment of AF, and analysis adjusted for two or more cardiovascular risk factors. A study was deemed to be low risk of bias if all 5 categories were yes, moderate risk of bias if 3-4 categories were yes and high risk of bias if <3 categories were yes.

Publication bias was considered using asymmetry testing if there were more than 10 studies in the meta-analysis, and if statistical heterogeneity was <50%.[24]

Data analysis

We used RevMan 5.025 (Nordic Cochrane Centre) to conduct random effects meta-analysis using inverse variance method for pooled odds ratios (OR). Where possible, we chose to pool adjusted risk estimates from the primarystudies, otherwise we used raw outcome data to yield unadjusted risk estimates. Furthermore, where multiple groups were reported, we chose to pool the extreme groups (i.e. the highest intensity or highest frequency of exercise compared to the lowest), because this would belikely to improve the chance of detecting any potential association. We planned to perform subgroup analysis based on intense exercise (e.g. vigorous, heavy workload, etc), non-vigorous exercise (e.g. leisure time activity), sportsactivity or among competitive athletes, and based on the quality of studies (low to moderate compared to moderate and high).

Statistical heterogeneity

Statistical heterogeneity was assessedusingI^2statistic, with I^2 values of 30%–60% representing a moderate level of heterogeneity.[25] If I^2 was above 60% for the pooled analysis, we sought to explore sources of heterogeneity in subgroups of studies.

Results

A total of 19 studies were included in this review which included 2 post-hoc analysis of randomized controlled trials,[10,12] 10 cohort studies[8,11,16,17,21-23,26-28] and 7 case-control studies[7,9,29-33] with 511,503 participants. The process of study selection is shown in Figure 1.

Study design and participant characteristics

These studies evaluated participants' physical activity as early as 1955 and took place in USA, Europe and Australia. The number of participants ranged from 57 to 310,716 participants and their ages ranged from 41 years to 73 years. The study design and participant characteristics are shown in Table 1.

Risk of bias

Table 2 shows the risk of bias of included studies. Ten studies were deemed to be high risk of bias. Six studies were deemed to be moderate risk of bias and three studies were of low risk of bias.

Studies of physical activity in general population

A total of ten studies (508,051 participants) were included in the evaluation of AF in general population and follow up of up to 19 years.[10-12,16,21-28] Eight studies were included in the analysis of intensive physical activity (vigorous, high intensity or heavy workload) and risk of AF.[10-12,16,22,26-28] The pooled analysis of these studies suggested no significant increase in AF with intensive physical activity (RR 1.00 95% CI 0.82-1.22, I^2=73%,152,925 participants) (Figure 2). Considering any physical activity or leisure time activity and risk of AF there were four studies[10,21,27,28] (112,784 participants) and the pooled result of these studies suggests no significant association with AF (RR 0.95 95% CI 0.72-1.26, I^2=84%).(Figure 3).

We considered the study by Thelle et al[23] separately from the meta-analysis because this study evaluated physical activity and use of flecainide. This study did not actually attempt to measure occurrence of AF, but relied on flecainide uses a surrogate marker for AF. This study found that there was significantly increased risk of flecainide use with intermediate (HR 1.36 95%CI 1.05-1.77) and intensive (HR 3.14 95% CI 2.17-4.54) exercise among men.

Studies of athletes or people engaged in specific sporting activities

Nine studies (3,452 participants) evaluated risk of AFin participants ofsportingactivity or in athletes (cyclist, runners, skiers, handball players, sportsmen) and all studies were of moderate to high risk of bias.[7-9,17,29-33] Six studies with 1,973 participants had results which could be pooled in meta-analysis these studies showed a borderline significant increase in AF(RR1.98 95%CI 1.00-3.94, I^2=59%,) (Figure 4).[7-9,29,32,33] Two case-control studies evaluated the approximate hours of physical activity and the study by Calvo et al[30] reported significant increases in AF with more cumulative heavy sports activity (>2000h OR 4.25 95% CI 11.34, 172 participants) while other study by Elosua et al[7] evaluating sports practice found no significant difference with any hours of sports activity.

The study by Mont et al[16] (1170 participants) could not be pooled because it was unclear the number of participants in each participant group. They reported 32 cases of AF in sportsmen and 19 cases in non-sportsmen.

The study by Heidebuchel et al[17] was considered separately from the other studies because AF was evaluated in 137 participants who had ablation treatment for atrial flutter. This study found that a history of endurance sports was associated with a significant increase risk of AF (RR 1.81 95% CI 1.10-2.98) but not among participants with continued endurance sports after ablation (RR 1.68 95% CI 0.92-3.06).

