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1 **Mini Review**

2 **Title:** The counterintuitive role of exercise in the prevention and cause of atrial fibrillation

3 **Short title:** Exercise and AF Pathophysiology

4
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19 BJRБ conceived and drafted the manuscript; GYHP and DHJT edited and revised the
20 manuscript. BJRБ created the figure. BJRБ, GYHL, and DHJT approved the final version of
21 manuscript.

23 **Abstract**

24 Atrial fibrillation (AF) is the most common cardiac arrhythmia characterised by irregular atrial
25 activity. AF is related to increased risk of thromboembolic events, heart failure, and
26 premature mortality. Recent advances in our understanding of its pathophysiology include a
27 potentially central role for inflammation and presence of cardiovascular risk factors. The role
28 of physical activity and exercise in the development and progression of AF, however, are not
29 yet fully understood. Physical activity is protective for modifiable cardiovascular risk factors,
30 including those associated with AF. Indeed, emerging research has demonstrated beneficial
31 effects of exercise on AF-specific outcomes, including AF recurrence post-ablation.
32 Counterintuitively, the prevalence of AF in veteran endurance athletes seems higher
33 compared to the general population. In this review, we discuss the novel evidence and
34 underlying mechanisms underpinning the role of exercise as medicine in the development
35 and management of AF, but also the counterintuitive detrimental role of excessive endurance
36 exercise. Finally, we advocate regular (but not long-term high-intensity endurance) exercise
37 training as a safe and effective strategy to reduce the risk of incident AF, and to minimise the
38 associated risk of secondary cardiovascular events.

39

40

41 **Key words:** Atrial Fibrillation, Exercise, Physical Activity, Pathophysiology

42

43 **Background**

44

45 Atrial fibrillation (AF) is the most common cardiac arrhythmia affecting more than 33 million
46 people worldwide and the prevalence is expected to rise exponentially with an ageing
47 population (1, 2). AF is associated with an increased incidence of stroke, coronary events, and
48 development of dementia (3, 4). The risk of incident AF is associated with various
49 cardiovascular risk factors, which in turn contribute to the risk of AF-related complications
50 (5). AF is characterised by irregular, usually fast, atrial activity with consequent deterioration
51 of atrial function. AF can be paroxysmal, persistent, or permanent in nature, with the latter
52 associated with worse prognosis (6). The pathophysiological processes involved in the
53 development of AF include cardiac structural abnormalities such as left ventricular
54 hypertrophy and left atrial enlargement, upregulated inflammatory pathways, exacerbated
55 by cardiovascular disease and/or risk factors, and genetic predisposition (7-10). These
56 mechanisms are discussed in detail, in relation to excessive exercise training and the
57 development of AF in section 2.

58 The primary aims of treatment for AF are stroke prevention (i.e. oral anticoagulation),
59 symptom management with heart rate or rhythm control, and management of cardiovascular
60 and comorbidities (11). Whilst drug therapies aim to control arrhythmia, they are associated
61 with adverse side effects and high healthcare costs (12, 13). Furthermore, ablation
62 successfully reduces AF episodes and burden in some with paroxysmal AF, though ~40%
63 demonstrate AF recurrence within 3 months post-procedure (14). This highlights the need for
64 additional strategies to reduce risks for AF development and progression, lower the risk of
65 AF-related cerebrovascular events (e.g. stroke), and improve quality of life (15, 16). Regular
66 physical activity (PA) is a well-established, non-pharmacological therapy that enhances
67 cardiometabolic health (17). Counterintuitively, excessive endurance training seems to
68 increase the risk of incident AF. Key characteristics of this 'athletic AF' often include patients
69 age ≤ 60 years, prolonged practice of endurance training, preserved ejection fraction, minor
70 substrate criteria, and absence of common AF risk factors (18). Although our understanding
71 of PA, exercise and AF has improved in recent years, many questions remain unanswered.

