

# The ambiguity of physical activity, exercise, and atrial fibrillation

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## **Abstract**

Although commonly associated with cardiovascular disease or other medical conditions, atrial fibrillation (AF) may also occur in individuals without any known underlying conditions. This manifestation of AF has been linked to extensive and long-term exercise, as prolonged endurance exercise has shown to increase prevalence and risk of AF. In contrast, more modest physical activity is associated with a decreased risk of AF, and current research indicates a J-shaped association between AF and the broad range of physical activity and exercise. This has led to the hypothesis that the mechanisms underlying an increased risk of AF with intensive exercise are different from those underlying a reduced risk with moderate physical activity, possibly linked to distinctive characteristics of the population under study. High volumes of exercise over many years performed by lean, healthy endurance trained athletes may lead to cardiac (patho)physiological alterations involving the autonomic nervous system and remodelling of the heart. The mechanisms underlying a reduced risk of AF with light and moderate physical activity may involve a distinctive pathway, as physical activity can potentially reduce the risk of AF through favourable effects on cardiovascular risk factors.

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## Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting more than 6 million Europeans.<sup>1</sup> AF is associated with a five-fold increased risk of stroke, a three-fold increased risk of heart failure, and a two-fold increased risk of myocardial infarction and death,<sup>2,3</sup> which necessitates preventive measures. Although most commonly associated with cardiovascular disease or other medical conditions, AF may also occur in individuals without any underlying known medical conditions, often called lone or idiopathic AF.<sup>1</sup> This latter manifestation of AF has been linked to extensive and long-term endurance exercise,<sup>4</sup> but knowledge of exercise, physical activity, and risk of AF is still limited and rather ambiguous. Elite athletes with years of systematic exercise and non-elite athletes with a high volume of endurance exercise show increased prevalence and risk of AF.<sup>5,6</sup> On the other hand, studies of the general population indicate that light-to-moderate physical activity may be protective against AF.<sup>7-11</sup> In this paper, we discuss possible mechanisms underlying these seemingly contradictory associations, suggesting there may be at least two distinct mechanisms underlying the associations between physical activity and AF. Moreover, this study adds to the existing literature by aiming to identify whether study characteristics can explain some of the diversity in existing findings.

## AF risk in populations with different level of physical activity and exercise

### Current and former elite athletes

Research on exercise at professional elite level involves elite athletes with years of high-volume exercise, and Wernhart and Halle<sup>12</sup> have defined elite athletes as “*individuals performing at a competitive level with a high exercise performance*”, characterized by a high maximal oxygen uptake (VO<sub>2max</sub>) and years of systematic training and a large metabolic turnover. The body of research on AF in elite athletes can typically be classified according to *current* and *former* elite athletes, the latter constituted by former athletes mostly in endurance sport aged >45 years.

One of the first studies on exercise and AF reported a 9% prevalence of AF in young elite athletes, substantially higher than the age-matched population prevalence of AF.<sup>13</sup> Another study on athletes competing at both Olympic, national and regional level could not replicate these findings, reporting a prevalence of AF <1% in these athletes<sup>14</sup> (*Table 1*). Studies of former elite athletes demonstrate a higher prevalence of AF compared with the general population prevalence,<sup>5, 15, 16</sup> although not totally consistently<sup>17</sup> (*Table 1*). A meta-analysis including six case-control studies concluded that the risk of developing AF was 5 times higher in athletes than in controls (mean age 51 years, 93% men).<sup>18</sup>

However, the external validity of these findings is difficult to assess due to a number of methodological limitations, and some authors have concluded that the evidence for an association between vigorous exercise and AF is weak.<sup>19-21</sup> Many of the studies have a cross-sectional design and are lacking a sedentary control group, the number of

participants and AF cases is limited, and participants are highly selected by involving mainly men competing at elite level.<sup>5, 6, 13, 15, 16</sup> Most studies did not adjust for potential confounders, and the lifestyle of an elite athlete may be different from the general population in many aspects, which could possibly obscure unadjusted findings. Moreover, athletes may be more aware of their body and sensitive to symptoms, possibly resulting in more diagnoses of AF. Only the studies of Pelliccia et al.<sup>14</sup> and Furlanello et al.<sup>13</sup> include women.

