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Exploring the Association Between Physical Activity and Atrial Fibrillation: A Systematic Review of Meta-Analyses

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Abstract

Background: Numerous studies suggest intensive and prolonged exercise is a risk factor for atrial fibrillation (AF); many other studies have shown that regular exercise can protect against AF in the general population. Meta-analyses of these studies have produced conflicting results. Thus, we performed a systematic review of meta-analyses to understand better the evidence base linking exercise and AF.

Methods: We conducted a systematic review of meta-analyses that evaluated the association between physical activity (PA) and AF. A search of MEDLINE, Scopus, and Google Scholar was performed. The Assessing Methodological Quality of Systematic Reviews 2 (AMSTAR 2) measurement tool was used to evaluate the methodological quality of the included reviews.

Results: A total of twelve meta-analyses met the inclusion criteria. Five meta-analyses reported consistent evidence that the risk of AF was increased among athletes compared to non-athletes. The increased risk of AF ranged from OR 1.64(1.10-2.43) to OR 5.3(3.6-7.9). The results were less consistent among studies of different degrees of PA as three reviews suggest that PA was associated with a reduction in AF, but most studies reported no difference in AF risk. Subgroup analyses suggest that individuals younger than 54-60 years and men were more likely to develop AF with PA.

Conclusion: PA has a dose-dependent J-shape effect on AF risk, with increased risk at very low and very high levels of PA. This effect seems to be gender-specific and more pronounced in younger males.

Key Words

Atrial Fibrillation; Exercise; Sports; Sedentary Lifestyle; Physical Activity; Meta-Analysis; Systematic Review

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Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in adults, with an estimated prevalence of 1-2% in the general population[1]. Due to the increasing number of elderly adults and the increasing prevalence of cardiometabolic risk factors associated with AF, an upsurge of AF prevalence has been predicted [2, 3]. A better

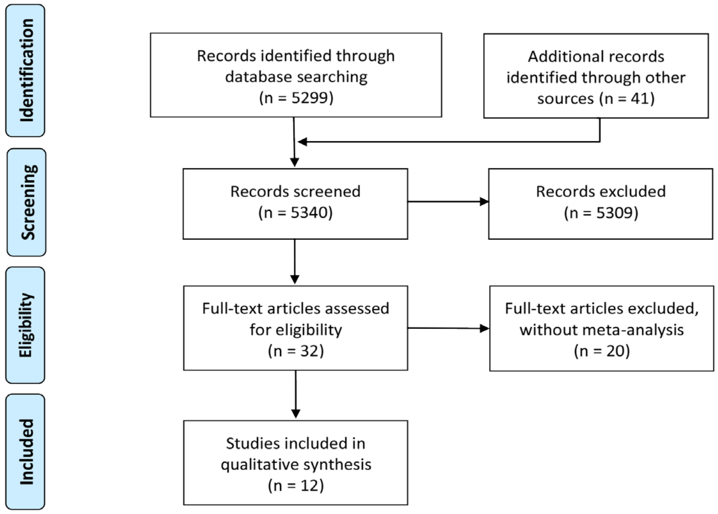

Figure 1: **PRISMA flow chart describing study selection.**

understanding of AF pathophysiology and preventable factors may lead to the development of appropriate preventive programs that could play a significant role in promoting community health and reducing the costs associated with disease management[4,5].

Through its favorable effects on weight, lipids, blood pressure, and cardiorespiratory fitness, physical activity (PA) associates with a lower risk of heart disease.[6] Although numerous studies have suggested that intensive and prolonged exercise as in endurance sports is a risk factor for AF, many other studies have shown that regular exercise can be a protective factor for AF in the general population[7-9]. Over the past two decades, more than 40 studies and twelve meta-analyses have investigated the link between physical exercise and the risk of developing AF. Systematic reviews allow us to enhance our understanding based on accurate, succinct, credible, and comprehensive summaries of the best available evidence on a topic[10]. However, in the case of exercise and AF, the available meta-analyses have produced conflicting results[7,8,11-20]. To improve understanding of this relationship, we performed a systematic review of meta-analyses, evaluating the association between PA and AF from different aspects. In addition, we discussed the possible mechanisms for this association.

2. Methods

2.1 Protocol

We aimed to identify systematic reviews with meta-analysis,which examine the association between PA and AF. This systematic review of meta-analyses was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA Statement[21].

2.2. Eligibility criteria

All studies that evaluated the association between PA and AF, were considered eligible. However, only systematic reviews with meta-analysis were included in the current study. Original papers, case reports, letters, conference abstracts, or comments were not included in this study. There were no restrictions on the definition of PA, which included varying degrees of PA or exercise as well as participants in sports or comparisons of athletes and non-athletes.

2.3. Search

Databases including MEDLINE, Scopus, and Google Scholar, were searched to identify all relevant reviews, without language restriction, published before January 1, 2021. The search terms included the following keywords: ("atrial fibrillation" OR "arrhythmias, cardiac" OR "auricular fibrillation") AND ("physical activity" OR "endurance" OR "exercise" OR "sports" OR "athletes").

2.4. Study selection

Titles and abstracts were screened for the exclusion of unrelated articles. References and citations of included studies were also reviewed for additional reviews that met the inclusion criteria. The selection of studies to be included was independently performed by two reviewers (AM; ASSH).

2.5. Data collection process

Using a data extraction table, the required information from each meta-analysis, including first author's name, publication year, types of included studies, used databases, main inclusion criteria, pooled sample size, age and gender, main findings, and results of subgroup analysis were extracted. In addition, for the results of meta-analyses, the effect estimates (odds ratios, relative risk, hazard ratios) and the number of studies pooled were collected, and any reported measure of statistical heterogeneity. The table was initially completed by one of the first authors (ASSH) and then verified by the other first author to control the accuracy of data entry (AM). After finalizing the first draft of this systematic review of meta-analyses, all corresponding authors (n=11) of the included meta-analyses (n=12) were invited to assess the correctness of the included data and contribute their expert opinion to the manuscript. Seven out of 11 authors accepted the invitation, whereas four authors did not respond. Those seven authors (JA, HA, CR, NDB, MM, CSK, TLLL) revised the entire manuscript and confirmed the authenticity of the final systematic review report after some minor changes.

