

Physical activity, atrial fibrillation and the dose-response relationship: a systematic review and meta-analysis

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4 **List of abbreviations**

5 AF Atrial fibrillation

6 CI Confidence intervals

7 GRADE Grading of Recommendations Assessment, Development and Evaluation

8 Hr Hour

9 IQR Inter-quartile range

10 LA Left atrium

11 MeSH Medical subject headings

12 MET Metabolic equivalent of task

13 MVPA Moderate-to-vigorous physical activity

14 n Number

15 NFL National Football League

16 NIH National Heart, Lung, and Blood Institute

17 OR Odds ratio

18 PA Physical activity

1	PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
2	REML	Restricted maximum likelihood method
3	SD	Standard deviation
4	WHO	World Health Organization
5	Wk	Week
6	XC	Cross-country

7 **ABSTRACT**

8 **Background and aim**

9 Regular physical activity (PA) may reduce atrial fibrillation (AF) risk in the general
10 population, however, contemporary data suggests individuals engaging in the highest
11 levels of PA may exhibit a paradoxical rise in AF risk. The point at which the dose-
12 response curve reverses remains unclear. This meta-analysis aimed to assess the
13 association between PA and AF across the full continuum of PA exposure.

14 **Methods**

15 Four databases were searched (from January 1990 to June 2025). Eligible studies
16 included those that reported PA exposure compared against a sedentary control group
17 and assessed AF incidence or prevalence. PA exposures were standardised to metabolic
18 equivalent of task hours per week (MET-hr/wk). Pooled odds ratios (ORs) were calculated
19 using a weighted random-effects model. A weighted restricted cubic spline model of
20 logarithmic odds was used to produce a dose-response curve.

Results

37 studies were included ($n = 1,298,291$ individuals). In the general population, PA was associated with a reduction in odds of AF by 22% (22 studies; OR 0.78; 95% CI 0.68, 0.89). Athlete status was associated with an increase in the odds of AF (15 studies; OR 2.74; 95% CI 1.72, 4.39). Dose-response analysis (26 studies; $n = 1,022,790$ individuals) showed 26 MET-hr/wk of PA was associated with the greatest reduction in odds of AF, with doses beyond 78 MET-hr/wk associated with increased odds of AF; the equivalent of 6-7 hours per week of endurance training.

Conclusion

PA and AF demonstrate a U-shaped relationship whereby beyond a quantitative dose threshold of 78 MET-hr/wk, the protective effect of exercise may reverse.

Graphical abstract

Key question

What is the risk of atrial fibrillation (AF) in those performing physical activity (PA) in the general population and in endurance athletes? Can AF risk be quantified in a dose-response model?

Key finding

- In the general population, PA reduced AF odds by 22%, whilst endurance athletes showed a 2.74-fold increase in odds
- Dose-response analysis showed 26 MET-hr/wk of PA produced the greatest reduction in odds of AF, with odds increasing beyond 78 MET-hr/wk

Take home message

PA reduces the risk of AF in the general population, but 78 MET-hr/wk, the equivalent of 6–7 hours per week of endurance training, was identified as a threshold for when AF risk increases



Four
databases
1990–2025



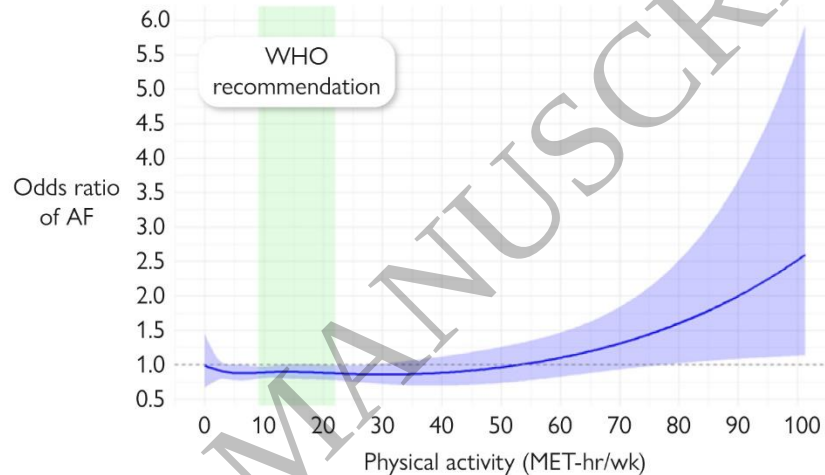
37 studies
included



1 298 291
individuals



6–7 hr-wk of
endurance
training



2

3 *Alt Text: Graphical abstract showing the dose-response curve where physical activity levels just above*
 4 *World Health Organization recommendations are associated with the greatest reduction in AF risk,*
 5 *whereas levels over 78 MET-hr/wk (6-7 hours of endurance exercise) are associated with increased AF*
 6 *risk.*

Keywords

8 Physical activity; exercise; athletes; atrial fibrillation.

Lay summary

10 Exercise reduces the risk of developing heart disease. However, very high levels of
 11 exercise have been shown to increase the risk of atrial fibrillation (AF), an irregular heart
 12 rhythm. We aimed to assess this in more detail by bringing together the many studies
 13 that have looked into this question.

14 Our key findings were:

- 15 • People who were physically active had a lower risk of developing AF than those
 16 inactive.
- 17 • Very high amounts of endurance exercise, such as over 6-7 hours of cycling,
 18 running, or swimming each week at intensities typical of well-trained endurance
 19 athletes, was associated with a higher risk of AF.

1 These findings are important, as it helps to inform clinical teams and patients about the
2 doses of exercise that maximise the cardiovascular benefits and the potential risks at
3 more extreme doses.

7 INTRODUCTION

8 Atrial fibrillation (AF) is the most common cardiac arrhythmia seen in clinical practice with
9 an estimated global point prevalence of 1-3%. (1) Increasing age strongly increases the
10 risk of AF, with a lifetime risk of 25% above the age of 40 years. (2) Stroke is the major
11 cause of morbidity and mortality associated with AF, with the condition conferring a five-
12 fold increased risk of ischaemic stroke. (3)

13 The World Health Organization (WHO) recommends that adults perform 150-300 minutes
14 of moderate-intensity, or 75-150 minutes of vigorous-intensity physical activity (PA) per
15 week. (4) Individuals meeting these recommendations have almost half the incidence of
16 AF compared to those who do not. (5) However, it is increasingly recognised that
17 individuals engaging in the highest levels of exercise, such as endurance athletes, may
18 be at increased risk of AF, with a previous meta-analysis reporting a 2.46-fold higher risk.
19 (6) This has led to the proposal of a U-shaped relationship, termed the extreme exercise
20 hypothesis. (7)

21 This hypothesis remains largely conceptual and has not yet been analytically tested. In
22 particular, previous meta-analyses have not significantly demonstrated a U-shaped
23 relationship comparing AF risk across varying levels of PA. Additionally, several relevant

studies have been published in recent years, underscoring the need for an updated meta-analysis.

This systematic review and meta-analysis aims to provide updated estimates of AF risk in both the general population engaging in PA and in athletes. Importantly, this is the first to assess the association between AF risk across the full continuum of PA exposure using a novel standardised approach that allows different measures of PA across studies to be expressed on a standardised scale.

METHODS

This systematic review and meta-analysis has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (Supplementary Figure 1) guideline and registered on PROSPERO (CRD42024468244).

Population

Studies of individuals from the general population undertaking PA, and athletes, were included. Studies involving individuals with inherited cardiac conditions or previously known structural heart disease at baseline were excluded. Given the lack of a universally accepted definition of an athlete, the original study definitions were used, which varied between studies.

Exposure

The exposure of interest was any form of PA, defined as self-reported from PA questionnaires, accelerometer activity, or classified through sporting participation and

athlete identification, either past or present. Where multiple groups of PA were reported in the general population, the highest level of PA was extracted for primary analyses, with all PA groups extracted for the secondary analysis dose-response curve.