### Endurance exercise on a non-professional level

Endurance exercise aims to improve aerobic capacity, often measured as  $VO_{2max}$ . In this paper, we distinguish elite athletes from non-elite athletes. Although the latter population is non-professional, many still perform at a high level and have been exposed to high volumes of exercise over many years. Typically, these non-professional elite athletes have full-time job and family commitments in addition to extensive exercise. In a Danish report, athletes who exercise with high intensity almost daily and >6 hours/week, constitute <5% of the total population.<sup>22</sup>

Studies of these non-professional athletes with a high endurance exercise volume for many years may further illuminate the issue (*Table 3*). Myrstad et al. assessed the prevalence of self-reported AF in male Norwegian veteran skiers participating in the 54-kilometer Birkebeiner cross-country ski race and in the general population.<sup>23-25</sup> The authors showed that the prevalence of self-reported AF after exclusion of participants with coronary heart disease was 13.0% in the veteran skiers and 9.8% in the general population. Further analyses showed that endurance sport practice gave a significant added risk of AF corresponding to an OR of 1.90.<sup>24</sup> Moreover, in a study of 3,545 Norwegian men, Myrstad et al.<sup>25</sup> showed that cumulative years of regular endurance

exercise were associated with a 16% significant gradually increased risk of AF per ten years of exercise. The increased risk was significant both among skiers and among the men from the general population (20% per ten years of exercise). Regular endurance exercise was also associated with a gradually increased risk of atrial flutter.<sup>25</sup> These findings corresponds with another study following skiers participating in the Birkebeiner cross-country ski race for 30 years, showing a high prevalence of AF (12.8%) among the skiers.<sup>26</sup> These results are supported by a study of participants of the 90 km cross-country race Vasaloppet, following the participants from 1989 to 2005, using the Swedish In-Patient Register to ascertain AF.<sup>27</sup> Those who finished  $\geq$ five races had 29% higher risk of AF than those who completed one race. Risk of AF was non-significantly increased in those who had the fastest relative finishing time.

### Female athletes

The association between exercise and AF in women has also been examined in a cohort of 278 female veteran cross-country skiers with a mean age of 62 years. The prevalence of self-reported AF was 8% in female skiers, and women who had exercised for  $\geq$ 40 years had a twofold increased risk of AF compared with women who had never exercised regularly.<sup>23</sup> These findings, along with results from Andersen et al.,<sup>27</sup> indicate that prolonged endurance exercise might cause AF also among women.

### The general population

While intensive endurance exercise seems to increase the risk of AF, the effect of lower levels of physical activity on AF risk seems ambivalent. Several population-based, prospective studies show a linear, decreasing trend in AF risk with increasing leisure-time physical activity,<sup>10, 28</sup> and walking or running time, pace or distance<sup>8, 9, 11, 29</sup> (*Table 3*). Some studies show a similar non-significant association.<sup>30-32</sup> Overall, all these studies

show a linear trend towards lower AF risk with increasing physical activity, even in the highest physical activity level.

In contrast, some studies report a higher risk of AF among the most vigorous physically active individuals compared with the least active (*Table 3*). Thelle et al.<sup>33</sup> found that vigorous physical activity was associated with a higher risk of lone AF, defined by a Flecainid or Sotalol prescription, in men but not in women aged 40-45 years. Aizer et al.<sup>34</sup> observed that vigorous exercise 5-7 days/week showed a higher risk of AF compared with no vigorous activity. Morseth et al.<sup>7</sup> found a J-shaped association between physical activity level and AF risk in a general population of men and women aged 30-67 years at baseline, although vigorous physical activity non-significantly increased the risk of AF compared with inactive individuals. Myrstad et al.<sup>24</sup> confirmed the J-shaped relationship between physical activity and AF by combining data from a general population and endurance trained cross-country skiers. One of the few studies on occupational physical activity and AF showed an increased risk of AF with high physical activity, whereas leisure-time physical activity in this study was not related to risk of AF.<sup>35</sup>

The majority of studies showed a trend towards a lower AF risk with light and moderate physical activity, although significant only in a few studies,<sup>7,8,11</sup> and no studies showed an increased risk with light or moderate physical activity (*Table 3*). The volume of physical activity necessary to decrease the risk of AF seems low. For example, Morseth et al.<sup>7</sup> showed that the next lowest physical activity level, involving recreational walking, cycling, or other forms of activity >4 hours a week, showed a 20% reduced risk of AF. Similarly, >405 kcal per week of leisure-time physical activity reduced the AF risk

by 25%,<sup>8</sup> and walking at least 20 minutes per day seems to be protective against AF,<sup>29</sup> compared to the least active individuals.