2.6. Heterogeneity assessment

The heterogeneity between estimates of the AF risks for exposure to a high volume of PA concerning lower PA volume was investigated through Cochrane Q-test and I^2 statistic. Heterogeneity assessment was evaluated by a random effect analysis in which study weights were computed as $wi = 1/(si^2 + t^2)$ where si^2 was the variance estimate from the i-th study, and t^2 was the overall variance. The heterogeneity was investigated for estimates from all meta-analyses as a whole and meta-analyses based on the general population and athletes as well. The sensitivity analysis was conducted in the form of influence analysis, excluding a study at the time. Heterogeneity assessment was reported by forest plot. Heterogeneity assessment, forest plots, and influence analyses were performed using the metan and metaninf function of the STATA software (vers.12). We did not aim to perform an estimate of a meta-analysis of meta-analyses in order to avoid duplication bias.

2.7. Quality assessment

The Assessing Methodological Quality of Systematic Reviews 2 (AMSTAR 2) measurement tool was used to evaluate the

Table 1: Characteristics of include dreviews

Reference	Primary studies (n); Types	Participants (n)	Main Databases	Main inclusioncriteria	Age (A) Gender (G)	Subgroupanalyses	Main aim/question of review
Abdulla [7], 2009	6 Case-control [6]	1550	Medline EMBASE Cochrane	Case–-control studies reporting the number of AF or AFlu in athletes compared with controls	A: 51 ± 9 years G: 93% male	N/A	Is the risk of AF higher in athletes than in the general population?
Nielsen [8], 2013	10 Case control [6] Cross-sectional [4]	1550 (onlycase-controls)	Medline EMBASE Cochrane	Case–-control studies reporting number of incidental AF or AFlu in athletes compared with non-athletes	A & G: N/A	-Athletes and non-athletes -PA categories	To examine the relationship between PA and risk of new-onset AF or AFlu.
Ofman [11], 2013	4 Prospectivecohort [4]	95526	Medline EMBASE Cochrane	Both prospective cohort and case–-control studies examining the relation of regular PA and AF risk	A & G: N/A	N/A	To examine the association between regular physical activity and the risk of AF
Kwok[12], 2014	19 Post hoc RCT [2] Cohort [10] Case-control [7]	511503	Medline EMBASE	1. Studies assessing the link between the history of PA and the subsequent risk of AF 2. Studies assessing outcomes in athletes for PA 3. There was no strict definition of PA	A: Range 41-73 years G: N/A	-Nature of PA -Studies quality	To examine the relationship between AF and the extent of PA
Brunetti[13], 2016	11 Post hoc RCT [1] cohort [5] Case-control [5]	81787	Medline	1. Studies assessing the risk of developing AF in subjects practicing PA or sport activity 2. There was no strict definition of PA	A: Range 43-73 years G: N/A	-Gender -Age groups	To examine the association of age and gender with the Incidence of AF in subjects practicing PA
Mohanty[14], 2016	22 Cohort [12] Case-control [5] Post hoc RCT [1] Cross-sectional [2] Prospective observational [1] Retrospective [1]	656750	Medline Bio Med Centra Cardio source EMBASE clinicaltrials.gov ISI Web of Science	1. Report relation between PA and incidence of AF 2. A case-control or population-based design 3. Specify AF incidence and number of participants for men and women	A & G: N/A	-Athletes and non-athletes -Gender -PA categories	To examine the association of different intensities of PA with the risk of AF in Men and Women
Zhu [15], 2016	13 Post hoc RCT [2] Prospective cohort [10] Case-control [1]	568072	Medline Cochrane Science Direct	Studies estimating the association between PA and developing AF in the general population	A & G: N/A	-PA categories -Region -Gender	To examine the association between PA and incident AF, as well as to determine whether a sex difference existed
Ricci [16], 2018	19 Cohorts [18] Case-control [1]	29855 (all were AF subjects)	Medline EMBASE Cochrane CINAHL	Studies reported relative risk (RR) estimates of the association between PA and AF in the general population	A & G: N/A	-Region -Publication date -Studies quality -Adjustment for CAD RFs	To examine the association between PA volume and AF risk
Ayinde [17], 2018	8 Cohorts [6] Case-control [2]	9113	Medline EMBASE Scopus SPORT Discus	Studies assessed the association between competitive or semi-competitive sports and AF	A & G: N/A	-Studies quality -Age groups	To examine the association between competitive sports sport and AF risk
Li [18] 2018	9 Cohort [3] Case-control [4] Cross-sectional [2]	8901	PubMed Embase Cochrane	1. Case-control or cohort studies that focused on the association of endurance exercise and AF 2. Comparison of athletes group with non-athletes group (control).	A: mean age 39-72.8 years G: N/A	-Gender -Mean age -Study type -Sample size -Sports mode	To quantitatively assess the risk of AF in athletes and the general population
Garlipp [19] 2019	11 Cohort [10] Post hoc RCT [1]	276323	Medline BVS Health Cochrane	All cohort studies, prospective, cross-sectional, observational and randomized clinical trials with patients who performed physical exercises and the development of AF.	A: Range 12-90 years G: N/A	N/A	To analyze the effects of physical activity on the incidence of AF
Mishima [20] 2020	15 Prospective cohort studies	1,464,539	Medline Embase	Prospective cohort studies, with a minimum follow-up of 4 years, reporting the association between PA and incident AF	A: median age 55.3 years G: 51.7 % female	-Gender	to systematically summarize the evidence on the 82 association between PA and risk of AF

AF: Atrial fibrillation; AFlu: Atrial flutter; N/A: Not available; PA: physical activity; CAD RFs: Coronary artery disease risk factors; RCT: Randomized Controlled Trial