Comparator

The comparator for general population PA studies was the lowest reported level of PA or sedentary behaviour, and for athlete studies the comparator was non-athletes. Definitions of these groups were based on those provided by the original study.

Outcome

The outcome was the incidence or prevalence of AF by either hospital records, ambulatory ECG recordings or self-reported AF. Surrogates for AF diagnosis, such as medication use, were excluded.

Search strategy

Components were included in the search string including Medical Subject Headings (MeSH) or other subject terms, synonyms, and search filters. Search terms included atrial flutter to ensure any subgrouping on atrial fibrillation was not missed, but studies reporting only atrial flutter were excluded. We searched OVID MEDLINE, Web of Science, OVID Embase, and EBSCO SportDiscus. Searches were run from 1st January 1990 up to 30th June 2025 using the search strategies in Supplementary Table 1. Searches were compiled in Rayyan (8) where duplicates were removed manually.

Screening

1 Titles and abstracts were screened independently by two reviewers (CLD, SP).
2 Discrepancies were resolved by a third reviewer (GPM) and discussion by the study team.
3 Cohort, cross-sectional, and case-control studies were included, whilst randomised and
4 non-randomised controlled trials, systematic reviews, editorials, conference abstracts,
5 and animal models were excluded. The full-text of articles included after title and abstract
6 screening was retrieved and assessed by two reviewers (CLD, SP).

7 **Data extraction**

8 Data including the first author's name, year of publication, study design, study quality,
9 geographical location, PA exposure, PA duration, AF events per group, sample sizes, age,
10 sex ratio, and past medical history were extracted. Odds ratios were calculated where AF
11 events and total sample sizes were available in PA and control groups, termed critical
12 data. Missing data were requested from the corresponding authors. If no response was
13 received within two weeks, the study was excluded if critical data was not available or
14 included if only non-critical data were missing.

15 **Dose-response quantification**

16 To obtain a standardised PA metric, the 2024 Adult Compendium of Physical Activities
17 was used which quantifies the energy expenditure of different physical activities and
18 intensities. (9) Each specific activity has an activity code with assigned Metabolic
19 Equivalent of Task (MET) hours. Each MET is defined as the energy expenditure of 1 kcal
20 per kilogram of body weight per hour. Therefore, all included studies where PA was
21 provided as an activity or intensity and duration, excluding occupational PA, were
22 standardised by converting them into MET hours per week (MET-hr/wk). Where

categories of low, moderate, high, or vigorous were used, MET values were assigned using the midpoint of the Compendium defined ranges (1.0-1.5 MET, 1.6-2.9 MET, 3.0-5.9 MET, and ≥ 6.0 MET, respectively). (9) To aid interpretation, MET-hr/wk values were converted into approximate hours per week of cycling, running, and swimming (Supplementary Table 2).

Data synthesis and meta-analysis methods

Data analysis was conducted using RStudio (v4.5.3 2026) with the meta package. Unadjusted odds ratios with 95% confidence intervals were reported. Statistical heterogeneity was assessed using the I^2 statistic and if over 50%, this was explored using subgrouping by sport type. Individual studies and pooled estimates were graphically displayed using forest plots. Publication bias was visually assessed using funnel plots and tested using Egger's regression.

Given the high degree of expected heterogeneity, between-study variance (Tau^2) was estimated using the restricted maximum likelihood (REML) method, which reduces bias. A random-effects model with inverse variance weighting was applied to pool odds ratios. For studies with zero events, a continuity correction of 0.5 was applied. Meta-regression was performed using age and sex distribution. Mean age was used where available, and median age was used when a mean was not reported. Where available, age represented the combined low and high PA groups contributing to each study-specific effect estimate. If unavailable, the reported age of the overall study population was used as the best available proxy. Studies without a reported age were excluded from the age meta-regression. Additional sensitivity analyses included excluding poor quality studies (as

assessed through quality assessment), excluding studies reporting self-reported AF, and performing leave-one-out analyses.

The primary analyses reported the odds of AF for those undertaking PA in the general population and in athletes. Secondary analyses included sex-specific odds of AF and the generation of a dose-response curve. Dose-response modelling was completed using an inverse-variance weighted restricted cubic spline model on logarithmically transformed odds ratios, which were back-transformed to standard odds ratio scale. Spline-based model estimates of odds ratios and confidence intervals were obtained for key PA doses.

Study quality assessment

Each study was independently assessed for quality by CLD and SP using the National Heart, Lung, and Blood Institute (NIH) Study Quality Assessment Tool. (10) The tool consists of 14 criteria for cohort and cross-sectional studies and 12 for case-control studies, each rated as 'Yes', 'No', or 'Cannot Determine' (Supplementary Table 3). Following NIH guidance, we designated questions 6, 9, and 11 (cohort and cross-sectional) and questions 6, 9, and 10 (case-control) as potentially fatal flaws. Studies with any fatal flaw answering 'No' had a high risk of bias and were rated as poor quality. Studies with more than one 'No' response to other questions were rated as fair. Studies with only one 'No' were rated as good.

Certainty of evidence

Certainty of evidence for the primary outcomes was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Evidence was assessed across the GRADE domains of risk of bias, inconsistency, indirectness, imprecision, and publication bias. For observational studies, initial certainty was rated at 'low', with the certainty downgraded by one level for serious concerns or two levels for very serious concerns within each domain. (11)

RESULTS

Search results

A total of 4,127 articles were identified from databases and other sources. The screening process is detailed in Figure 1 where 37 studies were included in the final analysis dataset. Two studies initially included were excluded due to a more recent publication covering the same sample of participants. (12, 13) A further study was later excluded whereby flecainide was used as a surrogate measure for a diagnosis of AF. (14)

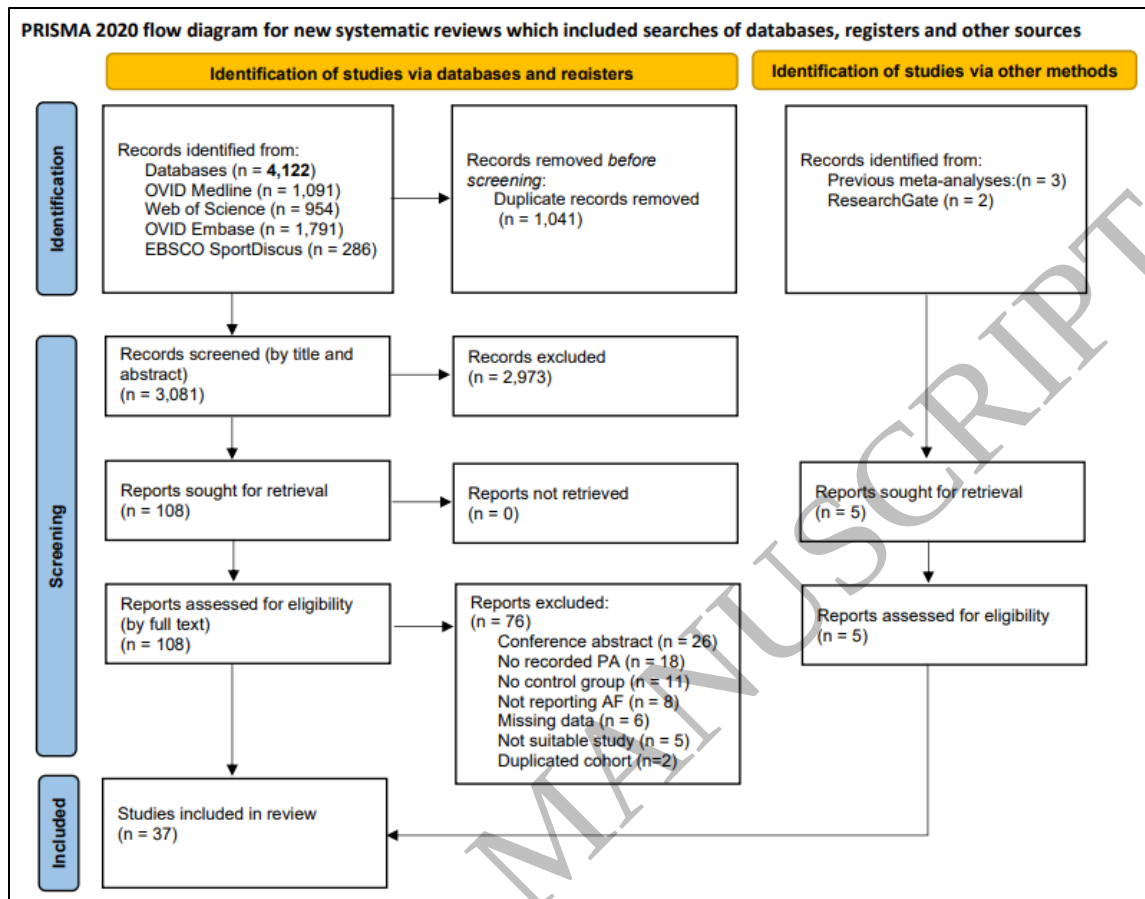


Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 screening process flow diagram. Alt text: PRISMA flow chart depicting 4122 articles retrieved from all databases, 3081 screened by title and abstract, 108 screened by full text, 5 included from other sources, and 37 included in this review.