72 In this review, we first discuss novel evidence and potential underlying mechanisms
73 supporting the role of regular exercise as medicine in the development and management of
74 AF. Second, we review the literature regarding the potential detrimental role of excessive

75 endurance exercise on AF and its pathophysiological mechanisms. Finally, we summarise the
76 evidence and provide future perspectives for the role of regular PA and exercise in the
77 management of AF.

78
79

80 **1. Physical activity and exercise in the prevention and management of AF**

81

82 *Primary prevention of AF*

83 Regular PA reduces the risk of numerous chronic diseases, preserves physical and mental
84 health as we age, and extends longevity (17). Indeed, regular aerobic exercise training is a
85 well-known preventative tool for cardiovascular disease able to reduce common risk factors
86 (hypertension, hypercholesterolaemia, hyperglycaemia), and alleviate (or even reverse)
87 vascular dysfunction (19, 20). In line with these observations, there is now promising evidence
88 for the prevention of AF via regular PA. Light-to-moderate-intensity PA has been associated
89 with significantly lower AF incidence in older adults (21). Specifically, one fourth of new cases
90 of AF in older adults may be attributable to absence of moderate leisure-time PA. In a
91 database study of nearly 5,800 participants, although vigorous-intensity PA nor overall
92 'intentional exercise' load were independently associated with incident AF, modelling both
93 together resulted in a significantly reduced incidence of AF in the top tertile of total exercise
94 compared with those who reported no exercise (22).

95 In a recent UK Biobank cohort analysis ($n=402,406$), Elliott et al. (23) found that achieving
96 >500 MET-min/week (metabolic equivalents) was associated with reduced risk of incident
97 AF. Given the PA guidelines (150 minutes moderate-intensity or 75 minutes vigorous-intensity
98 PA) equate to ≥ 450 MET-min/week, the findings from Elliott et al. provide evidence that
99 these general PA guidelines not only promote cardiovascular risk factor control, but also
100 independently reduce AF development. In fact, exceeding current PA guidelines, i.e. 500-1500
101 MET-min/week, was associated with 5-10% and 6-20% reduced incidence of AF in males and
102 females, respectively. This is supported by a large population-based cohort study
103 ($n=>500,000$), which found a U-shaped dose-response relationship between PA level and AF
104 risk (24). Achieving 500-1000 MET-min/week was associated with a 12% reduction in
105 incident AF. Those achieving <500 or >1000 MET-min/week however, demonstrated an
106 attenuated risk reduction. The attenuated risk reduction observed at higher levels of PA is not
107 a consistent finding in the literature. The association of accelerometry-derived MVPA and

108 incident AF was explored in >5000 participants split into quartiles of ascending MVPA levels
109 (25). At 3.5 years follow-up, the risk of AF reduced in a dose-response manner, with the
110 biggest reduction in risk at the highest PA level (38% reduced risk of AF in quartile 4).

111 These recent studies support the notion that regular PA is protective from incident AF. The
112 varying effects of PA intensity, however, are not yet fully understood. Morseth *et al.* (26)
113 found a significantly reduced risk of incident AF when participants walked or cycled >4
114 hours/week. Yet, this positive effect was diminished when individuals participated in
115 vigorous-intensity PA. Whether this effect is related to intensity, or to the interwoven relation
116 between PA volume and intensity, remains unclear. Nonetheless, an attenuation of the effect
117 size of larger volumes and/or intensity of PA is also supported by others, with some
118 suggestion for the presence of strong between-individual differences. The potential negative
119 effects of excessive endurance training and the impact of sex differences are discussed in
120 section 2. Despite the complex nature of the dose-response relationship between PA, exercise
121 and AF, the majority of studies suggest beneficial effects in the primary prevention of AF when
122 adopting or modestly exceeding (2-3 times) current PA guideline levels.