Table 2: A summary of main findings of conducted meta-analyses

Reference	Studies and Participants (n)	Effectsize (95% CI)	Narrative findings	Definition forphysical activity
			Studies comparing athletes versus non-athletes	
Abdulla [7], 2009	6 studies 1550	OR=5.29 (3.57 - 7.85)	The risk of AF or atrial flutter was significantly higher in athletes than in controls.	N/A
Nielsen [8], 2013	6 studies 1550	OR=5.3 (3.6- 7.9)	AF increased in athletes compared to non-athletic	N/A
Kwok [12], 2014	6 studies 1973	RR=1.98 (1.00 - 3.94)	The risk of AF was increased in athletes or participants with a history of sports activity (low-quality studies) in comparison with controls	N/A
Ayinde [17], 2018	8 studies 9113	OR=1.64 (1.10 - 2.43)	Athletes have an increased risk of AF compared to the general population. Age appears to modify the risk of AF in athletes	Competitive or semi-competitive sports (no further definition)
Li [18] 2018	9 studies 8901	OR=2.34 (1.04–5.28)	The risk of AF was significantly higher in athletes than in the general population	N/A
			Studies comparing high PA versus low PA	
Ofman [11], 2013	4 studies 95,526	OR=1.08 (0.97-1.21)	AF was not different in maximum versus the minimal amount of PA	Based on cumulative PA per week (4-5 categories)
Nielsen [8], 2013	3 studies N/A	OR=0.92 (0.80 - 1.05)	AF was not different in high PA compared with low PA	N/A
Zhu [15], 2016	10 studies N/A	RR=0.98 (0.90 - 1.06)	Comparing the most physically active vs. the least physically active groups	PA categories
Ricci [16], 2018	19 studies 29,855	RR= 0.97 (0.85 - 1.10)	High PA, in comparison to low PA, did not affect AF risk	Based on MET-h/week <3 (light intensity PA like slow walking) 3–6 (moderate intensity PA like slow cycling) >6 (vigorous-intensity PA like fast running).
Garlipp [19] 2019	11 studies 276,323	RR=0.914 (0.833 - 1.003)	Individuals who exercise are less likely to have AF.	N/A
			Studies comparing high PA versus no PA	
Nielsen [8], 2013	3 studies N/A	OR=0.78 (0.68 - 0.89)	AF reduced in high PA compared with no PA	N/A
Kwok [12], 2014	8 studies 152,925	RR=1.0 (0.82 - 1.22)	Engaging more intensive PA in comparison with controls had no effect on AF risk	N/A
Mohanty[14], 2016	7 studies 93,995	OR=2.47 (1.25 - 3.7)	A sedentary lifestyle compared to moderate or intense activities was RF for AF	Study reports (Based on 3 to 5 PA or exercise levels)
Brunetti[13], 2016	11 studies 81,787	OR=0.92 (0.84 - 1.01)	The risk of AF was not significantly higher in subjects practicing PA than in controls	Nostrictdefinition
Zhu [15], 2016	11 studies N/A	RR=1.07 (0.93 - 1.25)	The risk of AF was not significantly increased in individuals with intensive physical activity (vigorous, high intensity, or heavy workload)	High-intensityexercise>2000 hours
Garlipp [19] 2019	11 studies 276,323	RR=0.914 (0.833 - 1.003)	Individuals who exercise are less likely to have AF.	N/A
			Studies comparing high PA versus moderate PA	
Nielsen [8], 2013	3 studies N/A	OR=1.01 (0.88 - 1.17)	AF was not different in high PA compared with moderate PA	N/A
			Studies comparing high/moderate PA versus low/no PA	
Nielsen [8], 2013	2 studies N/A	OR=0.89 (0.83 - 0.96)	AF reduced in moderate/high PA compared with none/very low PA	N/A
Kwok [12], 2014	4 studies 112,784	RR=0.95 (0.72 - 1.26)	Spending more time on PA in comparison with controls had no effect on AF risk	N/A
Mishima [20] 2020	15 studies 1,464,539	HR 0.94, (0.90-0.97)	PA at guideline-recommended levels and above are associated with a significantly lower AF risk. However, at 2000 MET-minutes per week and beyond, the benefit is less clear	N/A

AF: Atrial fibrillation; CI: confidence interval, N/A: Not available; PA: physical activity; MET-h: Briefly, a metabolic equivalent (MET-h) is defined as an energy expenditure of 1 kcal/kg per h and is roughly equivalent to the energy cost of sitting quietly. OR: odds ratio, RR: risk ratio

methodological quality of the included meta-analysis[22]. The AMSTAR contained 16 items for quality assessment of the reported information. Then studies were classified into four different groups critically low, low, moderate, and high based on the result of quality assessment calculated online via https://amstar.ca/. Quality assessment was performed by two different assessors (AM and ASSH) and a third assessor (CR) for discrepancies.

3. Results

3.1. Selection of meta-analyses

A total of 5340 unique abstracts were retrieved in electronic databases and manual cross-checking of reference lists. From this, 5309 were