Study characteristics

A total of 1,298,291 individuals were included in the analysis, consisting of 220,169 individuals from the general population performing the highest reported level of leisure-time PA (compared against 315,506 individuals at the lowest level or sedentary) and 214,523 athletes engaged in sports (compared against 548,093 non-athlete controls).

In total, 29,557 cases of AF were included across all groups. Study characteristics of general population PA studies (n=22) and athlete studies (n=15) are shown in Table 1 and Table 2, respectively. The combined representative age of the low and high PA groups

1 contributing to the effect estimates are presented in the main tables. Corresponding
2 group-specific age data, where available, together with available data on alcohol
3 consumption and hypertension prevalence, are presented in Supplementary Tables 5, 6.

ACCEPTED MANUSCRIPT

Table 1. Study characteristics of general population PA studies. Age is presented as mean $\pm$ SD* or median (IQR)** and represents the combined low and high PA groups contributing to the study specific effect estimate, where available. Superscript ^a denotes age reported for the overall study population because group-specific ages were unavailable. N/a indicates that age was not reported. Follow-up duration given as mean $\pm$ SD* or median (IQR)**. PA: physical activity; AF: atrial fibrillation; MET: metabolic equivalent of task hours; hr: hour; wk: week; MVPA: moderate to vigorous physical activity.

Author, year	Country	Study type	Total sample size	Total female (%)	Age (years)	Follow-up duration (years)	PA measure	Reported PA	PA groupings
Mozaffarian et al., 2008 (15)	United States	Prospective cohort	2183	58	73 $\pm$ 5.6*	12 *	Questionnaire	Quintiles of leisure time PA as kcal/wk.	• <35 kcal/wk • 35 to 404kcal/wk • 405 to 885kcal/wk • 890 to 1838kcal/wk • >1840kcal/wk
Everett et al., 2011 (16)	United States	Prospective cohort	13899	100	53 (49-59)**	14.4 (13.7-14.8) **	Questionnaire	Quintiles of leisure time PA as MET-hr/wk.	• <2 MET-hr/wk • 2 to <5.9 MET-hr/wk • 5.9 to <12 MET-hr/wk • 12 to <23 MET-hr/wk • >23 MET-hr/wk
Azarbal et al., 2014 (17)	United States	Prospective cohort	53506	100	63.4 $\pm$ 7.3 ^a	15.5 *	Questionnaire	Quintiles of leisure time PA as MET-hr/wk.	• Sedentary • 0 to <3 MET-hr/wk. • 3 to <9 MET-hr/wk

									• >9 MET-hr/wk
Bapat et al., 2015 (18)	United States	Prospective cohort	5793	53	61.7 ± 10.2*	7.7 ± 1.9 *	Questionnaire	Any vigorous PA	• No vigorous PA • Any vigorous PA
Drca et al., 2015 (19)	Sweden	Prospective cohort	14397	100	61.9*	12 (7.5-12) **	Questionnaire	Any exercise activity.	• <1hr/wk • 1hr/wk • 2 to 3hr/wk • >4hr/wk.
Sun et al., 2015 (20)	China	Cross-sectional	3993	55.4	53.8 ^a	N/A	Questionnaire	Mixture of PA activities	• Low: sedentary • Moderate: walking, cycling >4hr/wk • High: Vigorous PA, running, skiing, sport >3hr/wk.
Morseth et al., 2016 (21)	Norway	Prospective cohort	8666	49.7	36.9 ± 10.4*	20 *	Questionnaire	Mixture of PA activities	• Low: reading, TV, sedentary. • Moderate: walking, cycling, exercise >4hr/wk. • High: Heavy gardening, vigorous sports >4hr/wk.

Skjelboe et al., 2016 (22)	Denmark	Prospective cohort	4848	54.1	48.2 ± 12.7 ^{*a}	20.3 *	Questionnaire	Mixture of PA activities	• Low: sedentary, light walking or biking <2hr/wk. • Moderate: light PA for 2-4hr/wk. • High: light PA >4hr/wk or 2-4hr/wk heavy gardening, vigorous walking or biking. • Very high: Heavy exercise, sport, vigorous PA >4hr/wk.
Albrecht et al., 2018 (23)	Netherlands	Prospective cohort	4678	58.2	69.6 ± 8.9 [*]	12.3 (8.7- 15.9) ^{**}	Questionnaire	MET-hr/wk of PA	• <58.1 MET-hr/wk. • 58.1 to 94.2 MET-hr/wk • >94.2 MET-hr/wk
Garnvik et al., 2018 (24)	Norway	Prospective cohort	18051	54.1	50 ± 15.5 [*]	8.1 *	Questionnaire	Tertiles of PA distribution	• Inactive • Low. • Medium. • High.

Choi et al., 2019 (25)	South Korea	Prospective cohort	4513	51.9	52.5 (46-61)**	11.6 (8.1-11.8) **	Questionnaire	Mixture of PA activities. Including occupational activities i.e., driving, ironing	• <11.3 MET/day • 11.3 to 19.4 MET/day • 19.5 to 35.5 MET/day • >35.6 MET/day
Ho Lee et al., 2019 (26)	South Korea	Prospective cohort	126814	38.6	37.1 ± 7.7*	5.6 (2.7-8.4) **	Questionnaire	Mixture of PA activities	• Sedentary: no regular PA. • Insufficient: <600 MET-min/wk. • Sufficient: >600 MET-min/wk. • Health enhancing: vigorous PA >1500 MET-min/wk.
Jin et al., 2019 (27)	South Korea	Retrospective cohort	211352	50	49.7 ± 14.3*	4 **	Questionnaire	Mixture of PA activities	• No PA • 1 to 500 MET-min/wk • 500 to 1000 MET-min/wk • >1000 MET-min/wk