Analysis considering the quality of studies

The results of the analysis considering the quality of studies is shown in Table 4. There was no difference in risk of AF with intensive physical activity among studies of low risk of bias (RR 1.04 95% CI 0.87-1.24, I^2=54%, 3 studies) and studies of high risk of bias (OR 1.04 95% CI 0.73-1.49, I^2=77%, 5 studies). For the studies of any physical activity or leisure time activity and risk of AF, stratified analysis based on quality showed no difference in risk of AF with increased physical activity or leisure time activity (2 low quality studies, OR 0.80 95% CI 0.52-1.24 I^2=8%, 2 high quality studies OR 1.12 95% CI 0.94-1.32, I^2=88%).

Discussion

Our results suggest that there is no significant increase in AF with either moderate or rigorous physical activity. In terms of athletes and sports, there was a non-significant trend towards increased risk of AF but all the included studies were at high risk of bias. While there are studies supporting a possible association between AF and physical activity, in general many are case-control in design and are of poor methodological quality. Thus the current evidence suggests that there is no evidence of significant harm with any type of physical activity.

Our findings support previous reviews by Ofman[18] and Muller-Riemenschneider[20] which do not support statistically significant associations between regular physical activity and increased incidence of AF and that the overall quality of the evidence indicating increases in risk of AF is low. We have built on the findings of these reviews by adding the newer studies and the additional studies allowed us to perform subgroup analysis considering the quality of studies, the effect of vigorous and total physical activity.

We observed a lack of significant findings overall and a high degree of statistical heterogeneity in most analyses. While some studies report a positive association between physical activity and AF, the overall non-significance suggests that majority fail to demonstrate any significant association. The differences in findings reported by individual studies gives rise to statistical heterogeneity which may be attributed to methodological differences in study design, population studied, type of assessment of physical activity or sports activity, ascertainment of AF and timing of these evaluations. In addition, the discrepancy in findings may also be explained by different degree of biases in the included studies. There could be situations where AF may be erroneously attributed to recall bias or confounding where athletes or participants in sports activity might be more health conscious and receive regular evaluations for cardiac arrhythmias compared to control participants. Furthermore, publication bias may explain major differences in findings in individual studies. Studies with positive associations between physical activity and atrial fibrillation may be more likely to be published but these positive findings may be related to smaller sample sizes or poor methodological quality.

A few of the studies explored additional factors that might influence risk of AF with physical activity. Frost et al considered men and women separately and found that there was no difference for either gender.[11] Drca et al considered the exercise level at age 30 separately from baseline physical activity and found that greater than 5h/week at age 30 was associated with increased risk of AF but this was not significant considering physical activity at study baseline.[21] This is important as it is not clear if previous exercise affects long term risk of AF. Mozaffarian et al examined the presence of absence of cardiovascular disease the increased AF was present in both the cohort with no history of cardiovascular disease and the group with history of cardiovascular disease.[28] Mont et al found that cumulative physical activity was significantly associated with AF even after adjustment for height and left atrial anteroposterior diameter.[31]

One of the main challenges of studies which evaluate the association between physical activity and AF is reliably quantifying physical activity. General population studies usually assessed physical activity using self-reported questionnaires. While some questionnaires, such as the Minnesota Leisure Time Physical Activity Questionnaire, are validated, they are prone to recall bias. In addition, if the physical activity can be accurately recorded, frequency, duration and intensity of activity need to be considered. While frequency and duration of exercise can be objective by considering number of sessions per week or hours of physical activity, the intensity of physical activity is more difficult to quantify and is very important. The other indicators of physical activity are consideration of athletic or sports activity. The difficulty is there is significant heterogeneity in the exact physical activity depending on the sport. Furthermore, for elite athletes, their lifestyle factors are different from normal population such as strict diet regimes and restrictions on smoking and alcohol, which may confound the risk of developing AF.

Our study has limitations. As with any systematic review, our results are limited by the quality of the available studies. We have attempted to strengthen our analysis by using a comprehensive risk of bias assessment to identify the best quality studies and pool the good and poor quality studies separately. We did not exclude the poor quality studies because we wanted to provide the most comprehensive review of the available literature and evaluate with meta-analysis technique with robust quality assessment. There was also significant heterogeneity in the reporting of physical activity. To account for this we considered several exposures such as intensity and any leisure time activity in separate analyses. We did not include enough studies in any of our analyses to assess for publication bias but we suspect there may be some publication bias where negative studies are less likely to be published. In attempts to reduce risk of publication bias, we did not exclude unpublished literature and several conference abstracts were in our analysis.

While a prospective randomised study would be the ideal design to determine a potentially causal relationship between physical activity and atrial fibrillation, there are major issues with feasibility which relate to adherence to intervention, and need for prolonged follow-up. Fidelity of delivery of the 'exercise' intervention and sustained adherence may be problematic, and confounding within the trial may subsequently arise from variation in everyday physical activity from occupational and leisure activity. Furthermore, the incident rate of atrial fibrillation may be low, and cases may only develop over prolonged follow-up of several years, thus necessitating a large expensive long-term trial. An alternative approach would be to prospectively enroll participants who have differing levels of exercise frequency and intensity, and then to evaluate atrial fibrillation outcomes through primary care or health insurance databases.