Studies of physical activity and AF risk in the general population embrace large variations in physical activity levels, from vigorous exercise several days per week to mostly sedentary individuals, and although all studies used questionnaires to measure physical activity, the inquiries and categorizing vary widely. Depending on measurement instruments, prevalence of physical activity may vary largely between studies.

We therefore examined whether the results might vary according to study characteristics.

**Gender.** The majority of studies included both men and women, although three of the studies show a linear, inverse relationship between physical activity and AF risk included women only.<sup>9, 28, 30</sup> Two of the three studies on higher AF risk with high physical activity included both genders;<sup>7, 33</sup> however, two of these studies had too low power to examine vigorous physical activity and AF in women.<sup>7, 33</sup> Thus, it may seem premature to conclude that gender differences could explain these variations in results. However, a recent review concluded that both total physical activity and vigorous physical activity increased the risk of AF in men and decreased the risk in women, suggesting different risk patterns of AF with physical activity in men and women.<sup>36, 37</sup>

**Age and populations.** Age ranges are rather similar across studies, as the majority of studies have included a baseline age range from 45 years and above. Although some studies have restricted recruitment to certain populations, such as physicians<sup>34</sup> or runners and walkers,<sup>11</sup> differences in population characteristics do not seem to explain



the variation in results. We are not aware of any studies on physical activity, exercise, and AF in non-Caucasians, but AF incidence has shown to be lower in people of Hispanic, African and Chinese origins than in Caucasians,<sup>38</sup> and given that the higher incidence of AF in Caucasians may be related to factors such as larger left atrial diameter,<sup>39</sup> studies on physical activity, exercise, and AF in multi-ethnic populations are needed.

**Measurements methods and physical activity levels.** Studies have used varying definition of physical activity and exercise, which could possibly influence the findings. Morseth et al.,<sup>7</sup> Myrstad et al.,<sup>24</sup> and Thelle et al.<sup>33</sup> used the same question on leisure-time physical activity, with four physical activity levels, ranging from mostly sedentary to vigorous exercise, defined as participation in hard training or sports competitions, regularly and several times per week.<sup>7, 33</sup> These studies showed an increased AF risk with vigorous exercise, although significant in two of the studies.<sup>24, 33</sup> Aizer et al.<sup>34</sup> based their analyses on regular engagement in exercise vigorous enough to work up a sweat, and found an increased AF risk among those who exercised vigorously more than 4 days a week.

Studies showing a decreasing risk of AF with increasing physical activity<sup>8, 9, 11, 28</sup> define the highest physical activity as activity beyond a certain limit, mainly defined by energy expenditure (METs or kcal), which is not directly comparable to the above-mentioned studies. However, the highest level of physical activity in studies showing a reduced AF risk was defined as energy expenditure >9 MET-hours/week,<sup>28</sup> >3.4 MET-hours/day,<sup>11</sup> or >1840 kcal/week as the highest category,<sup>8</sup> which could translate into more modest exercise than in the studies showing an increased AF risk with vigorous exercise.<sup>7, 24, 33,</sup>

<sup>34</sup> However, although various definitions of physical activity levels may partly explain

these ambiguous findings with vigorous exercise, the usefulness of physical activity quantity calculations is limited with self-reported physical activity and exercise. All existing studies rely on self-reported physical activity, which is prone to recall bias<sup>40</sup> and overestimation,<sup>41</sup> which may also vary with measurement instruments, physical activity levels, and populations. Therefore, we look forward to studies using more objective and accurate measures to quantify volume and patterns of physical activity in relation to AF.

## **Mechanisms of AF and physical activity**

Taken together, current research indicates a J-shaped relationship between physical activity and risk of AF in men (*Figure 1*). This J-shaped relationship has led to the hypothesis that different mechanisms could explain the higher risk of AF with prolonged endurance exercise on one hand, and the lower risk with moderate physical activity on the other hand<sup>42, 43</sup> (*Figure 1*).