Kunutsor et al., 2020 (28)	Finland	Prospective cohort	1227	0	53 ± 5 ^a	25.2 (16.4- 29.3) **	Questionnaire	XC Ski activity per year	• 0 MET-hr/yr • 1 to 200 MET-hr/yr • >200 MET-hr/yr
O'Neal et al., 2020 (29)	United States	Prospective cohort	2606	54	63.6 ± 8.5 [*]	3.5 (2.7-4.2) **	Accelerometer	Accelerometer of daily MVPA	• 0.7 min/day • 4.4 min/day • 13 min/day • 40 min/day
Arafa et al., 2022 (30)	Japan	Prospective cohort	3206	53	N/A	14.7 **	Questionnaire.	Stair climbing usage	• <20% • 20 to 39% • 40 to 59% • >60%
Boursiquot et al., 2022 (31)	United States	Prospective cohort	1340	100	78.3 ± 6.7 [*]	3.8 **	Accelerometer	Grouped by total sedentary time hr- day. Daily MVPA extracted.	• 10.22 to 13.86 hr/day • 9.27 to 10.22 hr/day • 8.27 to 9.27 hr/day • 3.25 to 8.27 hr/day
Fletcher et al., 2022 (32)	United States	Prospective cohort	2916	59	75.6 ± 5 [*]	6.3 ± 2 *	Questionnaire	MVPA minutes per week	• No MVPA • Low: <150 min/wk moderate or <75 min/wk vigorous • Recommended: 150 to 299 min/wk

									moderate or 75–149 min/wk vigorous. • High: >300 min/wk moderate or >150 min/wk vigorous
Heitmann et al., 2022 (33)	Norway	Prospective cohort	1705	52.4	58.6 ± 10.7 ^{*a}	16.6 ± 6.6 *	Questionnaire	Hard (sweating) leisure time PA duration	• Inactive • Low: 0 to 1 hr/wk • Moderate: 1 to 2 hr/wk • Vigorous: >3 hr/wk
Mei et al., 2024 (34)	China	Prospective cohort	2241	63.1	69.7 ± 6.2 ^{*a}	2.6 **	Questionnaire	MET-hr-wk of PA	• <24.5 MET-hr/wk • 24.5 to 49 MET-hr/wk • >49 MET-hr/wk
Wang et al., 2024 (35)	United States	Prospective cohort	5554	55	53.9 ± 5.7 [*]	24 (18.8-25.5) **	Questionnaire	PA Questionnaire	• Light: <600 MET-min/wk • Reduced moderate: 600 to 900 MET-min/wk • Moderate: 900 to 1200 MET-min/wk

									Vigorous: >1200 MET-min/wk
Qin et al., 2025 (36)	United Kingdom	Prospective cohort	42187	55.5	54.9 ± 8.1*	13.7 (12.8-14.4) **	Accelerometer	Accelerometer walking pace	- Slow: <3 miles per hour - Average: 3 to 4 miles per hour - Brisk: >4 miles per hour

Table 2. Study characteristics of athlete studies. Age is presented as mean $\pm$ SD* or median (IQR)** and represents the combined low (non-athlete) and high (athlete) PA groups contributing to the study specific effect estimate, where available. Superscript ^a denotes age reported for the overall study population because group-specific ages were unavailable. N/a indicates that age was not reported. Follow-up duration given as mean $\pm$ SD* or median (IQR)**. PA: physical activity; AF: atrial fibrillation; XC: cross-country (skiing); NFL: National Football League.

Author, year	Country	Study type	Total sample size	Total female (%)	Age (years)	Follow-up Duration (years)	Reported PA	PA groupings
Karjalainen et al., 1998 (37)	Finland	Prospective cohort	440	0	48.5 $\pm$ 6.3*	11 *	Top ranked orienteers	- Unspecified controls - Orienteers
Elosua et al., 2006 (38)	Spain	Case-Control	160	0	43.2 $\pm$ 11.9*	N/A	Mixture of sports practice	- No sport practice - Any sport practice
Baldesberger et al., 2008 (39)	Switzerland	Retrospective cohort	126	0	66 $\pm$ 6.5*	N/A	Former Professional Cyclists	- Golfers - Former professional cyclists
Molina et al., 2008 (40)	Spain	Cohort	473	0	45.7 $\pm$ 12.8*	11.6 *	Participation in the Barcelona marathon	- Sedentary controls - Marathon runners
Mont et al., 2008 (41)	Spain	Case-Control	191	31	47.8 $\pm$ 10.9 ^a	N/A	Self-reported participation in heavy-intensity mixed sports	- No sports activity - Mixture of heavy sports activity
Van Buuren et al., 2012 (42)	Germany	Cross-sectional	57	0	57.1 $\pm$ 5.6*	N/A	Former professional handball players	- Sedentary controls - Former professional handball players

Woodward et al., 2015 (43)	New Zealand	Cohort	1635	27.6	N/A	6 *	Participation in a 160km cycling event	0-2 hr/wk cycling 6+ hr/wk cycling
Myrstad et al., 2016 (44)	Norway	Cross- sectional	4955	11.6	N/A	N/A	Participation in the 1999 or 2010 54km XC ski event	- Non-athletes - XC skiers
Schreiner et al., 2016 (45)	United States	Cross- sectional	149	N/A	71.5 ± 6*	N/A	Competitive swimmer, including former Olympians	- Non-athletes - Swimmers
Aagaard et al., 2019 (46)	United States	Cross- sectional	1385	0	54.6 ± 9.8*	N/A	Former NFL players	- Non-athletes - Former NFL players
Svedberg et al., 2019 (47)	Sweden	Cohort	736102	34.8	40.7 ± 12.5*	8.8 **	Participation in a 30, 45, or 90km XC ski event	- Non-skiers - XC skiers
Johansen et al., 2022 (48)	Norway	Cohort	2312	0	69.6 (66.8- 74.2)**	10 *	Participation in the 2009 or 2010 54km XC Ski event	- Non-skiers - XC skiers
Drca et al., 2023 (49)	Sweden	Cohort	1596	100	32.1 ± 8.5*	28.8 ± 4.4 *	Sub 3:15 marathon, athletics national championship athletes, and top-ranked cyclists.	- Non-athletes - Elite athletes

Myrstad et al., 2024 (50)	Norway	Cohort	1421	100	68.8 ± 2.8*	10 *	Participation in the 2009 or 2010 54km XC ski event	• Non-skiers • XC skiers
Flannery et al., 2025 (51)	Australia	Retrospective cohort	11616	26	62 (56, 68)**	N/A	Former world-class rowers	• Non-athletes • Former professional rowers

General Population Physical Activity Risk of AF

The highest levels of PA in the general population were associated with a 22% reduction in the odds of AF compared to the lowest levels or sedentary behaviour (22 studies; Figure 2). Heterogeneity was high ($I^2=85.1\%$). Visual inspection of funnel plot asymmetry was observed, however, Egger’s test revealed no evidence of publication bias ($p = 0.233$; Supplementary Figure 2).