Future studies should avoid the retrospective case control design because risk estimates from studies of this methodology may besubject to recall bias. Exercise should be considered in terms of frequency, duration and intensity as well as the age of starting the activity and whether the participant is still physically active. Because of the significant number of potential confounders multivariate analysis needs to be performed. Furthermore, the sample should be population based so that the risk of AF with physical activity can be compared against expected incidences. One notable ongoing study is the Berlin Beat of Running study, which is a prospective observational study which enrolled endurance athletes and followed up participants after 1 year for cardiac arrhythmia and brain lesions.[34]

In conclusion, we found no significant increase in AF with a higher level of physical activity. This was the case considering the intensity, frequency of exercise as well as the case for athletes or sportsmen. The caveat is that some of the studies are at risk of bias. These findings support clinical guidelines encouraging patients to exercise as there is no evidence for harm associated with increased physical activity and the overall CV benefit of regular physical activity is likely to outweigh the any suggested but unfounded risks such as AF.

List of Table and Figures

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Table 1: Study design, sample size and participants

Study	Design	Dates	Country	Sample size	Age	% Male	Participants inclusion criteria
Aizer 2009	Post-hoc analysis of RCT	Baseline randomization in 1982 with follow up to 2001	USA	22,071	52 years	100%	Participants were part of the Physicians' Health Study who were male physicians age 40-84 years in 1982 who were randomized to aspirin and/or beta-carotene.
Baldesberger 2008	Case-control study	Cyclist were in Tour de Suisse 1955 to 1975	Switzerland	62 cases and 62 controls	66 years	100%	Participants were professional cyclist who raced in the Tour-de-Suisse during the years 1955 to 1975 and controls were senior golfers, who never performed high-endurance training. Note: Control group were golfers who had some physical activity.
Bapat 2014	Cohort study	Unclear dates	USA	Unclear	Unclear	Unclear	Participants were in prospective cohort study with a complete baseline physical activity survey.
Calvo 2014	Case-control study	Unclear dates	USA	115 cases and 57 controls	Unclear	Unclear	Participants were patients with lone AF and health controls matched by age and sex.
Drca 2014	Cohort study	Baseline questionnaire in 1997-1998	Sweden	44,410 men	57-64 years	100%	Participants were AF-free men aged 45-79 years.
Elosua 2006	Case-control study	Oct 1997 to Mar 1999	Spain	51 cases, 109 controls	43 years	73%	Participants were younger than 65 years of age with lone AF were identified from hospital records of 1,160 patients seen at outpatient arrhythmia clinic.
Everett 2011	Post-hoc analysis of RCT	Baseline enrolment 1993 and randomized treatment complete in 2004	USA	34,759 women	55 years	0%	Participants were enrolled in Women's Health Study, a randomized, double-blind, placebo-controlled trial of aspirin and vitamin E.

Faselis 2014	Cohort study.	1986 to 2011	United States	4,401	56 years	Unclear.	Participants were African-Americans with normal sinus rhythm who underwent routine exercise tolerance testing at Veterans Affairs Medical Centers Washington DC.
Frost 2005	Prospective cohort study	Dec 1993 to Dec 2001	Denmark	57,053	55 years	51%	Participants were men and women aged 50-64 years who were born in Demark and living in Copenhagen and Aarhus areas with no previous cancer diagnosis.
Ghorbani 2014	Prospective cohort study	1986 to 2010.	United States	28,169	68 years	100%	Participants were men in the United States who did not have AF.
Grundvold 2013	Prospective cohort study	1972 to 2007.	Norway	2,014	50 years	100%	Participants were healthy men aged 40 to 59 years from 5 governmental institutions in Oslo.
Heidbuchel 2006	Prospective cohort study	1999 to 2002	Belgium	137	58 years	83%	Participants were consecutive patients who underwent ablation for atrial flutter at the University of Leuven.
Karjalainen 1998	Cohort study	1985 to 1985	Finland	262 runners, 373 controls	49 years	100%	Participants were top level male veteran orienteers who had done long term vigorous exercise aged 35 to 59 years and controls were men aged 35 to 59 years.
Kuiman 2014	Prospective cohort study	Baseline in assessment in 1994	Australia	4,267	52 years	44%	Participants were adults on the Electoral Registers for the Busselton district.
Molina 2008	Case-control study	1990 to 2003	Spain	183 runners, 290 controls	43 years	100%	Participants were a group of marathon runners living in the Barcelona area and a population sample of sedentary men aged 25 to 74 years.
Mont 2002	Retrospective cohort study	Oct 1997 to Mar 1999	Spain	1160, 70 had AF	46 years in AF	100%	Participants were patients seen at the Outpatient Arrhythmia Clinic.
Mont 2008	Case-control study	Jan 2001 to June 2005	Spain	107 cases, 107 controls	48 years	69%	Participants were consecutive paroxysmal or persistent lone AF patients between 18 and 65 years and controls were age- and sex-matched healthy relatives or visitors of the patients.