### **Potential mechanisms explaining an increased AF risk with endurance exercise**

Cardiac adaptations to vigorous exercise include increased vagal tone, lower resting heart rate, and increased stroke volume, chamber dilatation and hypertrophy, better systolic and diastolic function, modified metabolism and electric characteristics.<sup>44-46</sup> These adaptations, often expressed as *athlete's heart*, are assumed to be physiological, reversible adaptations to the increased demands during exercise.<sup>47</sup> However, the alterations have been shown to possibly increase the risk of AF, thereby contributing to the pathophysiological mechanisms linked to the increased AF risk with intensive and long-term endurance exercise.<sup>48</sup> Several mechanisms have been proposed, but the exact mechanisms behind the observed increase in AF risk with intensive exercise remains

speculative.

**Autonomic activation.** The autonomic nervous system seems to play a part in both initiating and maintaining AF,<sup>49-51</sup> and canine experiments have shown that autonomic nerve stimulation in the atrium and pulmonary vein initiates arrhythmias.<sup>49</sup> Both increased parasympathetic and increased sympathetic nervous system activity has been observed to facilitate AF in athletes, as AF may be triggered during exercise (adrenergically induced AF) and rest (vagally induced AF).<sup>52, 53</sup> Furlanello et al.<sup>13</sup> showed that among young athletes with paroxysmal AF, AF occurred during exercise in more than 60% of the athletes. Mont et al.<sup>53</sup> showed that vagally induced AF was more common in physically active (57%) than in sedentary AF patients (18%).

Prolonged exercise may lead to long-term changes in autonomic activation, which could expose athletes to increased risk of AF later in life.<sup>45</sup> This may be particularly linked to increased vagal tone, as vagally induced AF seems to be more apparent in older athletes<sup>52</sup>. Regular endurance exercise leads to increased vagal tone,<sup>45</sup> and low resting heart rate is common among endurance athletes.<sup>26</sup> Increased vagal activity reduces the atrial refractory period, facilitating re-entry, which may trigger AF.<sup>54</sup> In a study of non-elite male endurance athletes (mean age 42 years), lifetime training volume >4500 hours was associated with prolongation of signal-averaged P-wave duration, higher parasympathetic tone, and more frequent premature atrial contractions, compared with lifetime training <1500 hours.<sup>45</sup> In exercising rats, prevalence of AF increased after 16 weeks of daily exercise,<sup>46</sup> and the exercising rats had significantly reduced resting heart rate and increased parasympathetic tone after 16 weeks of exercise, compared with sedentary rats. However, resting heart rate and vagal tone were normalized in the exercising rats after 4 weeks of detraining.<sup>46</sup>

**Atrial dilatation.** Left atrial size is a risk factor for AF,<sup>55</sup> and cross-sectional studies show enlargements of the left atrium in athletes,<sup>14, 45, 56-62</sup> which is also shown in experimental animal models.<sup>63</sup> Longitudinal studies confirm left atrial remodelling after a period of high-volume exercise.<sup>64-66</sup> Only a few studies have linked exercise and atrial dimensions to AF. A case-control study<sup>67</sup> showed that AF patients had higher cumulated physical activity levels and larger left atrial dimensions than controls. In marathon runners<sup>6</sup> and cross-country skiers, large left atrial dimension is associated with a higher risk of AF.<sup>26</sup> However, a study of young, competitive athletes showed enlarged left atrial dimensions but low prevalence of AF (1%).<sup>14</sup> Furthermore, atrial remodelling has shown to be reversible after detraining.<sup>13, 63, 68</sup>

Atrial dilatation due to long-term endurance training has been linked to increased volume and pressure overload during exercise. In animal experiments, raising atrial pressure, which induces atrial dilatation, leads to a shortening of the atrial refractory period and increases vulnerability to AF.<sup>69</sup> Volume and pressure overload could therefore potentially trigger AF during exercise, and it is also speculated that repeated stretch of the atrial wall during extensive exercise over many years may lead to atrial enlargement, stretch-induced microtrauma, inflammation and fibrosis, which are potential substrates for AF.<sup>4, 70, 71</sup>

**Atrial ectopy.** Ectopic beats are an important trigger of AF, and some studies have shown that supraventricular premature beats are more common in athletes,<sup>45, 56, 72</sup> suggesting that increased atrial ectopy could be responsible for the increased AF risk in athletes.<sup>73</sup> However, a third study could not confirm these results.<sup>15</sup>