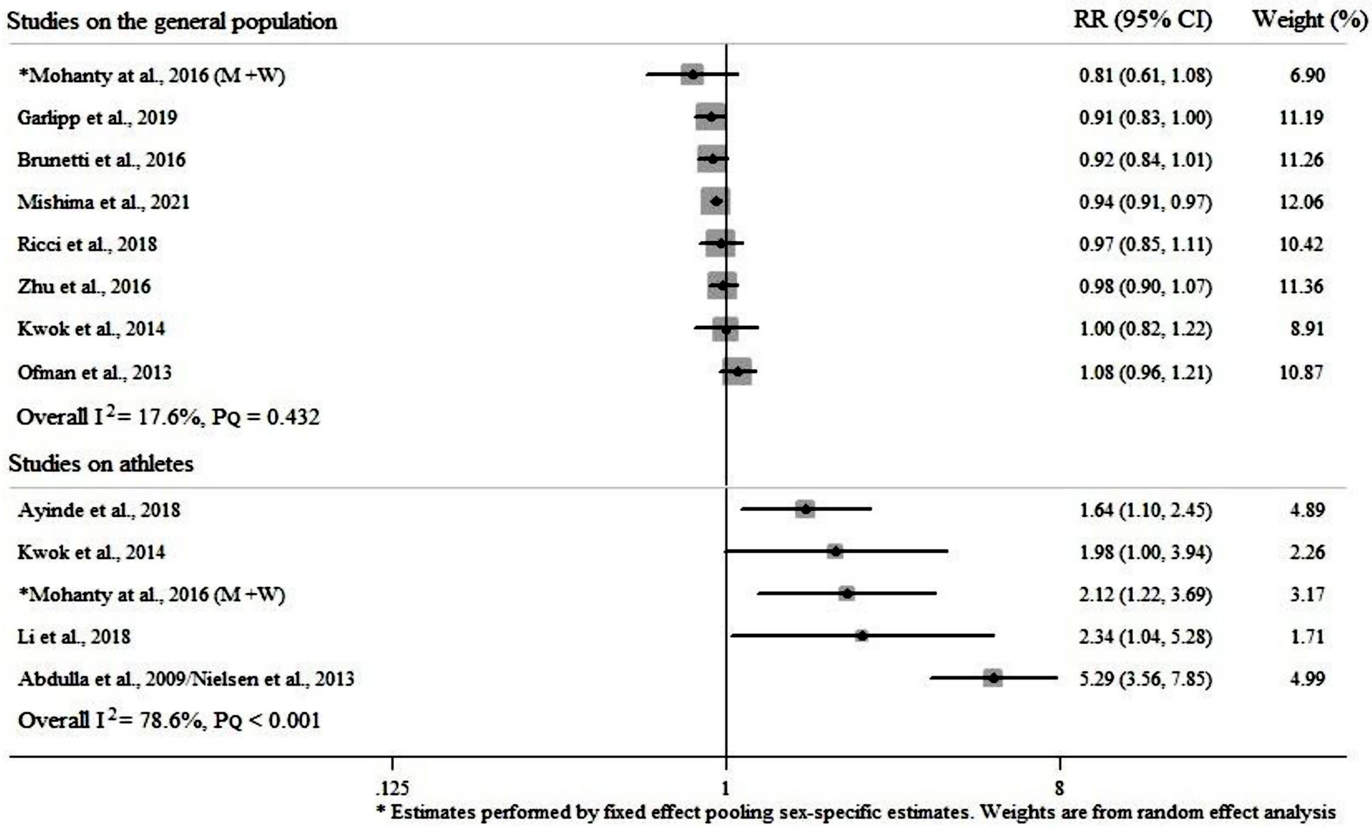

Figure 2: Forest plot of meta-analytical estimates of AF risk for higher vs. lower physical activity volume in athletes and the general population. PQ is the P-value for the Cochrane Q test for heterogeneity

excluded, and the full text of the remaining 32 review articles was studied in detail. Finally, 12 meta-analyses were included in this review (Figure 1).

3.2. Characteristics of included meta-analyses

The included systematic reviews and meta-analyses are summarized in Table 1. The reviews were published over an 11-year period between 2009-2020. The review with the largest pooled sample size was authored by Mishima et al. (n=1,464,539)[20], while the smallest was the first published study by Abdulla et al. (n=1,550)[7]. The pooled gender ratio was reported only in two studies [7, 20], and the pooled age was reported by six studies [7, 12, 13, 18-20]. Most of the reviews, included studies of only case-control or cohort/post hoc analysis of randomized controlled trials in design, but two reviews did include cross-sectional studies (Table 1).

Subgroup analyses were performed in most of the studies (11/12). The most common types of subgroup analyses were for PA categories and gender. Ricci et al.[16] performed the greatest variety of subgroup analyses, including region, publication date, studies quality, and adjustments for CAD risk factors (Table 2-3). Most of the conducted meta-analysis compared AF risk in two groups of high PA versus no PA (n=6), or high PA versus low PA (n=6); followed by athletes versus non-athletes (n=5), high/moderate PA versus low/no PA (n=4), and high PA versus moderate PA (n=1) (Table 2).

3.3. Main findings

3.3.1. Studies comparing athletes versus non-athletes

Five meta-analyses assessed the differences in AF risk between athletes and non-athletes [7, 8, 12, 17, 18]. These found a significantly higher risk of AF or atrial flutter in athletes compared with non-athletes or controls (odd ratio (OR) range [95% CI] 1.64 [1.10-2.43] - 5.3 [3.6-7.9] and relative risk (RR) range 1.98 [1.00-3.94] [7, 8, 12, 17, 18] (Table 2).Results from heterogeneity assessment pointed out a large variability when all studies were considered a whole (I^2 = 88.6%). Nevertheless, a low variability among AF risks estimates from studies conducted on the general population was observed (I^2 = 17.6%). On the other hand, a consistent heterogeneity among AF risks estimates from meta-analyses conducted among athletes was observed (I^2 = 78.6%) (Figure 2). The heterogeneity from meta-analyses conducted among athletes was nullified (I^2 = 0%) in a sensitivity analysis, excluding the study with the highest AF risk[7].

3.3.2. Studies comparing high versus low/no physical activity

Five out of five meta-analyses revealed no difference between low PA and high PA for risk of AF [8, 11, 15, 16, 19] (Table 2).

3.3.3. Studies comparing high versus no physical activity

Two different categories of results were found in this group of studies. Three studies found no significant difference in AF risk between high PA and no PA[12, 13, 15], whereas three others found a protective effect of high PA on AF development[8, 14, 19] (Table 2).