Mozaffarian 2008	Prospective cohort study	1989 to 2001	United States	5446	73 years	42%	Participants were men and women ≥65 years who were randomly selected and enrolled from Medicare eligibility lists in 4 US communities in 1989 to 1990 and an additional 687 black participants were recruited and enrolled in 1992 in the Cardiovascular Health Study.
Myrstad 2011	Case-control study	Unclear, participants participated in 2009 ski race.	Norway	423	Median 67 years	92%	Participants were men and women aged >65 years who completed the Birkebeiner cross-country ski race in 2009 and controls were from the Tromso-VI health survey matched for age and sex.
Thelle 2013	Cohort study	1985 to 1999	Norway	310,716	41 years	48%	Participants were women and men aged 40-42 years in 18 Norwegian counties.
van Buuren 2011	Case-control study	Unclear	Germany	33 athletes, 24 controls	57 years	100%	Participants were form top level handball players older than 50 years and sedentary healthy age-matched controls who had not been engaged in sports at a higher level at any time.

Table 2: Quality assessment of included studies

Study ID	Design (prospective collection of recent exercise)	Exercise ascertainment (validated measure of exercise)	Choice of control group (from same cohort as cases)	AF Ascertainment (use of medical records, ECG monitoring, validated method, monitoring committee)	Adjustment for confounders (adjusted for at least 2 cardiovascular risk factors)	Risk of bias
Aizer 2009	Yes, post-hoc analysis of RCT where participants were asked on questionnaire regarding their exercise habits and information was collected at 3 and 9 years.	Yes, use of the question exercise vigorous enough to break as sweat has been validated to correlated with maximal oxygen uptake capacity and maximum exercise capacity on treadmill testing.	Yes, control group were in Physician's Health Study.	Yes, AF was self-reported and a validation study was performed on 400 randomly selected participants who reported AF to determine reliability.	Yes, adjusted for multiple cardiovascular risk factors.	Low
Baldesberger 2008	No, case-control study where participants were former athletes.	No, participants provided information on data on current and previous exercise but there was uncertain validation.	No, control group were senior golfers from two regional golf clubs who never performed high endurance training.	Yes, 12-lead resting electrocardiogram and ambulatory Holter electrocardiogram.	No, unadjusted.	High
Bapat 2014	No, cohort study where participants completed a baseline physical activity survey.	No, participants completed a baseline physical activity survey.	Yes, control group were part of same cohort.	No, unclear method of AF ascertainment.	Yes, adjusted for multiple cardiovascular risk factors.	High
Calvo 2014	No, case-control study where participants completed lifetime exercise activity questionnaire.	No, lifetime exercise activity questionnaire that was not validated.	No, controls were age and sex matched.	No, unclear method of AF ascertainment.	No, unclear.	High
Drca 2014	No, cohort study where participants reported physical activity retrospectively.	Yes, physical activity validity was assess using a questionnaire in 111 men and compared to two 7-day activity records performed 6 months apart.	Yes, control group were part of same cohort.	Yes, cases of AF identified through computerised linkage with ICD -9/10 codes.	Yes, adjusted for multiple cardiovascular risk factors.	Moderate
Elosua 2006	No, case-control study where participants completed a questionnaire about sports practice.	No, exercise was not validated.	No, controls were age matched controls from general population of Girona.	No, AF was from hospital records.	Yes, adjusted for age and hypertension.	High
Everett 2011	Yes, post-hoc analysis of RCT where participants were asked to reported physical activity at 36, 72 and 96 months and at end of randomized study and at 2 years follow up.	Yes, use of questionnaire that was previously found to be valid and reliable.	Yes, control group were in Women's Health Study.	Yes, incident AF was followed up with questionnaire and review of medical documentation and there was an end point committee of physicians to	Yes, adjusted for multiple cardiovascular risk factors.	Low