**Fibrosis.** Some animal studies and a few human studies have elucidated the role of

fibrosis in exercise-induced AF.<sup>63, 74-76</sup> In rats, 16 weeks of exercise showed collagen deposition and increased fibrosis marker expression in the atria and ventricles, with an increased susceptibility to arrhythmia.<sup>63</sup>

In humans, studies of veteran athletes showed an increase in markers of myocardial fibrosis<sup>74</sup> and a high prevalence of myocardial fibrosis shown on cardiac magnetic resonance imaging<sup>75</sup> compared with sedentary controls. Similarly, Breuckmann et al.<sup>76</sup> showed a three times higher prevalence of myocardial fibrosis in non-elite marathon runners than in controls. Whether this increased prevalence of fibrosis in athletes facilitates AF is uncertain.

**Inflammation.** Swanson<sup>77</sup> postulated a hypothesis on inflammation as a possible mechanism linking exercise and AF. Long-term, intensive exercise has been reported to generate a systemic inflammatory response,<sup>78</sup> which in turn may lead to development of AF, as C-reactive protein and Interleukin-6 Levels can be elevated in AF patients.<sup>79-82</sup> This is further supported by a study of elite mountain marathon runners showing transient acute inflammation, as well as conduction delay in the atria and increased atrial wall tension, after a mountain marathon race,<sup>83</sup> and the authors speculated that these changes may lead to atrial remodelling and increased risk of AF.

**Gastro-oesophageal acid reflux.** Based on results from separate literature taken together, Swanson<sup>84</sup> hypothesizes that vigorous exercise may induce gastro-oesophageal acid reflux,<sup>85-87</sup> which in turn has been shown to increase the risk of AF by 39% in a large population study of 163,627 participants.<sup>88</sup> This hypothesis needs further elaboration.

**Performance enhancing drugs.** Performance enhancing supplements such as anabolic

steroids and stimulants may have an arrhythmogenic effect.<sup>89</sup> Only a few case reports indicating increased AF risk with anabolic steroids have been reported,<sup>48</sup> and due to the unknown extent of use of illegal performance enhancing drugs, the effects of supplements on AF risk are largely unknown.

**Genetic predisposition.** With a ~10% prevalence of AF in most athlete studies, most athletes do not develop AF, introducing the question of whether some people are predisposed to AF. To date, GWAS has identified 26 loci that are associated with AF.<sup>90</sup> The clinical significance of these GWAS variants and their ability to predict mechanisms of AF development are yet unknown, and the AF risk prediction only slightly improved by adding genetic information.<sup>91</sup> To our knowledge, no study has examined the association between genetic predisposition, exercise, and AF.

### Potential mechanisms explaining the lower AF risk with light-moderate physical activity

Cardiac adaptations to exercise are generally assumed to be beneficial, although vigorous physical activity, particularly prolonged endurance exercise, may lead to cardiac “overadaptation” and (patho)physiological changes, thereby increasing the risk of AF. To what extent these adaptations also occur with light and moderate physical activity is not known, as there is only a handful of studies on cardiac adaptations to more moderate physical activity. Dawes et al.<sup>92</sup> examined self-reported physical activity in relation to cardiac remodelling in a healthy adult population. Using cardiac magnetic resonance imaging, the authors found that increasing physical activity levels were associated with greater left ventricular mass, ventricular end-diastolic volume, ventricular stroke volume, and slightly lower right and left ventricular ejection fractions. The study of Dawes et al. suggests that cardiac alterations occur with

moderate physical activity or exercise between 3 and 5 hours per week, and the effects of physical activity on cardiac structure were greater than that of systolic blood pressure.<sup>92</sup>

In the Framingham Heart Study,<sup>93</sup> which included middle-aged adults, higher levels of moderate-vigorous physical activity, although well below the doses of athletes, were associated with larger left atrial size and lower arterial stiffness. A recent study of 4342 elderly report that higher levels of physical activity were associated with improved diastolic and systolic function but no clinically significant associations between physical activity and left atrial dimensions.<sup>94</sup>