123 *Secondary prevention of AF*

124 Pathak *et al.* (27, 28) found that greater cardiorespiratory fitness (CRF) was associated with
125 increased freedom of AF and for every 1 MET increase in CRF (via exercise training) AF
126 recurrence was reduced by 9%. Similarly, in >64,500 adults Qureshi *et al.* (29) observed that
127 every 1 MET increase in CRF was associated with a 7% lower risk of incident AF. More recently,
128 Garnvik *et al.* (30) collected self-reported PA and estimated CRF from 1,117 patients with
129 prevalent AF over ~8 years. Primary findings showed that meeting the PA guidelines resulted
130 in a 45% and 50% lower risk of all-cause and cardiovascular disease mortality, respectively,
131 compared with inactive patients. In addition, each 1 MET increase in CRF was associated with
132 12% lower all-cause mortality and 15% lower cardiovascular disease mortality. Furthermore,
133 achieving less than the recommended PA levels was associated with a reduced risk of
134 mortality compared with inactive patients, advocating that, even below the recommended
135 levels of PA, some PA is better than nothing for secondary prevention of AF. Whilst these
136 observation studies provide promising evidence for the benefits of regular PA in the
137 secondary prevention of AF, future study designs that can infer causation are needed.

138 One randomised controlled trial (RCT) demonstrated that weight reduction with intensive risk
139 factor management (e.g. goals for regular exercise, lipid management, glycaemic control, and
140 blood pressure reduction) resulted in beneficial cardiac remodelling and reduced AF burden
141 and severity in overweight/obese patients (27, 31). The authors proposed that such beneficial
142 effects may be attributable to a decrease in left atrial size and ventricular wall thickness (i.e.
143 anti-AF cardiac remodelling). It is important to emphasize that the ARREST AF trial targeted
144 multiple risk factors and it is therefore not possible to attribute these beneficial effects to PA
145 alone.

146 Another RCT compared cardiac rehabilitation to usual care for patients treated with catheter
147 ablation for 210 patients with AF (32). Findings revealed a significantly higher (~1 MET) CRF
148 at 4-months in the cardiac rehabilitation group compared to usual care. In addition to physical
149 symptoms, over one third of AF patients have elevated levels of depression and anxiety (12)
150 and impaired quality of life (33) compared to the general population. Symptoms of depression
151 have also been documented as the strongest independent predictor of future quality of life
152 in AF patients and thus NHS burden (12). Osbak et al. (34) conducted a small-scale RCT
153 reporting that 12-weeks of exercise training significantly increased exercise capacity and
154 improved quality of life in patients with AF. Given exercise elicits an effect size over three
155 times that of anti-depressant medication in reducing depression (35), it is an extremely
156 promising addition to routine AF care. Whilst this work highlights the ability of AF patients to
157 improve fitness, cardiac structure and their quality of life, further work is needed to
158 investigate the impact of exercise-based rehabilitation in patients with AF on clinically
159 relevant outcome measures such as mortality, morbidity, and adverse events.

160 A recent systematic review of four interventional studies ($n=498$ participants) found lifestyle
161 and risk factor management significantly decreased AF episode severity, frequency, and
162 duration (36). Supporting the notion of exercise as an AF-specific medical intervention, one
163 previous study demonstrated improved sinus rhythm maintenance in patients with persistent
164 AF, following external electrical cardioversion and rhythm control therapy (usual care) plus
165 exercise, counselling, and dietary restriction compared to usual care alone (37). Exercise
166 interventions may not only be beneficial for AF-specific outcomes but may also reduce the
167 risk of AF associated secondary cardiovascular events. Indeed, Proietti *et al.* (38) observed
168 that regular exercise in patients with AF was associated with lower risk of all-cause mortality

169 and thromboembolic events irrespective of sex, age, or risk of stroke. Finally, one RCT
170 demonstrated that 12-weeks of aerobic interval training significantly reduced AF burden
171 (measured via implantable loop recorders) from 8.1 to 4.8%, with no significant change in the
172 no exercise control (39). Collectively, PA provides a promising first line treatment for
173 individuals diagnosed with AF, associated with enhanced quality of life (34), AF-specific
174 outcomes (37), and secondary cardiovascular events (30).

175

176 ***What potential mechanisms explain the benefits of regular physical activity in AF?***

177 Several pathways have been suggested to contribute to the benefits of regular PA in the
178 primary and secondary prevention of AF. The most important pathways have been discussed
179 below and presented in Figure 1.