				confirmed incident AF.		
Frost 2005	Yes, prospective cohort study where participants completed a questionnaire about physical activity.	No, exercise was not validated.	Yes, control group were part of the Danish Diet, Cancer and Health Study.	Yes, AF identified from Danish National Registry with ICD-8/10 codes and single reviewer checked for incident AF in medical records.	Yes, adjusted for multiple cardiovascular risk factors.	Moderate
Ghorbani 2014	Yes, prospective cohort study where particpants prospectively provided habitual physical activity information.	Yes, physical activity assess with validated questionnaire.	Yes, control group were part of same cohort.	No, unclear method of AF ascertainment.	No, unclear.	Moderate
Heidbuchel 2006	Yes, prospective cohort study where participants evaluated with detailed questionnaire.	No, sports activity was evaluated by detailed questionnaire which was not validated.	Yes, control group were part of same group of participants with ablation for atrial flutter.	Yes, follow-up information on AF from outpatient visits, reports of referring cardiologists and mail/telephone contact with the patients and patients received routine Holter at 24 hours after ablation and at 6 weeks.	Yes, adjusted for multiple cardiovascular risk factors.	Moderate
Karjalainen 1998	No, cohort study where participants were top level veteran orienteers.	No, physical activity not formally assessed.	No, control group were enrolled in earlier study.	No, AF from questionnaire on cardiac arrhythmias.	No, unadjusted.	High
Knuiman 2014	Yes, prospective cohort study where some vigorous exercise assessed by questionnaire.	No, exercise assessed in questionnaire with uncertain validation.	Yes, control group were part of Busselton Health Study.	Yes, AF from hospital admission and death records and based on ICD codes.	Yes, adjusted for age, height, hypertension treatment, and BMI.	Moderate
Molina 2008	No, case-control study where participants were marathon runners and a group of sedentary men.	Yes, Minnesota leisure time physical activity questionnaire which has been validated.	No, control group were a group of sedentary men in region close to Barcelona.	Yes, AF from outpatient evaluation of questionnaire, physical examination and electrocardiogram.	Yes, adjusted for age, systolic and diastolic blood pressure.	Moderate
Mont 2002	No, retrospective cohort study where participants were asked about sports activity for at least 3 h a week for 2 years.	Yes, Minnesota leisure time physical activity questionnaire which has been validated.	Yes, control group was 20 healthy controls with no regular activity.	No, AF indentified through clinical chart review.	No, unadjusted.	High
Mont 2008	No, case-control study where participants complete questionnaire on physical activity.	Yes, validated questionnaire on accumulated lifetime physical activity.	No, control group were relatives or visitors.	No, unclear method of AF ascertainment.	No, adjusted for unclear variables	High
Mozaffarian 2008	Yes, prospective cohort study where participants were assess at baseline, third and seventh annual visits.	Yes, modified Minnesota leisure time physical activity questionnaire.	Yes, control group derived from Cardiovascular Health Study.	Yes, AF identified from annual ECG, 6-month telephone contact and hospital records with AF cases	Yes, adjusted for age, systolic and diastolic blood pressure.	Low

				reviewed centrally by events committee.		
Myrstad 2011	No, case-control study where participants were cross-country skiers who completed questionnaire.	No, questionnaire on physical activity not validated.	No, control group were from a general Norwegian population in the Tromso-VI health survey.	No, self-reported AF.	No, unadjusted.	High
Thelle 2013	No, cohort study where participants completed a questionnaire on physical activity.	No, questionnaire on physical activity not validated.	Yes, control group were part of same Norwegian cohort.	No, AF defined from flecainide use but not confirmed.	Yes, adjusted for age, systolic and diastolic blood pressure.	High
van Buuren 2011	No, case-control study where participants were not assessed for recent physical activity.	No, participants were former top-level handball players older than 50 years.	No, control group were healthy age-matched controls.	No, unclear method of AF ascertainment.	No, unadjusted.	High

Table 3: Physical activity groups, follow up and results

Study	Definition of exercise or physical activity	Type of control or comparator group	Outcome and follow up	Results
Aizer 2009	Questionnaire was used to determine frequency of habitual vigorous exercise.	Physicians in the same cohort with less frequency of habitual vigorous exercise.	AF with follow up of up to 19 years.	Frequency of habitual vigorous exercise (compared to nonexercisers) <1 day/wk RR 0.90 (0.68-1.20) 1-2 days/wk RR 1.09 (0.95-1.26) 3-4 days/wk RR 1.04 (0.91-1.19) 5-7 days/wk RR 1.20 (1.02-1.41)
Baldesberger 2008	Participants had to fill in data regarding their current and previous physical exercise.	Controls were selected among 309 male senior leisure time golfers consisting of all senior golfers from the database of two regional golf clubs, who never performed in high-endurance training.	AF with follow up of 30-50 years after year-long high endurance training.	Persistent AF in 2/62 former athletes and 0/62 control.
Bapat 2014	Baseline physical activity survey.	Controls were from the same cohort has high physical activity group.	AF. Unclear follow up.	No association between total intentional exercise and incident AF. After adjustment, there was a significant reduction in AF with vigorous exercise (HR 0.70 95% CI 0.52-0.94).
Calvo 2014	Lifetime exercise activity questionnaire.	Healthy controls matched for age and sex.	AF: Unclear follow up.	Cumulative heavy sport activity of more than 2000h was associated with increased risk of AF (OR 4.52 95% CI 1.88-11.34). Increase risk of AF in sedentary (OR 3.85 95% CI 1.04-14.29) and those with high intensity sports practice (OR 5.89 95% CI 1.27-27.31) compared to light/moderate sports activity.
Drca 2014	Self-administered questionnaire on time spent on leisure-time exercise and on walking or bicycling through their lifetime.	Controls derived from same cohort.	AF. Median follow up 12 years.	Exercise at age 30 years (h/week) <1 RR (relative risk) 1.00 (ref) 1 RR 1.08 (0.95-1.22) 2-3 RR 1.06 (0.94-1.20) 4-5 RR 1.13 (0.98-1.29) >5 RR 1.19 (1.05-1.36) Exercise at baseline (h/week) <1 RR (1.00) (ref)