The few studies on cardiac adaptations suggest that also moderate physical activity can lead to improved cardiac function. However, these alterations are probably modest and beneficial to the development of AF, as moderate physical activity is consistently associated with a reduced AF risk. Instead, some studies indicate that the lower AF risk may be linked to cardiovascular risk factors.<sup>8, 10, 30</sup>

Cardiovascular risk factors such as obesity, hypertension, and type 2 diabetes mellitus increase the risk of AF,<sup>95-97</sup> and physical activity modifies these cardiovascular risk factors,<sup>98</sup> for example by improving weight, glucose and lipid control, endothelial function, and lowering resting heart rate and blood pressure.<sup>99</sup> Everett et al.<sup>30</sup> and Mozaffarian et al.<sup>8</sup> both showed that adjustment for risk factors such as body mass index (BMI), diabetes, hypertension, hyperlipidemia, and cardiovascular disease attenuated the association between physical activity and AF. Mozaffarian et al.<sup>8</sup> discussed that the lower AF risk with increasing physical activity and walking in their study may be mediated in part by risk factors such as BMI, blood pressure, glucose,

cholesterol, and C-reactive protein levels. In the ARIC study,<sup>10</sup> physical activity attenuated the increased AF risk associated with overweight and obesity, although only in men.

On the other hand, Drca et al.<sup>9</sup> found that the inverse association between physical activity and risk of AF in women did not change with adjustment for risk factors like BMI, hypertension, diabetes and cardiovascular disease.

## **Conclusion**

Current research indicates a J-shaped relationship between physical activity, exercise, and AF, but the findings need to be interpreted in view of methodological limitations. Existing research points to a wide range of underlying mechanisms, of which most remain to be established. Although still speculative, current research seems to substantiate the hypothesis that the mechanisms underlying an increased risk of AF with intensive exercise are different from those underlying a reduced risk with moderate physical activity, possibly linked to distinctive characteristics of the population under study. High volumes of exercise over many years are performed by lean, healthy endurance trained athletes, responding to intensive exercise by cardiac (patho)physiological alterations. The mechanisms likely involve autonomic nervous system influence, remodelling of the heart, and trigger areas in pulmonary veins and atria. Genetic polymorphisms are likely to play a role, but evidence is lacking. The mechanisms underlying a reduced risk of AF with light-moderate physical activity may involve a distinctive pathway, as physical activity can potentially reduce the risk of AF through favourable effects on cardiovascular risk factors.



## Figure legends

**Figure 1.** Shape of the association between risk of AF and physical activity level, and proposed underlying mechanisms.

AF, atrial fibrillation

MET, metabolic equivalent of task

## **Declaration of conflicting interests**

The Authors declare that there is no conflict of interest.

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## **Author contributions**

DST, BM and MLL contributed to the conception or design of the work. BM and MM contributed to the acquisition, analysis, or interpretation of data for the work. BM drafted the manuscript. All authors critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Table 1: Prevalence and risk of AF in former and current elite athletes

Publication year, authors	Study population	Men (n)	Women (n)	Age (years)	Follow-up (years)	AF diagnosis	PA level/dose	Prevalence (%) or RR (95% CI) of AF, athletes vs control group
1998 Karjalainen et al. <sup>5</sup>	Veteran orienteers vs. healthy controls, Finland	262 athletes, 373 controls	0	Mean 47/49	10	Self-reported	High level for many years	RR athletes vs. controls: OR 5.5 (1.3-24.4)
1998 Furlanello et al. <sup>13</sup>	Young elite athletes, Italy	122 athletes	24 athletes	Mean 24	Cross-sectional	ECG	Elite athletes	Athletes 9%
2005 Pelliccia et al. <sup>14</sup>	Highly trained athletes of 38 different sports, Italy	1298 athletes	479 athletes	Mean 24	Cross-sectional	ECG	Highly trained athletes	Athletes <1%
2008 Baldesberger et al. <sup>15</sup>	Former professional cyclists vs. Golfers, Switzerland	62 athletes, 62 controls	0	Mean 66	38	ECG	Former professional cyclists	Cyclists 10%, controls 0%, <i>P</i> =0.03
2009 Bjørnstad et al. <sup>17</sup>	Former elite athletes, Norway	15 athletes	15	Mean 24	15	ECG	Former endurance elite athletes	0, no control group
2012 van Buuren et al. <sup>16</sup>	Former top-level handball players vs. healthy controls, Germany	33 athletes, 24 controls	0	Mean 57	Cross-sectional	ECG	>20 years with 18hours/week	Former athletes 30%, controls 0%