180 *Traditional cardiovascular risk factors.* Cardiovascular risk factors including hypertension (40),
181 diabetes mellitus and metabolic syndrome (41), obesity (42, 43), and obstructive sleep
182 apnoea (44) have been shown to independently increase incident AF. Indeed, hypertension
183 and obesity are associated with structural (atrial hypertrophy, fibrosis, and dysfunction) and
184 electrical (decreased conduction velocity) remodelling of the atria, in addition to the presence
185 of enhanced inflammatory markers (45). The structural, conduction, and sinus node
186 abnormalities leading to AF, also contribute to an abnormal atrial substrate (46).
187 Correspondingly, aggressive cardiovascular risk factor management has been shown to
188 markedly improve sinus rhythm and AF burden (likely via improvement in the AF substrate)
189 (27). In addition, improved CRF is associated with improved AF-free survival, AF burden and
190 symptom severity (28). Pathak et al. (28) proposed that long-term improvements in fitness
191 resulted in significantly reduced blood pressure, inflammation, and left atrial size, and
192 improved blood lipid status and glycaemic control, all of which contributed to a reduced AF
193 burden. Although the benefits of regular PA partly relate to improvement in traditional
194 cardiovascular risk factors, the overall effect of PA on risk factors is small to modest.

195 *Cardiac remodelling.* At a cardiac level, aerobic exercise training induces positive cardiac
196 remodelling (enlargement in cardiac dimension, improved contractility, and increased blood
197 volume) leading to an improvement in cardiac function and maximal cardiac output. Such
198 adaptations are associated with signalling pathways underlying cellular, molecular and
199 metabolic adaptations (47). Aerobic exercise training also promotes mitochondrial biogenesis

200 and oxidative capacity in cardiac myocytes, which contributes to a reduced risk of
201 cardiovascular disease and enhanced cardiac function (48). Regular exercise (4-5
202 sessions/week) is associated with attenuation of age-related cardiac remodelling including
203 decreased compliance and distensibility (i.e. cardiac stiffness) (49).

204 *Impact on thrombogenesis.* AF is associated with a prothrombotic or hypercoagulable state
205 by fulfilment of Virchow's triad for thrombogenesis (50). In AF, there are data supporting the
206 presence for 1. 'abnormal blood flow' (which we recognise as intra-atrial stasis, often within
207 dilated cardiac chambers); 2. 'abnormal vessel wall' (seen as structural heart disease and
208 intrinsic endocardial/endothelial damage/dysfunction), and 3. 'blood constituent
209 abnormalities' (referring to coagulation, fibrolysis and platelet abnormalities, in association
210 with inflammation and other growth factors that promote thrombogenesis). PA and exercise
211 impact these components of Virchow's triad; for example, regular exercise suppresses pro-
212 inflammatory cytokine production, enhances anti-inflammatory mediators and antioxidant
213 development, and promotes fibrinolytic activity (51). Moreover, 12-weeks of high intensity
214 interval training has been shown to improve platelet mitochondrial function in heart failure
215 patients (52).

216 *Endothelial function.* Endothelial damage/dysfunction may provide the final common
217 pathway of the combined effect of traditional cardiovascular risk factors (53). AF patients
218 demonstrate an impaired endothelial function (as measured by flow-mediated dilation) (54)
219 and some research suggests vascular dysfunction precedes incident AF (55). Exercise training
220 has well known beneficial effects on vascular function and structure. A specific and potent
221 impact of exercise training relates to improved artery endothelial function, primarily through
222 increased production and bioavailability of endothelium-derived nitric oxide (19). Thus,
223 exercise induced improvement in endothelial function may contribute to a lower risk for AF
224 development, recurrence, and risk for secondary cardiovascular events.