				1 RR 0.98 (0.87-1.10) 2-3 RR 1.01 (0.91-1.12) 4-5 RR 0.96 (0.84-1.09) >5 RR 1.05 (0.92-1.36)
Elosua 2006	Questionnaire on current and former sports practice.	Age matched controls selected from population of Girona.	Unclear.	Odds of lone AF: Former or current sport practice: OR 0.75 (0.36-1.57) Current practice of sport: OR 3.13 (1.39-7.05) Lifetime number of hours of sports practice: No practice OR 1.00 (ref) 100-1560 h/life OR 0.48 (0.18-1.30) 1561-5668 h/life OR 1.58 (0.66-3.78) >5668 h/life OR 0.87 (0.34-2.19)
Everett 2011	Questionnaire on recreational activity.	Controls were from same randomized controlled trial.	Median follow up 14.4 years.	Risk of AF events per quintile of weekly physical activity: 1 Event rate 231/6957, HR 1.00 (reference) 2 Event rate 201/6956, HR 1.12 (0.92-1.37) 3 Event rate 181/6957, HR 1.01 (0.82-1.24) 4 Event rate 175/6947, HR 1.01 (0.82-1.24) 5 Event rate 180/6942, HR 1.00 (0.81-1.25) Risk of AF by tertile of vigorous physical activity: No activity: HR 1.00 (ref) 1 HR 1.03 (0.87-1.23) 2 HR 1.01 (0.84-1.20) 3 HR 0.99 (0.82-1.19) Risk of AF with strenuous physical activity frequency: Rarely/never: 1.00 (reference) <1 HR 0.88 (0.74-1.06) 1 to 3 HR 0.86 (0.73-1.01) 4+ HR 0.98 (0.79-1.22)

Frost 2005	Questionnaire on physical activity during working hours and leisure time.	All participants were from same cohort of men and women born in Denmark in the Copenhagen and Aarhus areas with no previous cancer diagnosis.	AF or flutter. Mean follow up 5.7 years.	Risk of AF or flutter: Adjusted HR for men Sedentary sitting HR 1.00 (reference) Sedentary standing HR 1.01 (0.74-1.38) Light workload HR 0.97 (0.72-1.32) Heavy workload HR 1.09 (0.72-1.64) Adjusted HR for women Sedentary sitting HR 1.00 (reference) Sedentary standing HR 0.74 (0.45-1.22) Light workload HR 0.73 (0.45-1.19) Heavy workload HR 1.15 (0.36-3.70)
Ghorbani 2014	Validated questionnaire on physical activity.	Controls from same cohort of US men.	Symptomatic AF with 231,108 person years of follow up.	Risk of symptomatic AF Moderate physical activity Q1 HR 1.00 (reference) Q2 HR 1.10 (0.83-1.46) Q3 HR 1.14 (0.86-1.50) Q4 HR 1.13 (0.85-1.49) Q5 HR 1.12 (0.85-1.48) Vigorous physical activity Q1 HR 1.00 (reference) Q2 HR 1.12 (0.86-1.46) Q3 HR 0.92 (0.70-1.21) Q4 HR 0.87 (0.65-1.15) Q5 HR 1.04 (0.79-1.37) Total physical activity Q1 HR 1.00 (reference) Q2 HR 1.19 (0.90-1.58) Q3 HR 1.09 (0.82-1.46) Q4 HR 1.11 (0.83-1.48) Q5 HR 1.26 (0.95-1.67) Sedentary activity Q1 HR 1.00 (reference) Q2 HR 1.11 (0.83-1.47) Q3 HR 1.22 (0.92-1.61) Q4 HR 1.20 (0.90-1.59)