AF, atrial fibrillation

PA, physical activity

RR, relative risk

CI, confidence interval

OR, odds ratio

ECG, electrocardiography

Table 2: Risk of AF in non-elite endurance athletes

Publication year, authors	Study population	Men (n)	Women (n)	Baseline age (years)	Follow-up (years)	AF diagnosis	PA type, level, dose	Prevalence (%) or RR (95% CI) of AF, athletes vs control group	Shape of relationship
2008 Molina et al. <sup>6</sup>	Marathon runners vs. sedentary controls, Spain	252 athletes, 305 controls	0	Mean 45, range 20-60	11	ECG, lone AF	Total PA	Marathon runners vs. controls: HR 8.8 (1.6-61.29)	
2010 Grimsmo et al. <sup>26</sup>	Former Birkebeineren participants, Norway	78	0	Range 54-92 at follow-up	30	ECG, lone AF	Cross-country skiing	Athletes 12,8 %	
2013 Andersen et al. <sup>27</sup>	Vasaloppet participants, Sweden	47477	5278	Mean 38	16	Swedish In-Patient Register	Cross-country skiing, number finished races, finishing time	≥5 vs. 1 race: HR 1.29 (1.04-1.61). Finishing time: HR 1.20 (0.93–1.55)	Increased risk for each race
2014 Myrstad et al. <sup>24</sup>	Birkebeineren participants and the Tromsø Study, Norway	2277	0	Range 65-90	Cross-sectional	Self-reported	Sedentary to vigorous, long-term endurance training	Birkebeiner vs. sedentary: OR 1.9 (1.14-3.18). Moderate vs. sedentary: Lower risk, NS	J-shape
2014 Myrstad et al. <sup>25</sup>	Birkebeineren participants and the Oslo Health Study, Norway	3545	0	Range 53-92	Cross-sectional	ECG, self-reported	Sedentary to vigorous, long-term endurance training	Per 10y experience: OR 1.16 (1.06-1.29)	AF risk increases with years of endurance training
2015 Myrstad et al. <sup>23</sup>	Birkebeineren participants and the	0	1679	Range 53-75	Cross-sectional	Self-reported	Sedentary to vigorous, long-	≥40y endurance training vs. never: OR 2.18 (0.94-5.06)	J-shape

AF, atrial fibrillation

PA, physical activity

RR, relative risk

CI, confidence interval

ECG, electrocardiography

HR, hazard ratio

OR, odds ratio

NS, not significant at  $P < 0.05$

Table 3: PA and risk of AF in the general population

Publication year, authors	Study population	Men (n)	Women (n)	Baseline age (years)	Follow-up (years, mean)	AF diagnosis	PA type, level, dose	RR (95% CI), moderate vs sedentary PA	RR (95% CI), high vs. sedentary PA	Shape of relationship between PA and AF
2008 Mozaffarian et al. <sup>8</sup>	Cardiovascular Health Study, USA	2287	3159	Mean 73, range >65	12	ECG, hospital discharge	Leisure-time PA, quintiles, walking distance/pace	Walking distance, pace: RR 0.78-0.56. PA quintile III vs I: 0.75 (0.61-0.90)	PA quintile V vs. I: RR 0.64 (0.52-0.79). Intensity, high vs. none: RR 0.87 (0.64-1.19)	Walking: Inverse, linear, $P<0.001$ . PA: Inverse, linear, $P<0.001$ . Intensity: U-shape
2009 Aizer et al. <sup>34</sup>	Physicians' Health Study, USA	16921	0	Range 40-84	12	Self-reported	Vigorous exercise, days/week	1-2 vs. <1 day/week: NS	5-7 vs. <1 day/week: RR 1.2 (0.99-1.36)	Positive, linear association, $P=0.04$
2011 Everett et al. <sup>30</sup>	Women's Health Study, USA	0	34759	Mean 54, range 49-59	14	ECG, medical journal	Leisure-time PA, MET-hours/week	Middle vs. low PA: NS	High vs. low PA: NS	NS
2013 Williams et al. <sup>11</sup>	National Runners' Health Study II/National Walkers' Health Study, UK	19044	27763	Mean 44-59	6	Self-reported	Walking and running, MET-hours/day	2-3 vs. >1 MET-hours/day: RR 0.7, $P<0.05$	>3 vs. <1 MET-hours/day: RR 0.6, $P<0.001$	Inverse, linear