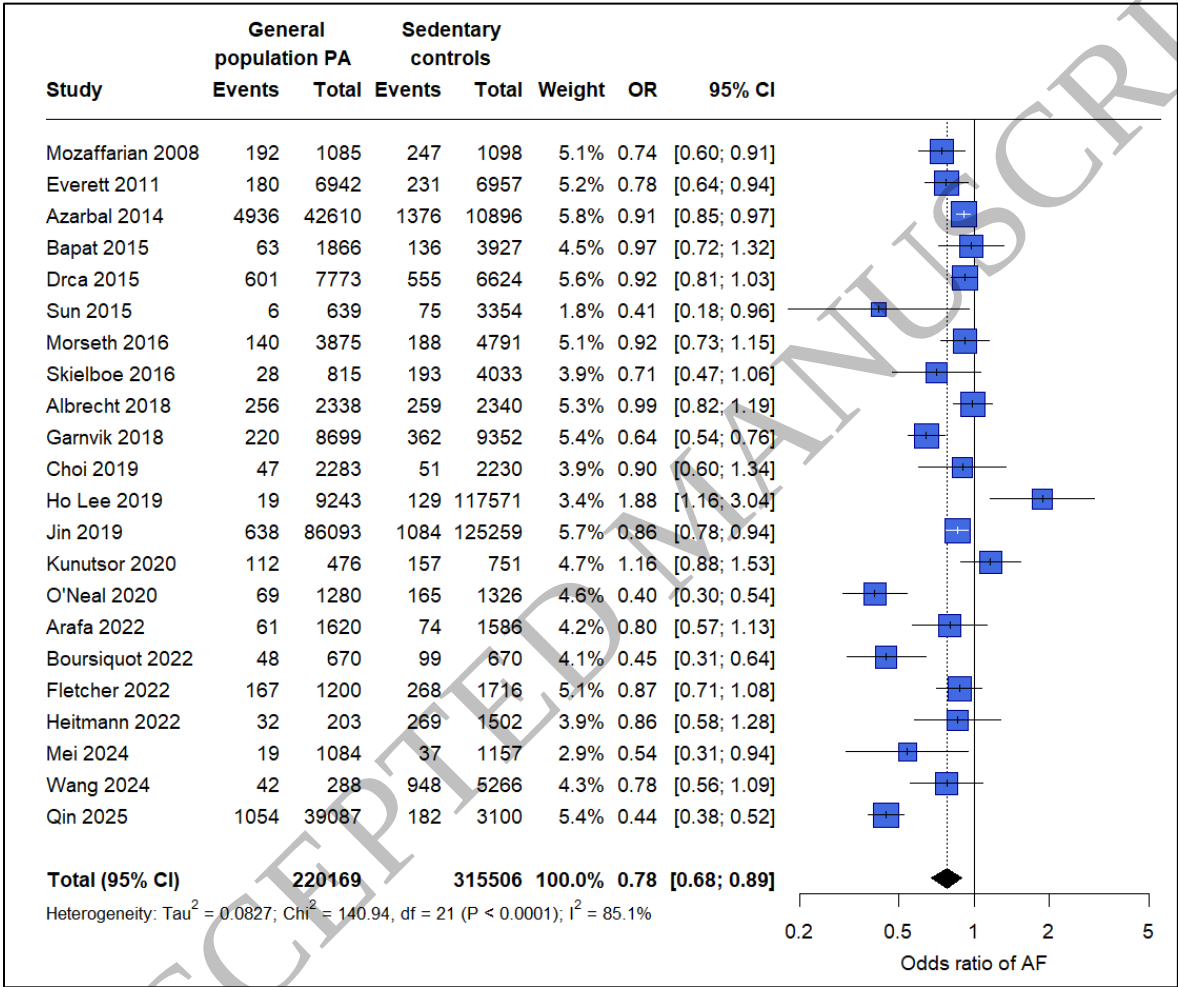


Figure 2. Forest plot of odds ratios with 95% confidence intervals for AF in general population PA versus sedentary or low activity controls.
Alt text: Forest plot showing 22 general population PA studies with odds ratio 0.78 with 95% confidence intervals 0.68 to 0.89.

Athletes' Risk of AF

Athletes were associated with a 2.74-fold increase in the odds of AF compared to non-athletes (15 studies; Figure 3). Heterogeneity was high ($I^2=95.1\%$). Visual inspection of funnel plot asymmetry was observed and Egger’s test was significant for publication bias ($p <0.001$; Supplementary Figure 3).

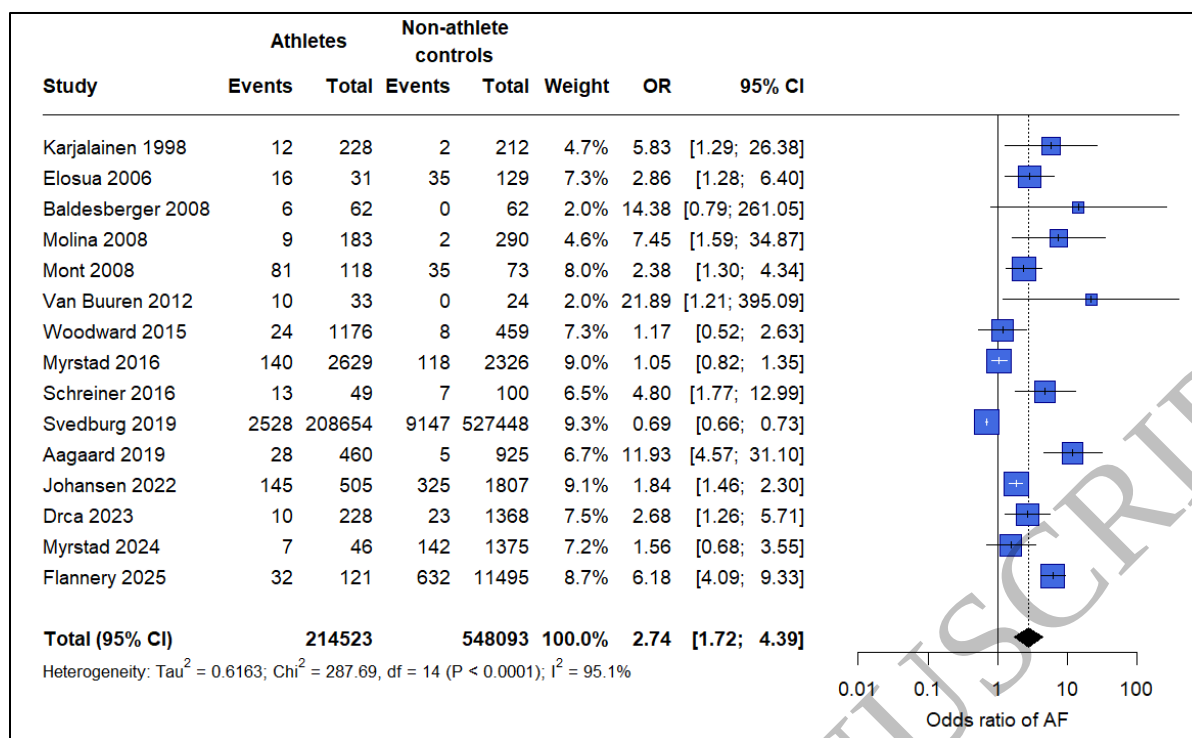


Figure 3. Forest plot of odds ratios with 95% confidence intervals for AF in athletes versus non-athlete controls. Alt text: Forest plot showing 15 athlete studies with odds ratio 2.74 with 95% confidence intervals 1.72 to 4.39.

Sex differences

General population

Limited studies reported PA and AF incidence stratified by sex. Among those that did, the highest levels of PA in the general population were associated with a 36% reduction in the odds of AF in females compared to the lowest levels or sedentary behaviour (Figure 4.A). In males, no significant association was observed (Figure 4.B).

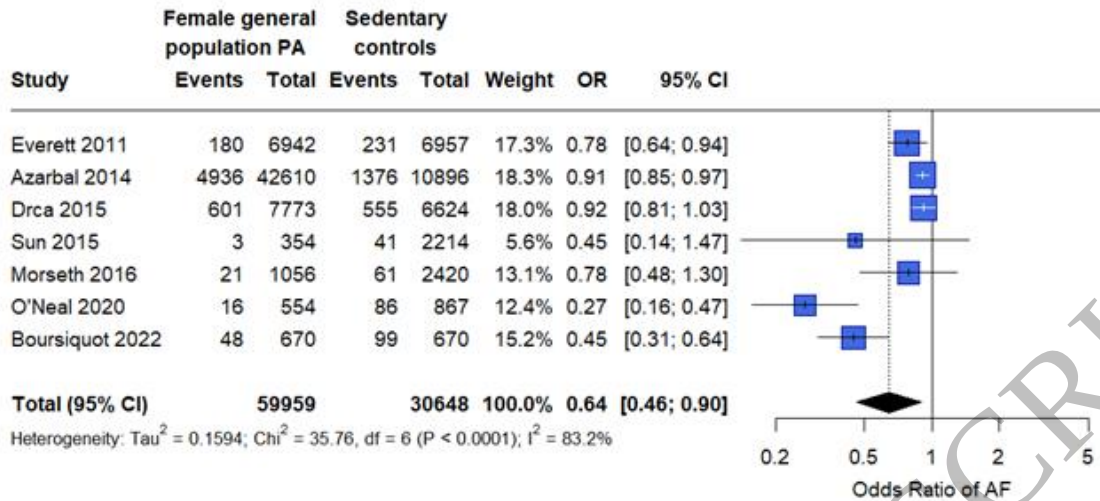
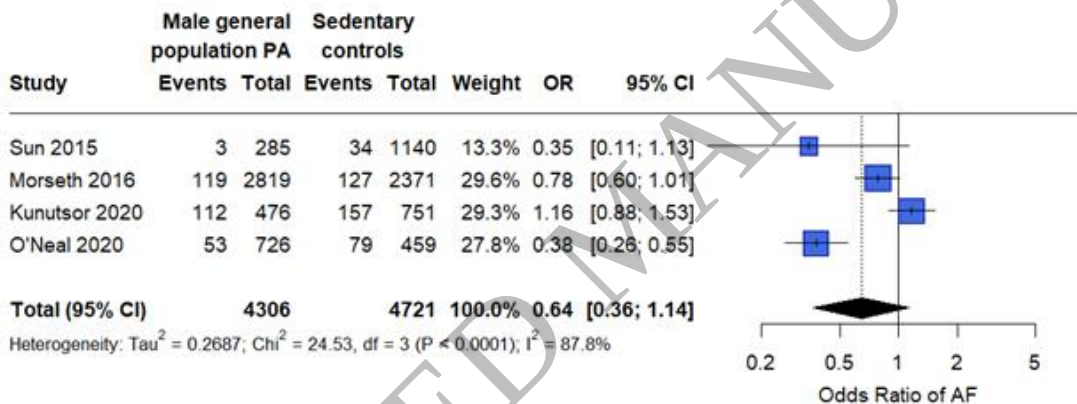
A**B**