Table 3: Studies comparing the impact of PA on AF based on different factors

Reference	Subgroups Effectsize (95% CI)		Narrative findings
Genders			
Brunetti[13], 2016	Male OR=7.49 (3.12 - 19.01)	Male and/or female OR=0.89 (0.81– 0.97)	The risk of AF seems higher in male subjects practicing physical exercise
Mohanty[14], 2016	Male Moderate 0.81 (0.26 - 1.003) Intense 3.30 (1.97 - 4.63)	Female Moderate 0.91 (0.78 - 0.98) Intense 0.72 (0.57 - 0.88)	Moderate and intense exercise compared to sedentary were protective factors for AF in women. Although moderate exercise was a protective factor, intense exercise was a risk factor for AF in men.
Mohanty[14], 2016	Male Athletes 3.3 (1.72 - 5.91) Non-athletes 3.4 (1.26 - 5.42)	Female Athletes 0.67 (-0.59 - 1.92) Non-athletes 0.85 (0.51 - 1.21)	Vigorous PA versus leisure-time exercise in man was found to be associated with a significantly high risk of AF in athletes with endurance sports practice
Zhu [15], 2016	Male Total PA RR=1.18 (1.02 - 1.37) Intensive PA RR=1.12 (0.99 - 1.28)	Female Total PA RR=0.92 (0.87 - 0.97) Intensive PA RR=0.92 (0.86 - 0.98)	Association between total PA exposure and the risk of AF Association between total intensive PA exposure (vigorous, high intensity, or heavy workload) and the risk of AF
Li [18] 2018	Male Athletes OR=4.03 (1.73–9.42)		The risk of AF was significantly higher in athletes compared with the general population, especially in male athletes <60 years old.
Mishima[20], 2020	PA above the guideline-recommended level Male HR 0.96 (0.93 – 1.00) Highest PA HR 1.03 (0.94 – 1.12)	PA above the guideline-recommended level Female HR 0.91, (0.88-0.95) Highest PA HR 0.88 (0.83 – 0.92)	PA above the guideline-recommended level was associated with a lower risk of incident AF in women and men. Highest PA was associated with a lower risk of AF in women, but not in men, compared to inactive.
Age			
Brunetti[13], 2016	Younger than 54 years OR=5.30 (3.43 - 8.20)	Olderthan 54 years OR=0.84 (0.76 - 0.92)	A reverse correlation between age and risk of AF seems to be evident
Ayinde[17], 2018	Younger than 54 years OR=1.96 (1.06 - 3.65)	Olderthan 54 years OR=1.41 (0.81 - 2.44)	Age appears to modify the risk of AF in athletes.
Li [18] 2018	Younger than 60 years OR=3.24 (1.23 - 8.55)		The risk of AF was significantly higher in athletes compared with the general population, especially in male athletes <60 years old.
Region			
Zhu [15], 2016	American RR=0.95 (0.86 - 1.06)	Non-American RR=1.05 (0.86 - 1.27)	The impact of total PA on AF risk was not related to the region of studies
Zhu [15], 2016	American RR= 1.02 (0.89 - 1.17)	Non-American RR: 1.23 (0.68 - 2.21)	Impact of Intensive PA (vigorous, high intensity, or heavy workload) on AF risk was not related to the region of studies
Ricci [16], 2018	American RR=1.24 (0.97 - 1.60)	Non-American Europe RR=0.86 (0.71 - 1.04) Australia and New Zealand RR=0.80 (0.62 - 1.03)	The impact of PA on AF risk was not related to the region of studies
Publicationrelatedissues			
Kwok[12], 2014	Low risk of bias OR=0.80 (0.52 - 1.24)	High risk of bias OR= 1.12 (0.94 - 1.32)	The impact of any PA or leisure-time activity on AF risk was not related to the bias risk of the studies
Kwok[12], 2014	Low risk of bias RR=1.04 (0.87 - 1.24)	High risk of bias OR=1.04 (0.73 - 1.49)	The impact of intensive PA on AF risk was not related to the bias risk of the studies
Ricci [16], 2018	NOS1>6 RR= 1.06 (0.92 - 1.22)	NOS≤6 RR= 0.87 (0.66 - 1.14)	The impact of PA on AF risk was not related to the quality score of studies
Ayinde[17], 2018	NOS ≥ 6 OR=2.23 (1.45 - 3.41)	NOS < 6 OR=1.22 (0.81 - 1.83)	The impact of PA on AF risk was related to the quality score of studies
Ricci [16], 2018	After median RR= 1.02 (0.66 - 1.57)	Before median RR= 0.96 (0.85 - 1.08)	The impact of PA on AF risk was not related to the publication date of studies
Li [18] 2018	Case control group OR=5.10 (3.07–8.46)		In the subgroup analysis based on study type, a significant risk was found in the case control group
Sample size			
Li [18], 2018	sample sizes <300 OR=4.91 (3.08 - 7.84)		Based on the sample sizes, the group with sample sizes <300 demonstrated significant results
Mode of sport			
Li [18], 2018	Single typesports OR=3.97 (1.16 - 13.62		In the subgroup analysis based on sports mode, a significantly increased risk was found in the group with a single type

1: NOS: Newcastle Ottawa Quality

3.3.4. Studies comparing high/moderate versus low/no physical activity

In this category, although Nielsen et al. and Mishima et al. reported a reduction in AF with moderate/high PA compared to none/very low PA[8, 20]; the review by Kwok et al. showed no significant difference between any physical activity or leisure-time activity and risk of AF (RR 0.95 [0.72-1.26])[12] (Table 2).

3.3.5. Studies comparing high versus moderate physical activity

The only conducted meta-analysis on this issue revealed that AF risk was not significantly different for individuals with high levels of PA versus moderate levels of PA (OR 1.01 [0.99-1.17]) [8] (Table 2).

3.4. Subgroup analyses

3.4.1. Gender and Age Subgroups

Subgroup analysis based on gender suggests that men have a greater risk of AF with PA[13-15, 18]. Mishima et al. reported that PA above the guideline-recommended level was associated with a lower risk of AF in women, but not in men[20]. In two meta-analyses, a subgroup analysis of patients younger and older than 54 years was performed [13, 17], and

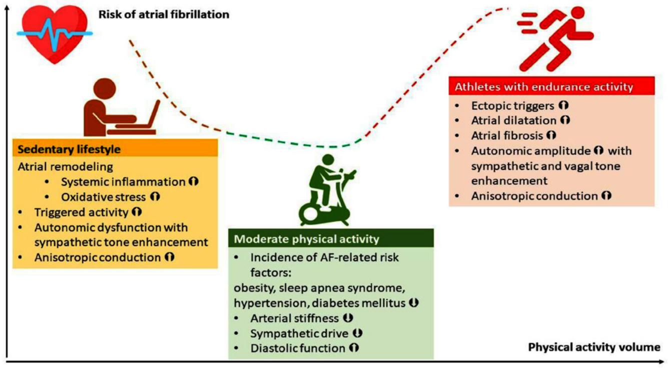

Figure 3: Different possible mechanisms through which physical activity may contribute to atrial fibrillation.

individuals younger than 54 years in both studies reported a higher risk of AF. In contrast, individuals older than 54 years showed no association between PA and AF[17] or a protective effect of exercise [13] (Table 3). Li et al. showed that AF risk was significantly higher in male athletes <60 years old the general population[18].