				Q5 HR 1.17 (0.88-1.55)
Heidbuchel 2006	Questionnaire on sports activity.	All patients had ablation for atrial flutter.	AF after ablation for atrial flutter with median follow up of 2.5 years.	History of endurance sports: RR 1.81 (1.10-2.98) Continued endurance sports after ablation: RR 1.68 (0.92-3.06)
Karjalainen 1998	Participants were top level veteran orienteers doing long term vigorous exercise. Controls responded in 1985 to a questionnaire which included physical activity.	Controls were from a previous study of men aged 35-59 years.	Lone AF but unclear follow up .	Men with risk factors for AF: event rate was 4/34 in orienteers and 15/161 in controls. Men without risk factors for AF: 12/228 in orienteers and 2/212 in controls.
Knuiman 2014	Questionnaire to assess physical activity.	Controls were derived from the same cohort in the Busselton district.	AF after 15 year follow up.	Some vigorous exercise each week: adjusted HR 0.80 (0.62-1.03).
Molina 2008	Minnesota leisure time physical questionnaire.	A group of sedentary men was taken from a representative of men aged 25-74 years who participated in population-based cross sectional study conducted in 1994 to 1996 in a region close to Barcelona.	AF at mean follow up of 11.6 years.	Rates of AF in runners 9/183 compared to 2/290 sedentary men. Risk of lone AF with: Sports practice HR 8.80 (1.26-61.29)
Mont 2002	Minnesota leisure time physical questionnaire.	Control patients were in the same population who attended the Outpatient Arrhythmia clinic between October 1997 to March 1999.	AF, mean duration of sports practice 21 years.	AF in sportsmen 32 compared to 19 non-sportsmen.
Mont 2008	Validated questionnaire concerning accumulated lifetime physical activity.	Controls were recruited from healthy relatives or visitors of patients seen at cardiology department. Both cases and controls belonged to same geographic area.	AF, follow up unclear.	Cumulated moderate and heavy physical activity: 0-2077 h OR 1.00 (ref) 2078-9318 h OR 5.60 (1.59-19.75) ≥9319 h OR 15.11 (3.75-60.83) Cumulated moderate physical activity 0-138 h OR 1.00 (ref) 139-6625 h OR 6.47 (1.53-27.61) ≥6626 h OR 22.89 (4.32-121.24)

Mozaffarian 2008	Modified Minnesota Leisure-Time Activities questionnaire.	Controls were in same population as cases.	AF with 12 years follow up	Leisure-time activity (quintiles): I 1.0 (ref) II 0.86 (0.71-1.03) III 0.75 (0.61-0.90) IV 0.78 (0.65-0.95) V 0.64 (0.52-0.79) Exercise intensity None 1.0 (ref) Low 0.85 (0.69-1.03) Moderate 0.72 (0.58-0.89) High 0.87 (0.64-1.19)
Myrstad 2011	Physical activity assessed using a questionnaire.	Controls and cases were part of same population in the Tromso-VI health survey.	AF with unclear follow up.	Prevalence of lone AF 13% 43/334 in skiers and 6% 11/190 in controls
Thelle 2013	Self-reported level of leisure time physical activity.	Controls and cases part of same population.	AF, unclear follow up	Physical activity and flecainide use: Men Sedentary: HR 1.00 Moderate: HR 1.12 (0.88-1.42) Intermediate: HR 1.36 (1.05-1.77) Intensive: HR 3.14 (2.17-4.54) Women Sedentary: HR 1.00 Moderate: HR 0.96 (0.71-1.29) Intermediate: HR 0.87 (0.55-1.38)
van Buuren 2011	Cases for former top-level handball players older than 50 years.	Controls were sedentary healthy age-matched controls who had not been engaged in sports at a higher level at any time.	AF, unclear follow up	AF 10/33 former athletes Healthy controls used with no AF.

Table 4: Physical activity and risk of atrial fibrillation considering the quality of studies

Outcome	High quality studies/low risk of bias		Lower quality studies/moderate to high risk of bias	
	Number of studies and participants	Risk ratio and 95% confidence interval	Number of studies and participants	Risk ratio and 95% confidence interval
Risk of AF with intensive physical activity	3 studies, 62,276 participants	RR 1.04 95%CI 0.87-1.24, I^2=54%	5 studies, 188,863 participants	RR 1.04 95%CI 0.73-1.49, I^2=77%
Risk of AF with any physical activity or leisure time physical activity	2 studies, 40,205 participants	RR 0.80 95% CI 0.52-1.24, I^2=88%	2 studies, 72,579 participants	RR 1.12 95%CI 0.94-1.32, I^2=8%

Figure 1: Study selection process

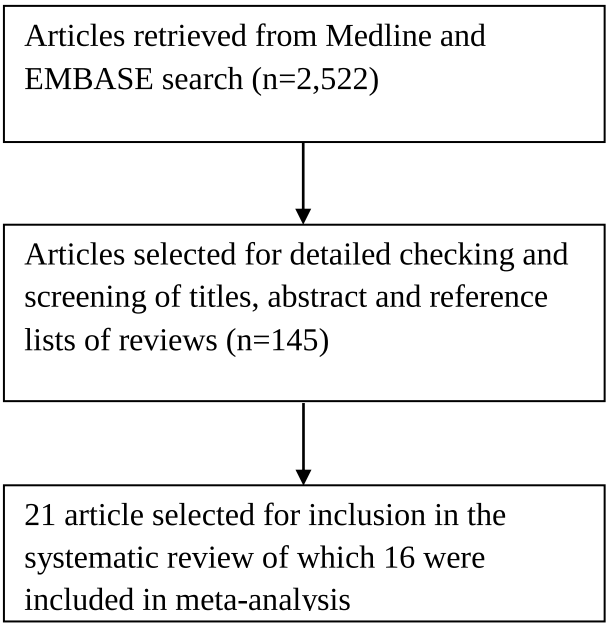

Figure 2: Risk of atrial fibrillation with participants who engaged in moreintensive physical activity