Figure 4. Forest plot of odds ratios and 95% confidence intervals for AF in A. Female general population PA, B. Male general population PA (versus sedentary or low activity controls). Alt text: Forest plot showing A. 7 female general population PA studies with odds ratio 0.64 and 95% confidence intervals 0.46 and 0.90. B. 4 Male general population PA studies with odds ratio 0.64 and 95% confidence intervals 0.36 and 1.14.

Athletes

Male athletes were associated with a statistically significant increase in odds of AF by 4.21-fold, compared to non-athletes (Figure 5.B). In female athletes, no significant association was observed (Figure 5.A).

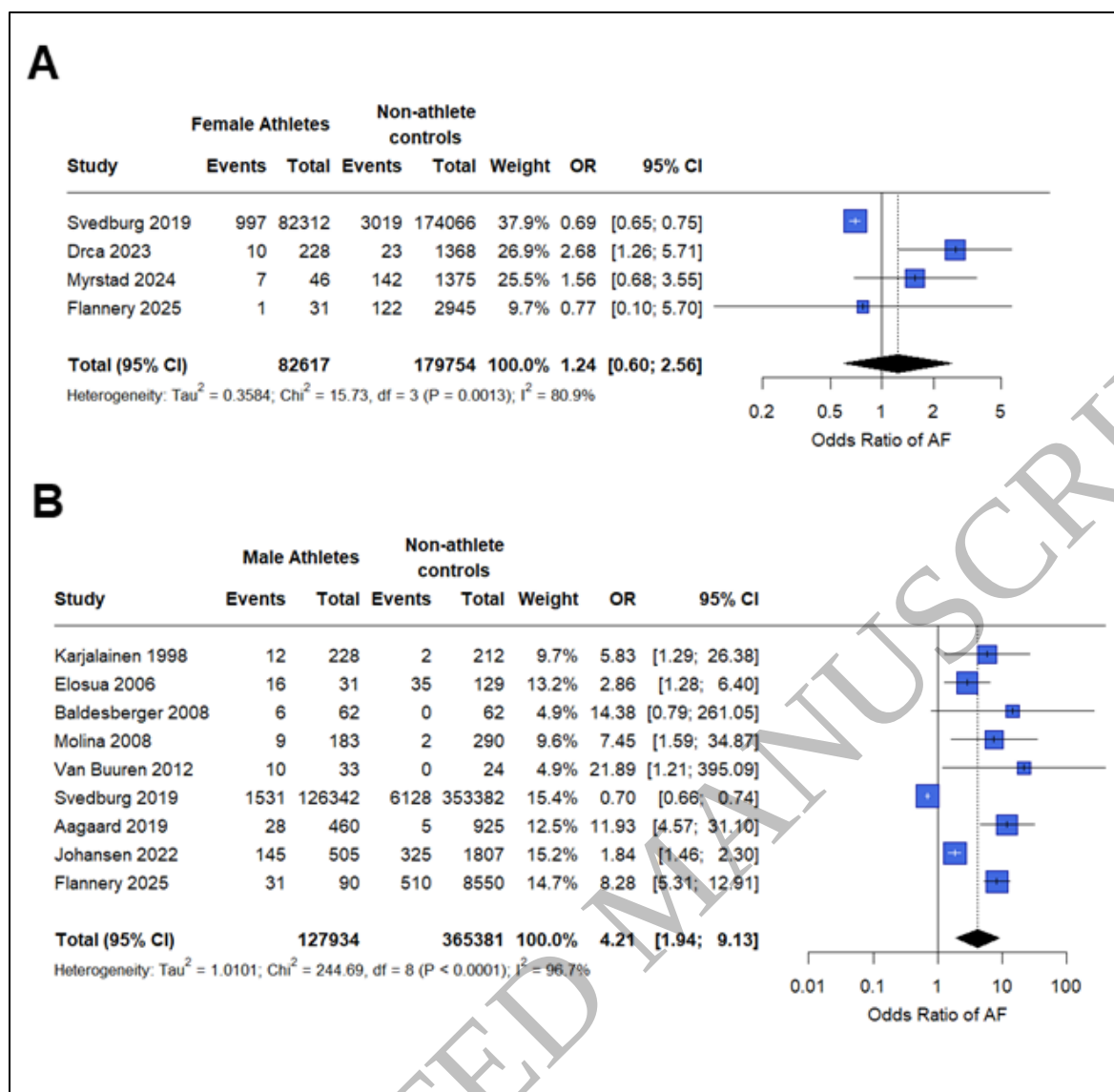


Figure 5. Forest plot of odds ratios and 95% confidence intervals for AF in A. Female athletes, B. Male athletes (versus non-athlete controls). Alt text: Forest plot showing A. 4 female athlete studies with odds ratio 1.24 with 95% confidence intervals 0.60 and 2.56. B. 9 male athlete studies with odds ratio 4.21 with 95% confidence intervals 1.94 and 9.13.

Sport type

When subgrouping by sport type to explore heterogeneity, cross-country (XC) skiing was the largest contributor (I^2 : 96.2%) (Supplementary Figure 4).

1 **Age**

2 Both athletes younger than 60 years old (8 studies; OR 3.41; 95% CI 1.62, 7.18, $p < 0.0001$)
3 (Supplementary Figure 5) and over 60 years old (5 studies; OR 3.23; 95% CI 1.64, 6.36, $p < 0.0001$)
4 (Supplementary Figure 6) were associated with an increase in the odds of AF.

5 **Dose-response relationship**

6 A total of 26 studies were eligible for inclusion in the dose-response analysis, ranging from general
7 population PA to athlete studies. This included 87 varying doses of PA, ranging from 0 to 101 MET-
8 hr/wk, representing 1,022,790 individuals (Figure 6).

9 Using spline-based model estimates, approximately 26 MET-hr/wk was associated with the lowest odds
10 ratio of AF (OR 0.86; 95% CI 0.75, 0.99). PA beyond approximately 78 MET-hr/wk was associated with
11 an increase in the odds ratio of AF (OR 1.54; 95% CI 1.01, 2.35).

12 A PA volume of 78 MET-hr/wk is equivalent to approximately 6-7 hours per week of cycling, running, or
13 swimming at intensities typical of well-trained endurance athletes (Supplementary Table 2).