225

226 **2. Excessive endurance exercise and AF**

227

228 Despite compelling evidence for exercise as medicine in AF, research has demonstrated that,
229 counterintuitively, long-term endurance training increases the risk of incident AF (56, 57). The
230 heightened prevalence of AF is not uniform across elite athletes but seems to favour a high-
231 volume of endurance training such as cycling, running, and cross-country skiing (58). In a

232 Swedish cohort study ($n = >52,000$), repeated participation and faster finishing time in long-
233 distance cross-country ski races (surrogate marker of exercise training history) were
234 associated with increased risk for AF (59). In agreement, Myrstad et al. (60) found that in older
235 Norwegian men, a history of endurance sport practice was a risk factor for AF, with an effect
236 comparable to traditional risk factors for AF (e.g. coronary heart disease and hypertension).
237 A later study by Myrstad et al. (61), combined two independent cohorts and demonstrated a
238 graded-dose-response relationship with an adjusted odds ratio for lone AF 1.26 (95% CI 1.10
239 to 1.44) per 10 years of exercise training.

240 There seems to be sex-related differences in terms of high levels of PA and risk of AF. For
241 example, Elliott et al. (23) found that vigorous-intensity PA was protective in females,
242 whereas in males, increasing levels of vigorous-intensity PA was associated with progressive
243 AF incidence, leading to a significant 12% increased AF risk at 5000 MET-min/week. Such sex-
244 dependent responses to vigorous-intensity exercise in AF have been previously alluded to
245 (62), yet the mechanisms underpinning these interactions are not yet fully understood. It is
246 however thought that men may be at an elevated risk of AF due to larger atria and a more
247 extensive remodelling compared with females (63). In summary, the relationship between PA
248 and AF is complex, and sex seems an important, yet not yet fully understood factor. Future
249 work is needed to tease out the mechanisms involved in the sex-related differences observed
250 in the associations of PA and AF.

251 Collectively, studies pertaining to the most active (lifelong) athletes provide evidence that
252 'more is not always better'. Whilst lower doses of regular exercise are associated with lower
253 incidence of AF, these benefits disappear when examining AF prevalence in cohorts who
254 perform very high volumes of high-intensity endurance exercise. This supports the presence
255 of a J-shaped curve between PA/exercise and incident AF (Figure 1) (26, 64). Defining the dose
256 of exercise associated with potentially detrimental effects on the primary and secondary
257 prevention of AF is challenging, and importantly limited by a lack of prospective studies that
258 objectively report exercise volume and AF occurrence. At least, the potentially 'harmful' dose
259 of exercise seems substantially higher than the recommended PA guidelines (with the latter
260 being AF protective).

261 Indeed, we have incorporated a large area of potential variance within figure 1 (shaded area
262 of interest) to denote uncertainty surrounding a number of important mediators regarding

263 excessive exercise levels and risk of AF. These include sex (whereby males seem to be at a
264 higher risk as exercise levels increase), intensity/type of PA (it is believed vigorous-intensity
265 endurance exercise may increase risk, though the impact of high-intensity interval training on
266 AF risk is unknown), age (as age increases, so does the risk of AF), and genetic predisposition
267 (there is a genetic risk of AF, independent of training response). It is also important to note
268 research caveats relating to trial design and sample size, for example the relatively small
269 participant numbers at the highest of activity levels (i.e. far right of the curve; Figure 1).
270 Below, we discuss the potential mechanisms which may explain the counterintuitive higher
271 risk for AF in those who engage in excessively high levels of vigorous-intensity PA and exercise.

272
273 ***What pathophysiological mechanisms may contribute to the higher AF burden in athletes?***
274

275 The pathophysiology of exercise-induced AF is not yet fully understood, though atrial
276 remodelling, inflammation, and autonomic imbalance may represent central underlying
277 mechanisms (Figure 1). Counterintuitively, these factors seem involved in both the beneficial
278 and deleterious mechanisms between PA, exercise, and incident AF. Whereby, with excessive
279 exercise levels (well exceeding the recommended guidelines) physiological atrial remodelling
280 becomes pathological remodelling (i.e. facilitates an AF substrate), inflammation is enhanced
281 (compared to a reduction with guideline PA levels), and vagal tone increases beyond an upper
282 (arrhythmia-specific) healthy threshold (Figure 1). Animal models have demonstrated that
283 long-term, vigorous-intensity endurance exercise promotes adverse cardiac remodelling and
284 an arrhythmia substrate (65). Following 16-weeks of endurance exercise (1h treadmill
285 running/day) murine models demonstrated increased AF susceptibility via autonomic
286 changes, atrial dilation, and fibrosis (66). Below, these potential pathways have been
287 discussed in further detail.