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Aizer 2009	0.182322	0.0826	16.4%	1.20 [1.02, 1.41]
Bapat 2014	-0.35667	0.15103	13.0%	0.70 [0.52, 0.94]
Everett 2011	-0.01005	0.095	15.8%	0.99 [0.82, 1.19]
Frost 2005 (men)	0.086178	0.21	10.2%	1.09 [0.72, 1.65]
Frost 2005 (women)	0.139762	0.59438	2.5%	1.15 [0.36, 3.69]
Ghorbani 2014	0.039221	0.14044	13.5%	1.04 [0.79, 1.37]
Knuiman 2014	-0.22314	0.12949	14.1%	0.80 [0.62, 1.03]
Mont 2008	2.715357	0.7108	1.8%	15.11 [3.75, 60.86]
Mozaffarian 2008	-0.13926	0.15822	12.6%	0.87 [0.64, 1.19]
Total (95% CI)			**100.0%**	**1.00 [0.82, 1.22]**

Heterogeneity: Tau² = 0.05; Chi² = 29.10, df = 8 (P = 0.0003); I² = 73%

Test for overall effect: Z = 0.01 (P = 0.99)

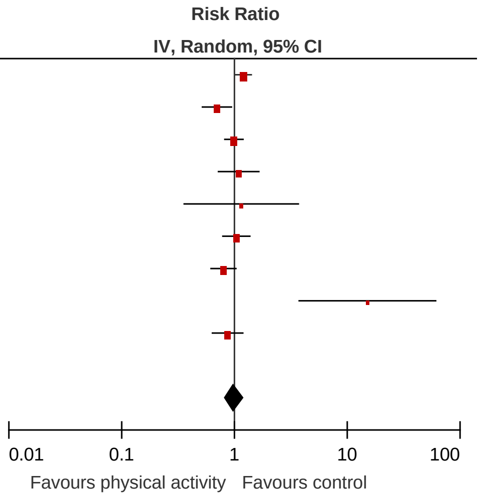

Figure 3: Risk of atrial fibrillationin participants who spentmore time spent on physical activity

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Drca 2014	0.04879	0.09971	26.1%	1.05 [0.86, 1.28]
Everett 2011	0	0.11068	25.4%	1.00 [0.80, 1.24]
Ghorbani 2014	0.231112	0.14391	22.9%	1.26 [0.95, 1.67]
Mozaffarian 2008	-0.44629	0.10668	25.6%	0.64 [0.52, 0.79]
Total (95% CI)			**100.0%**	**0.95 [0.72, 1.26]**

Heterogeneity: Tau² = 0.07; Chi² = 18.64, df = 3 (P = 0.0003); I² = 84%

Test for overall effect: Z = 0.34 (P = 0.73)

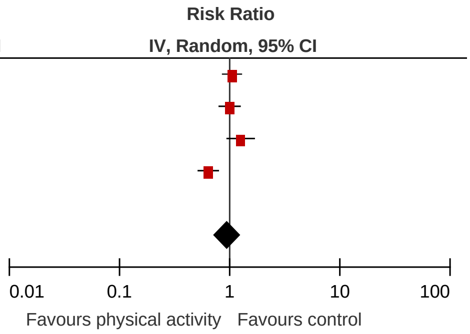

Figure 4: Risk of atrial fibrillation with sports participants or among athletes

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Baldenberger 2008 (cyclists)	1.609438	1.54408	4.5%	5.00 [0.24, 103.11]
Elosua 2006 (sports)	-0.28768	0.3757	24.7%	0.75 [0.36, 1.57]
Karjalainen 1998 (runners)	0.29267	0.33841	26.1%	1.34 [0.69, 2.60]
Molina 2008 (runners)	1.964311	0.77573	12.9%	7.13 [1.56, 32.61]
Mystad 2011 (skiers)	0.797507	0.32448	26.6%	2.22 [1.18, 4.19]
van Buuren 2011 (handball players)	2.736962	1.42295	5.2%	15.44 [0.95, 251.11]
Total (95% CI)			**100.0%**	**1.98 [1.00, 3.94]**

Heterogeneity: Tau² = 0.36; Chi² = 12.15, df = 5 (P = 0.03); I² = 59%

Test for overall effect: Z = 1.95 (P = 0.05)