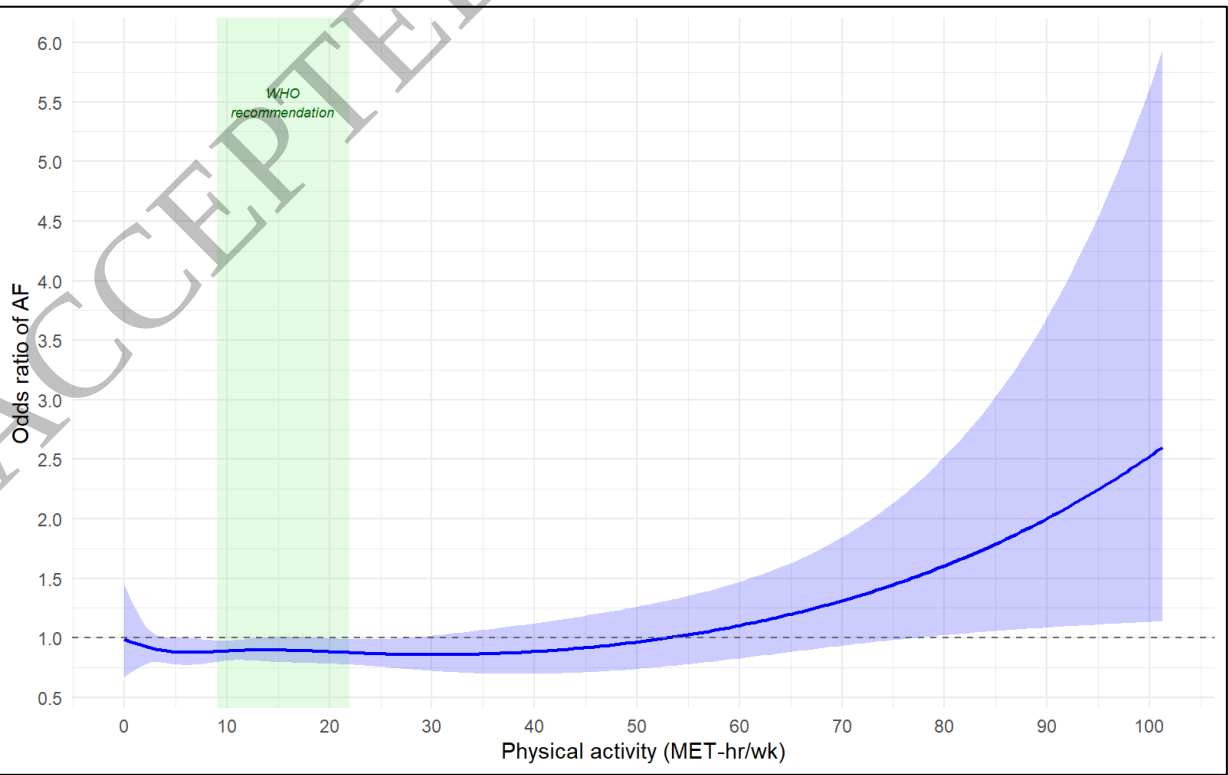


Figure 6. Dose-response relationship between PA and AF using a weighted restricted cubic spline model. The shaded green region represents the World Health Organization (WHO) recommended level of 150-300 minutes of moderate PA and 75-150 minutes of vigorous PA per week converted into 9-22 MET-hr/wk. Alt text: Dose-response curve where physical activity levels just above World Health Organization recommendations are associated with the greatest reduction in AF risk (26 MET-hr/wk), whereas levels over 78 MET-hr/wk (6-7 hours of endurance exercise) are associated with increased AF risk.

Quality Assessment

All athlete case-control studies were rated as of poor quality due to high risk of bias from question 9, where it could not be determined whether AF was a result of the exposure alone (Supplementary Figure 7).

In athlete cohort studies (Supplementary Figure 8), all but one were rated as poor quality, where the most frequent fatal flaw was that the exposure was not clearly defined (question 9).

In general population PA cohort studies, study quality was mixed but contained fewer fatal flaws than athlete studies (Supplementary Figure 9).

Certainty of evidence

The certainty of evidence for the primary outcomes was rated as 'very low' for the association between PA and AF in both the general population and in athletes. The evidence was downgraded primarily for risk of bias and inconsistency due to substantial heterogeneity across the included studies. Detailed GRADE assessments are presented in Supplementary Table 4.

Meta-regression in general population PA studies

Age and proportion of female participants were the only variables applicable for meta-regression. Neither significantly influenced the odds ratio (age: $\beta = -0.010$ per year, 95% CI -0.023 to 0.003, $p = 0.13$; proportion female: $\beta = -0.004$ per 1% increase, 95% CI -0.009 to 0.002, $p = 0.248$). Age explained 1.5% of the between-study heterogeneity ($R^2 = 1.5\%$), while the proportion of female participants explained none ($R^2 = 0\%$) (Supplementary Figure 10, 11).

Meta-regression in athlete studies

Age did not significantly influence the odds ratio (age: $\beta = 0.014$ per year, 95% CI -0.028 to 0.055, $p = 0.517$) and did not explain between-study heterogeneity ($R^2 = 0\%$) (Supplementary Figure 12). Due to the limited number of studies, sex was examined as a categorical moderator (male only, female only, and mixed sex cohorts). Study sex composition did not significantly influence the odds ratio (overall moderator test $QM = 3.83$, $p = 0.147$) and explained 3.5% of the between-study heterogeneity ($R^2 = 3.5\%$) (Supplementary Figure 13).

Further sensitivity analysis

Excluding poor quality studies, general population PA continued to be associated with a reduction in odds of AF (15 studies; OR 0.85; 95% CI 0.79, 0.92, $p = 0.0017$) (Supplementary Figure 14). Only a single athlete study remained after excluding poor quality studies (Supplementary Figure 15).

Excluding studies with self-reported AF and only including AF diagnosed on electrocardiography, general population PA continued to be associated with a reduction in odds of AF (19 studies; OR 0.82; 95% CI 0.72, 0.93, $p < 0.0001$) (Supplementary Figure 16) and increased odds of AF in athletes (12 studies; OR 2.97; 95% CI 1.67, 5.30, $p < 0.0001$) (Supplementary Figure 17).

Leave-one-out sensitivity analysis demonstrated that omission of any individual study did not change the overall interpretation of the findings. In the general population PA studies, pooled odds ratios ranged from 0.75 to 0.80 (Supplementary Figure 18), while in athlete studies they ranged from 2.40 to 3.06 (Supplementary Figure 19). All leave-one-out analyses remained statistically significant.

1 DISCUSSION

2 The U-shaped relationship between PA and AF risk

3 This study is the first meta-analysis to demonstrate the existence of a U-shaped relationship between
4 physical activity (PA) and the risk of atrial fibrillation (AF) across large cohorts of varying PA doses. We
5 showed that PA within the general population is associated with a 22% reduction in the odds of AF, with
6 26 MET-hr/wk associated with the greatest reduction. In contrast, endurance athlete status was
7 associated with a 2.74-fold increase in the odds of AF, with high doses beyond 78 MET-hr/wk associated
8 with the greatest increase.

9 In a previous meta-analysis of 16 general population PA studies, excluding athletes, each 10 MET-
10 hr/wk increase in PA corresponded to a 1.6% reduction in AF risk. (52) Another meta-analysis, including
11 both general population PA and athlete studies, found a decrease in AF risk up to 20 MET-hr/wk, above
12 which no association with AF was observed. (53) Whilst no previous meta-analysis have demonstrated
13 the U-shaped relationship, individual studies have observed such a relationship. A study of over
14 400,000 individuals from the UK Biobank found that total PA reduced AF incidence, however, in males,
15 83 MET-hr/wk of vigorous PA was associated with a 12% increase in AF incidence. (54) Compared to
16 sedentary controls, individuals with over 2000 hours of total lifetime high-intensity training were reported
17 to be at a higher risk of AF (OR 3.88 95% CI 1.55 to 9.73), whereas those below 2000 hours had a
18 significant reduction in the observed risk of AF (OR 0.38 95% CI 0.12 to 0.98). (55)

19 Our study had a much wider scope, was substantially larger than these previous studies, and
20 incorporated the full continuum of PA. We demonstrated that approximately 26 MET-hr/wk was
21 associated with the lowest risk of AF. It was not until approximately 78 MET-hr/wk (the equivalent of 6-
22 7 hours per week of endurance training) that higher levels of PA were associated with a significant
23 increase in AF risk. This study provides the first direct meta-analytical evidence for the existence of this
24 relationship and estimates where the critical points along the dose-response curve may lie. This

observed U-shaped relationship may reflect the balance between the beneficial cardiovascular adaptations associated with PA in the general population and the proarrhythmic effects of prolonged endurance exercise.