3.4.2. Geographic regions

Two meta-analyses reported that the influence of American and non-American studies on PA on AF risk, and the studies conclude that the impact of PA on AF risk was not significantly affected by the region where the study took place[15, 16] (Table 3).

3.4.3. Publication related issues

In two studies, the impact of "included studies quality" was assessed[16, 17], while in two meta-analyses, the effect of publication bias was investigated[16, 20]. These studies revealed that neither publication bias nor quality scores were associated with the impact of PA on AF risk. In another study, the effect of the publication date of studies was assessed, which showed no significant impact too[16] (Table 3). The impact of sample size and mode of sport on the risk of AF was also reported by Li et al.[18]

3.4.4. Levels of Activity

Ricci et al.[16] performed the only meta-analysis linking exercise dose to the risk of AF. They showed that in individuals with PA at volumes of 5–20 metabolic equivalents per week (MET-h/week), PA was associated with a significant reduction of AF risk (RR for 19 MET-h/week=0.92 (0.87 - 0.98). By comparison, PA volumes exceeding 20 MET-h/week were unrelated to AF risk (RR for 21 MET-h/week=0.95 (0.88 - 1.02).

3.4.5. Sports mode

In the subgroup analysis based on sports mode - performed by Li et al. [18], a significantly increased risk was found in the group with a single type of sport (OR=3.97, 95% CI=1.16–13.62, $P_{heterogeneity}$=.018, I^2=70.4%)

3.5. Quality assessment

The overall quality of the included studies using the AMSTAR-2 tool was evaluated and reported in Table 4.

4. Discussion

4.1. Main findings

The main findings of this systematic review can be summarized as follows: First, there is consistent evidence from few reviews that athletes are at greater risk of AF than non-athletes. Second, in a general population with both genders, there is evidence that high or moderate PA compared to low or no PA is associated with a lower risk of AF. Third, the literature suggests that men are more likely to develop AF with PA compared to women. Finally, patients younger than 54-60 years appear to have a greater risk of AF with increased levels of PA.

4.2. Overview of the results of twelve different meta-analyses

Abdulla and Nielsen published the first meta-analysis of 6 case-control studies in 2009 [7]. They then published another meta-analysis in 2013, which now included prospective comparative data on the intensity of PA in populations with and without AF [8]. Despite the addition of newer studies, they still found an increased risk of AF in athletes than non-athletes or the general population. Nevertheless, a new observation from the three prospective studies was that moderate/high habitual PA was associated with a significantly reduced risk of AF compared with none or very low-intensity PAOR=0.89[8].

Also, in 2013, Ofman et al. published a meta-analysis with the opposite result: "Our data do not support a statistically significant association between regular PA and increased incidence of atrial fibrillation" [11]. The reason for the disparate findings was likely that Ofman et al. evaluated the relation between increased level of PA and AF among non-athletes, while Nielsen et al. conclusion was mainly based on the comparison between athletes and non-athletes.

In 2014, Kwok et al. performed a larger meta-analysis of 19 studies including ≈ 511k individuals and confirmed the findings of Ofman et al. that there was no association between higher levels of PA and AF [12]. Further more, due to the larger size of the study, Kwok et al., were able to conduct subgroup analyses based on the effect of vigorous PA, level of PA.

The meta-analysis by Brunetti et al. from 2016 also confirmed previous findings that found no significant associations between PA and increased risk of AF[13]. Brunetti et al. even noted a trend towards a lower risk of AF, though the strength of this finding was limited by high heterogeneity [13]. The heterogeneity might be due to gender and age; they argued that AF development risk seemed to be increased in studies enrolling younger and male subjects[13].

The gender-dependency of AF hypothesis was then re-assessed by Zhu et al. and Mohanty et al. Zhuet al. showed that increased PA exposure was associated with an increased risk of AF in males, with a significantly reduced risk of AF in women [15]. Similarly, Mohanty et al., found intensive PA associated with an increased risk of AF in men and a decreased risk of AF in women [15].

Mohanty et al. also observed that a sedentary life style significantly increases the risk of AF while a moderate amount of PA reduces the risk of AF[14]. Ricci et al. described a J-shaped relation between PA volume and AF risk, where PA at volumes of 5 to 20 MET-h/week

Table 4: Evaluation of quality of included studies using the AMSTAR-2 tool

Reference	Components of PICO[1]	Registered protocol	Eligibility criteria	Search strategy	Duplicated study selection	Duplicated data extraction	Excluded studies list	Included studies description
Abdulla (7), 2009	Yes	No/Unclear	Yes	Partial Yes	Yes	Yes	No/Unclear	Partial Yes
Nielsen (8), 2013	Yes	No/Unclear	Yes	Yes	Yes	Yes	No/Unclear	No/Unclear
Ofman(11), 2013	Yes	No/Unclear	Yes	Partial Yes	Yes	Yes	No/Unclear	Yes
Kwok(12), 2014	Yes	No/Unclear	Yes	No/Unclear	Yes	Yes	No/Unclear	Yes
Brunetti(13), 2016	Yes	No/Unclear	Yes	No/Unclear	Yes	Yes	No/Unclear	No/Unclear
Mohanty(14), 2016	Yes	No/Unclear	Yes	Yes	Yes	Yes	No/Unclear	Yes
Zhu (15), 2016	Yes	No/Unclear	Yes	Partial Yes	Yes	No/Unclear	No/Unclear	Yes
Ricci (16), 2018	Yes	No/Unclear	Yes	Partial Yes	Yes	No/Unclear	No/Unclear	Yes
Ayinde(17), 2018	Yes	No/Unclear	Yes	Partial Yes	No/Unclear	Yes	No/Unclear	Partial Yes
Li (18), 2018	Yes	No/Unclear	Yes	Yes	No/Unclear	No/Unclear	No/Unclear	Yes
Garlipp(19), 2019	Yes	No/Unclear	Yes	Yes	Yes	Yes	No/Unclear	Yes
Mishima(20), 2020	Yes	Yes	Yes	Yes	No/Unclear	Yes	No/Unclear	Yes

1: **PICO:** Patient, intervention, comparison, outcome

Yes Partial Yes No/Unclear

was associated with a reduced AF risk, whereas both, sedentary lifestyle and intensive PA of more than 20 MET-h/week, showed no protective effect on AF risk and no difference in direct comparison.