2013 Thelle et al. <sup>33</sup>	CONOR cohort, Norway	147462	162078	Range 40-45	5	Norwegian Prescription Database, lone AF	Leisure and work PA, 4 levels	Moderate vs. sedentary: NS	Vigorous vs. sedentary: RR men 3.14 (2.17-4.54), women NS	Men: Flipped L, increasing, <i>P</i> <0.001
2014 Huxley et al. <sup>10</sup>	Atherosclerosis Risk in Communities Study, USA	6445	7774	Mean 54, range 45-64	22	ECG, hospital discharge	Leisure and work PA, MET-minutes/week	Middle vs. low PA: NS	High vs. low PA: HR 0.89 (0.80-1.00)	Inverse, linear, <i>P</i> =0.06
2014 Azarbal et al. <sup>28</sup>	Women's Health Initiative Observational Study, USA	0	81317	Range 50-79	11	Medical records or Medicare	Walking, recreational, strenuous exercise, MET-hours/week	3-9 MET-hours/week vs. none: NS	>9 MET-hours/week vs. none: RR 0.90 (0.85-0.96)	Inverse, linear, <i>P</i> =0.003
2014 Drca et al. <sup>29</sup>	Swedish men	44 410	0	Mean 60, range 45-79	12	Swedish Inpatient Register	Walking/bicycling; Light-to-moderate. Exercise: Moderate-to-high	Walking >60 min/d vs. almost never: RR 0.87 (0.77-0.97)	Exercise >5hours/week vs. almost never: RR 1.17 (1.03-1.32)	Walking: Inverse, linear, <i>P</i> =0.03. Exercise: Positive, linear, <i>P</i> =0.01
2014 Knuiman et al. <sup>31</sup>	Busselton Health Study, Australia	1861	2406	Range 25-84	16	Hospital admission	Doing any vigorous each week	Not assessed	Vigorous vs. none: HR 0.80 (0.62-1.03)	Not assessed
2015 Drca et al. <sup>9</sup>	Swedish Mammography Cohort	0	36513	60 (49-83)	12	Swedish Inpatient Register	Walking/bicycling; Light-to-moderate. Exercise: Moderate-to-high	Walking, ≥40 min/d vs. almost never: RR 0.81 (0.72-0.92)	Exercise >5 vs. <1 hours/week: RR 0.85 (0.75-0.95)	Walking: Inverse, linear, <i>P</i> >0.001. Exercise: Inverse, linear, <i>P</i> =0.02

2015	Multi-Ethnic	2722	3071	62 (45-84)	7	Medical records or Medicare	Total intentional exercise, vigorous exercise, MET-minutes/week	Lower or middle tertile vs. none PA: NS	Upper tertile PA: NS	HR for AF increased with total intentional PA
Bapat et al. <sup>32</sup>	Study of Atherosclerosis, USA									
2015	Taupo bicycle study, New Zealand	1874	725	≥16	7	Hospital discharge	Cyclists vs. national cohort, hours/week, km/week	No difference cyclists vs. general population		
Woodward et al. <sup>100</sup>										
2016	Tromsø Study, Norway	10300	10184	Mean 39 (men), 37 (women)	20	ECG	Leisure and work PA, 4 levels	Moderate vs. sedentary: HR 0.81 (0.68-0.96)	Vigorous vs. sedentary: NS	J-shape
Morseth et al. <sup>7</sup>										
2016		7258	8560	Range 20-93	20	ECG	Leisure and occupational PA, 4 levels	Leisure-time PA: NS Occupational PA: NS	Leisure-time PA: NS Occupational PA: NS High vs low PA: HR 1.21 (1.02-1.43) Very high vs low PA: HR 1.39 (1.03-1.88)	Leisure-time PA: NS Occupational PA: J-shaped
Skjelbo et al. <sup>35</sup>										

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AF, atrial fibrillation

PA, physical activity

RR, relative risk

CI, confidence interval

ECG, electrocardiography

NS, not significant at  $P < 0.05$

MET, metabolic equivalent of task

HR, hazard ratio