The role of sex

The previous meta-analysis involving 6,816 athletes did not report sex differences. (6) In the present analysis, we included 214,523 athletes, with sex-specific data for 127,934 males and 82,617 females. We demonstrated that male athletes have increased odds of AF by 4.21-fold, but despite the inclusion of more recent studies, the risk in female athletes remains uncertain.

Whilst enlarged left atrial (LA) volumes are a risk factor for AF, (56) studies have previously shown that female athletes have smaller indexed atrial volumes. (57) This may leave female athletes less exposed to AF risk. However, there were only four studies that we were able to include in our meta-analysis, and the results were largely dominated by a single cohort study in which any individual competing in a 30km+ XC ski race was classified as an athlete, potentially including those performing lower doses of PA, diluting the effect-size estimates. (47)

Three of the four studies on female athletes were rated as poor in our study quality assessment. The one study deemed good quality, Drca et al., 2023, was the first study to focus solely on elite-level female endurance athletes performing high doses of PA, followed up over 28.8 years, reporting a 2.68-fold increase in the odds of AF. (49) Therefore, the results of this meta-analysis should be interpreted with caution. This highlights the need for future studies to address the risk in female athletes performing high doses of PA.

Further analyses

We observed similarly higher odds of AF in athletes both below and above 60 years of age. However, these odds ratios were calculated from raw event counts rather than adjusted estimates and may therefore have been influenced by potential confounders. Meta-regression demonstrated that neither

age nor the proportion of female participants significantly influenced the pooled odds ratios, although the low representation of female participants across included studies may have limited the power to detect sex-specific associations.

Notably, alcohol consumption was higher in most high PA or athlete groups compared with sedentary or non-athlete groups, highlighting an unaccounted confounding risk factor. However, insufficient studies reported alcohol consumption for meta-regression to be performed. (58)

Additionally, athletes are typically more vigilant about their health, and professional athletes undergo closer monitoring than the general population. The rise in wearable ECG devices allows for self-diagnosis, patient-initiated monitoring and earlier interventions. (59) This may inflate AF incidence in this cohort through detection bias. However, the conclusions of our study were unchanged when studies reporting self-reported AF were removed in our sensitivity analysis.

Limitations

This meta-analysis is limited by substantial heterogeneity, largely due to inconsistent PA reporting methods, varied sport types, and different definitions of PA or athlete status. Subgrouping by sport type suggested that substantial heterogeneity originated from XC skiing studies, primarily from Scandinavian cohorts. To calculate our dose-response, we applied an externally validated method to convert different measures of PA into MET-hr/wk, standardising exposure and reducing reporting bias and between-study heterogeneity. Despite this, most included studies relied on self-reported PA, introducing potential recall bias. No athlete studies used device-recorded PA, and only three general population studies used accelerometer data, limiting meaningful subgroup analyses.

Most included studies did not report baseline cardiovascular risk factors, limiting the assessment of whether PA and AF risk differed according to underlying risk factors seen across populations of different ages. Although our meta-regression did not identify age as a significant moderator of the association

1 between PA and AF risk, this should be interpreted cautiously. Many studies included a broad range of
2 ages, which may contribute to the high heterogeneity.

3 Athlete studies were generally of poor quality, and we observed evidence of publication bias, which
4 may overestimate AF risk. Volunteer bias may also have contributed, as athletes with suspected
5 cardiovascular abnormalities may be more inclined to participate in cardiac-focused research.

6 A further limitation is the inconsistent and often overlapping definitions of high PA and athletes. Some
7 general population PA cohorts likely included athletes, while other cohorts defined athletes based solely
8 on participation in a single sporting event, potentially capturing recreationally active individuals.
9 Importantly, the term “athlete” does not consistently represent a comparable level of physiological
10 exposure to exercise across studies, limiting the ability to accurately assess the relationship between
11 cumulative exercise exposure and AF risk. These limitations contributed to the ‘very low’ certainty of
12 evidence for the primary outcomes according to the GRADE approach. (11) Therefore, the associations
13 between PA and AF should be interpreted cautiously.

14 Furthermore, MET-hr/wk conversions should be interpreted cautiously, as equivalent MET values may
15 not reflect equivalent physiological workloads in trained endurance athletes compared with the less-
16 trained general population. Our dose-response findings suggest that the potential increase in AF risk
17 occurs at exercise exposures substantially above PA guideline recommendations. The estimated
18 threshold of approximately 78 MET-hr/wk corresponds to around 6-7 hours per week of endurance
19 exercise at intensities typically achieved by highly trained athletes, rather than moderate levels of
20 activity recommended in the general population. Therefore, these findings should not discourage PA
21 participation. Instead, they highlight that the relationship between exercise and AF risk may depend on
22 the interaction of accumulated training exposure across a lifetime. Previous work has suggested that a
23 substantial lifetime endurance training exposure of approximately 1500 hours may be associated with
24 increased AF risk, (38) with cumulative training volume, rather than intensity alone, being the key
25 determinant of this risk. (60)

Knowledge gaps

Despite increasing research into exercise-associated AF over recent years, important knowledge gaps remain regarding the mechanisms driving this association and why only some athletes develop AF despite similar PA exposures. The relationship between PA dose, traditional AF risk factors, and individual susceptibility remains poorly understood. PA may provide greater protective effects among individuals with a higher burden of cardiovascular risk factors (older athletes), whereas prolonged exposure to PA in younger athletes with few traditional risk factors may contribute to increased AF susceptibility.

Potential mechanisms may be conceptualised using Coumel's triangle of arrhythmogenesis, (61) whereby athletes may develop an arrhythmogenic substrate (atrial dilation and fibrosis), modulators (increased vagal tone), and triggers (atrial ectopic beats) in response to prolonged endurance training, which may increase susceptibility to AF. (62) These exercise-induced adaptations are unlikely to occur at lower doses of PA seen in the general population, however, the progression from physiological adaptation to pathological remodelling remains uncertain.

The generalisability of current research is also limited. Most study populations consisted of White individuals from developed countries, making other ethnic groups underrepresented. Compared to White men, maximal indexed LA volumes are 2-4 mL/m² smaller in South Asian individuals and 1 mL/m² larger in Black individuals. (63) This highlights important ethnic differences in atrial physiology that are not currently accounted for in AF research among athletic populations. Similarly, women remain substantially underrepresented in athletic cohorts, limiting our understanding of sex-specific differences as discussed above.

Future directions

Future research should focus on large prospective cohorts of well-characterised athletes engaging in high volumes of PA, incorporating the assessment of cumulative PA exposure and AF incidence.

Studies should include detailed assessment of traditional AF risk factors to better identify those who may be particularly susceptible to exercise-associated AF.

Improved standardisation of PA assessment and athlete classification is needed to facilitate more consistent data synthesis across studies. Quantification of device-recorded PA, extraction of data from training platforms, and long-term monitoring may provide a more accurate assessment of cumulative PA dose than categorical athlete definitions alone.

Future studies should also prioritise the inclusion of women and individuals from diverse ethnic backgrounds to establish whether the relationship between PA and AF risk differs across demographic groups.

Ultimately, this may improve our understanding of exercise-associated AF and help identify PA thresholds. If confirmed in future larger prospective studies, these thresholds could inform risk stratification and targeted screening for earlier detection and management of AF.

CONCLUSION

This systematic review and meta-analysis supports the U-shaped association between PA and the risk of AF. Based on our data, the highest levels of PA within the general population are associated with a reduction in AF risk. On the other hand, male athletes appear to carry the greatest risk, while AF risk in female athletes remains uncertain due to limited data. Dose-response analysis suggests that well-trained athletes engaging in approximately 6-7 hours per week of endurance sports, such as cycling, running, or swimming, may represent the threshold beyond which AF risk begins to increase.

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7 DATA AVAILABILITY

8 Data and scripts for all analyses performed in this meta-analysis is available within a .ZIP folder in the
9 supplementary materials.

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