Two different meta-analyses by Ayinde et al.[17]. and Li et al.[18], both conducted in 2018, reconfirmed the early findings from Abdulla and Nielsen, and showed that athletes have an increased risk of AF compared to the general population. Subgroup analysis by Ayinde et al.[17] demonstrated an increased risk for adults younger than 54 years. Li et al. similarly reported an increased risk for men younger than 60 years.

Garlipp et al.[19] included studies with athletes and studies with the general population in their meta-analysis. The combined analysis of the studies did not suggest a significant increase in AF in subjects submitted to exercise (RR = 0.914, 95% CI = 0.833 – 1.003, heterogeneity: $p < 0.001$). Garlipp et al. concluded that individuals who exercise are less likely to have AF.

In 2020, Mishima et al.[20] published a meta-analysis with the most participants so far. It included 1,464,539 individuals. According to their results, individuals achieving the guideline-recommended level of PA (450 MET-minutes per week)had a significantly lower risk of AF (HR 0.94, 95% CI 0.90-0.97, p=0.001). Dose-response analysis showed that PA levels up to 1900 MET minutes per week were associated with a lower risk of AF, with less certainty beyond that level.

The publication of 12 meta-analyses on AF and PA in the last 12 years demonstrates a strong interest in the topic. Individual meta-analyses led to different, apparently contrary conclusions. Our interpretation of the existing body of evidence refers to a dose-response association between PA dose and AF risk. Whereas moderate PA seems to have a protective effect, it seems that no PA and vigorous exercise may increase the risk for AF. The next question is whether the pathophysiology supports the epidemiologic observations.

4.3. Potential mechanisms for altered risk of AF with physical activity

4.3.1. Athletes are more at risk of AF than non-athletes

AF pathophysiologyis characterized by Coumel's triangle consisting of focal triggers, arrhythmogenic substrate created by e.g. increased left atrial size with anisotropy and fibrosis, and additional factors as autonomic imbalance or disturbed electrolyte homeostasis[23-25].

Typical, non-athletic patients with AF are overweight elderly patients with arterial hypertension. Athletes with AF exhibit a different phenotype. So even though similar pathophysiology may exist in both non-athletic patients and athletes with AF, other mechanisms or a different degree of influence of the above-mentioned factors seems likely (Figure 3).

Athletes show specific characteristics that may favor the development of AF. These characteristics mainly occur in endurance athletes, which seem to be more prone to AF than athletes from non-endurance sports [26]. In addition, athletes exhibit an increased autonomic influence by both antipodes of the autonomous nervous system, the vagal and the adrenergic system[27].

Strong support of an exercise-induced model of AF came from Guasch et al., who compared exercised rats with sedentary control rats. Training caused enhanced atrial fibrosis, increased AF vulnerability, and vagal tone. Detraining reversed AF vulnerability and vagal tone[28]. Studying human subjects, Wilhelm et al. reported that vagal activity, p-wave duration, premature atrial contractions, and LA volume were associated with lifetime training hours in a study with runners[29].

Wijffels et al. observed in goats that atrial refractory period shortening (electrical remodeling) by pacing occurred directly, where as persistent AF occurred after two weeks. The authors hypothesized, therefore, that persistent AF needed a "second factor" [30]. A potential "second factor" could be an atrial structural disease such as tissue fibrosis [31].

Findings of direct histological substrate characterization in patients with AF have also confirmed atrial substrates' presence, mainly fibrosis, in the development and progression of AF[32].

Another risk factor for AF is arterial hypertension[33]. Arterial hypertension leads to impaired diastolic function by cardiac remodeling and associates with an enhanced risk of AF [33-35]. Thus, arterial hypertension induced and/or enhanced by exercise may also increase the probability of developing AF in athletes. However, as only a minority

Table 4: Evaluation of quality of included studies using the AMSTAR-2 tool (continued)

Reference	UseRoBassessmenttechniques	Report on the funding source for the included studies	Appropriate meta-analysis method	Assessment ofRoBimpact	Attention to RoB in interpreting/discussing the results	Heterogeneityexplanation	Publicationbiasassessment	Conflict of interest or Funding report
Abdulla (7), 2009	No/Unclear	No/Unclear	Yes	No/Unclear	No/Unclear	Yes	No/Unclear	Yes
Nielsen (8), 2013	No/Unclear	No/Unclear	Yes	No/Unclear	No/Unclear	Yes	Yes	Yes
Ofman(11), 2013	Yes	No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Kwok(12), 2014	Yes	No/Unclear	Yes	No/Unclear	No/Unclear	Yes	Yes	Yes
Brunetti(13), 2016	No/Unclear	No/Unclear	Yes	No/Unclear	Yes	Yes	No/Unclear	Yes
Mohanty(14), 2016	Yes	No/Unclear	Yes	Yes	No/Unclear	Yes	Yes	Yes
Zhu (15), 2016	Yes	No/Unclear	Yes	Yes	Yes	Yes	No/Unclear	Yes
Ricci (16), 2018	Yes	No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Ayinde(17), 2018	Yes	No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Li (18), 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Garlipp(19), 2019	No/Unclear	No/Unclear	Yes	No/Unclear	No/Unclear	Yes	No/Unclear	Yes
Mishima(20), 2020	Yes	No/Unclear	Yes	Yes	No/Unclear	Yes	Yes	Yes

1:**RoB:** risk of bias

Yes Partial Yes No/Unclear

of athletes develop AF, it is still unknown, which specific factors most likely determine the AF risk. In addition, genome-wide association studies in the general population described common variants in specific genomic regions related to AF[36]. Nonetheless, no typical mutation has been reported in athletes with AF.

4.3.2. In the general population, moderate physical activity seems to be protective against AF

Regular PA by physical work, moderate leisure-time sports, or daily commuting by walking or using a bicycle has many positive effects on physical and mental health. It increases general fitness, helps to maintain average weight, blood pressure,and blood sugar [26]. In addition, regular PA has positive effects on mood and mental health. It may balance the negative effects of the increasingly sedentary lifestyle in industrialized countries, and there is evidence that it increases life expectancy.

As regular PA counteracts risk factors for AF as overweight, arterial hypertension, and diabetes mellitus, it is not surprising that a sedentary lifestyle is associated with an increased prevalence of AF. In contrast, regular physical work seems to reduce the risk for AF.

Still though, our review cannot answer the often-asked: What distinguishes athletic activities that seem to increase the risk for AF from daily life physical activities that decrease the risk? It seems logical that PA volume and intensity are increased in athletes, compared to "normal" physical in the general population. Another factor might be the increased vagal and adrenergic activity in athletes, compared to the general population. Thus, the dose response relation between PA volume and AF risk appears to follow a J- or U-shaped curve. PA at the bottom of the curve with volumes of 5 to 20 MET-h/week may result in a reduced risk for AF, whereas lower and higher volumes of PA may lead to an increased risk for AF[16].

4.3.3. In the male gender, physical activity seems to act as a risk factor for AF development, while in females as a protective factor

Male gender has been found as a risk factor for AF in athletes [37]. At similar amounts of exercise, males showed - compared to females - a more pronounced atrial remodeling and an impaired diastolic function. In addition, arterial hypertension at rest and during exercise and an increased sympathetic tone in males might increase the AF susceptibility [37]. Another reason may be the taller stature of males that associates with increased LA size as an independent risk factor for AF [38,39]. However, Myrstad et al. observed that intensive endurance exercise might also increase AF's risk among athletic females [40].

4.3.4 Physical activity in individuals younger than 54-60 years old is associated with a higher risk of AF

We do not know yet why PA in individuals younger than 54-60 years is associated with a higher risk of AF. We hypothesize that this finding is caused by the effect of several competing, age-dependent risk factors and protective factors. Nevertheless, we can assume that exercise volume and intensity might be greater in younger individuals than in older individuals with the corresponding increased effects on the autonomous nervous system. Perhaps the susceptibility of the autonomous nervous system by intensive exercise decreases with advanced age? Perhaps intensive exercise makes AF occur earlier in people with a predisposition for the development of AF?

As advanced age on its own also is a risk factor for AF, the risk modifying effect of exercise seems to become less important or may even reduce the risk for AF in individuals older than 54-60 years.

4.3.5 Previous literature

Valenzuela et al.[41] first published a meta-analyses review to summarize the evidence on the association between PA/sports practice and AF risk. The authors included 11 meta-analyses in their research. We suggest a slightly different interpretation of the existing body of evidence than the interpretation of Valenzuela et al.. In their summary, they stated that"according to the meta-analytical evidence that is currently available, overall PA does not appear to influence the risk of AF, but sports practice, particularly in endurance events, can increase AF risk." In contrast to Valenzuela, we interpret the existing body of evidence that moderate PA compared to no PA is associated with a lower risk of AF in a general population. Whereas gender and age were not analyzed by Valenzuela et al., our results suggest that males and patients younger than 54-60 years are more likely to develop AF with increased levels of PA. As Valenzuela et al. we can confirm that athletes are at greater risk of AF compared to non-athletes. An essential aspect of our manuscript is that most of the authors of the included meta-analyses agreed to contribute and approved the results.

5. Limitations

Publication bias in the included papers of the conducted meta-analyses was a significant limitation to conclude the association between AF and PA. Possibly, negative or neutral studies were less likely to be published. Furthermore, grey literature often is not considered. Heterogeneity was the other limitation of the included studies in the meta-analyses, which was reported to be significant in most of them. Different study designs, different definitions for PA intensity and duration, different methods of AF diagnosis seem to be the potential causes of heterogeneity, and only some studies' reasons for the heterogeneity were determined.

Moreover, in case-control studies on athletes with cases and controls belonging to two different populations, the logistic analysis often lacked to be adjusted for confounding factors. Another limitation would be that many studies, e.g., on athletes, did not report the exposure to PA in terms of MET/h-week so that these could not be included in dose-response analysis. Furthermore, a critical limitation of exercise studies showing gender-specific effects is that the intensity of PA is not standardized in any of them. Possibly, what is a high PA for women, could be moderate PA for men. Specific studies with objectively assessed measures of PA (training schedules, accelerometry) should therefore be performed in the future. Finally, the difference between AF risks concerning PA from meta-analyses conducted in athletes and the general population is affected by the different study designs. In particular, estimates from retrospective case control studies conducted in athletes may have overestimated the effect of PA on the AF risk compared to the findings of prospective cohort studies conducted on the general population. However, the magnitude of the AF risk difference between athletes and the general population suggests the concrete existence of a possible association between AF risk and the volume of PA.

6. Conclusions

Our review suggests that athletes have an increased risk of AF compared to the general population. In the general population, PA has a dose dependent, J-shaped effect on AF risk, with increased risk at very low and very high levels of PA. This effect seems to be gender-specific and more pronounced in younger males. Population groups with a higher risk of AF may benefit from opportunistic screening for AF, especially with cardiac symptoms. Moderate physical activity seems to reduce the risk for AF.

Authorship and Contributorship

All authors mentioned earlier substantially contributed to the conception or design of the work (AM, ASS), or the acquisition, analysis, or interpretation of data (AM, ASS, JM, JA, HA, CR, NDB, CSK, SM, AN, JK, TLLL, SK, ND, SR, AA, AB, GH, MD). Furthermore, all above named authors contributed either to the drafting of the work (AM, ASS) or revised it critically (JM, JA, HA, CR, NDB, CSK, SM, AN, JK, TLLL, SK, ND, SR, AA, AB, GH, MD). All authors finally approved this manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved (AM, ASS, JM, JA, HA, CR, NDB, CSK, SM, AN, JK, TLLL, SK, ND, SR, AA, AB, GH, MD).

Joint first authorship

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