288 *Atrial remodelling.* Increased left atrial size is an independent risk factor for lone AF in normal
289 and clinical populations (9). In contrast, despite up to 20% of athletes presenting with
290 enlarged left atrial cavities, evidence linking this adaptation to incident AF is unclear (67).
291 Exercise-induced atrial enlargement may therefore be physiological rather than
292 pathophysiological, at least in athletes. Thus, left atrial dilation may not be a central
293 component of 'athletic AF'.

294 Atrial fibrosis is another component of the atrial arrhythmogenic phenotype (68). One study
295 reported 50% (6/12) male endurance athletes demonstrated evidence of myocardial fibrosis
296 by late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMR). This
297 was in contrast to no LGE demonstrated in 17 young athletes or 20 age-matched sedentary
298 controls (69). The study found that years of training ($p < 0.001$) and number of competitive
299 marathons ($p < 0.001$) predicted prevalence of LGE via CMR. Supported by murine models, 16-
300 weeks of endurance training resulted in left and right atrial fibrosis (66). Specifically, Guasch
301 et al. observed that fibrosis concomitant with vagal enhancement (see below) resulted in
302 heightened AF susceptibility. Following a detraining period, AF susceptibility was fully
303 reversed without a reversal in atrial fibrosis. Thus, although an important component, atrial
304 fibrosis is not the sole mechanisms involved in exercise-induced AF susceptibility.

305 Angiotensin II and transforming growth factor beta 1 (TGF β 1) are major pro-fibrotic signalling
306 molecules, both also involved in platelet-derived and connective tissue growth factors (70).
307 Elevated angiotensin II has been shown to precede atrial fibrosis in clinical populations such
308 as heart failure and angiotensin-converting enzyme inhibition (at least partly) reduces atrial
309 fibrosis (71). This highlights the multifactorial nature and seemingly central role of atrial
310 fibrosis in 'athletic AF'.

311 *Inflammation.* Inflammation is a well-established risk factor for incident AF and shares
312 common pathways with fibrosis (10). Several proinflammatory markers have been linked with
313 AF such as C-reactive protein (CRP), tumour necrosis factor (TNF- α), and interleukin (IL)-2, IL-
314 6, IL-8 (72). In fact, a causal relationship between TNF- α and exercise-induced AF has been
315 established in murine models (73). Acute exercise studies may shed light on the
316 pathophysiological mechanisms of repeated endurance exercise over years of training and
317 incident AF. In humans, Wilhelm et al. (74) demonstrated enhanced proinflammatory markers
318 (TNF- α , IL-6, and CRP) and atrial remodelling following a single mountain marathon. Findings
319 revealed a post-race (exercise-induced) atrial myocardial oedema and increased
320 proinflammatory markers. Further, the increase in proinflammatory markers were higher
321 than that previously reported in a flat marathon study (75), supporting the notion of an
322 intensity-dependent inflammatory response. Although further research is required to
323 investigate causation, recent work has implied cardiac dysfunction following intense
324 endurance exercise was associated with increased expression of pro-inflammatory cytokines

325 (76). Such findings demonstrate how repeated episodes of high-intensity endurance exercise
326 may contribute to an overall proinflammatory state, contributing to an AF substrate.

327 *Autonomic imbalance.* Bradycardia in athletes is likely explained through cardiac remodelling,
328 but also upregulated vagal tone and HCN4-channels (77). Athletic bradycardia, although
329 cardio-protective, has been implicated in the development of AF (78). For example, abrupt
330 shifts in autonomic tone, as seen during the onset and recovery of exercise training has been
331 shown to precede the onset of paroxysmal AF (79). There are also several characteristics that
332 support the involvement of vagal tone in AF more generally.

333 Several studies have reported an increased onset of AF at night (when vagal tone is highest)
334 and during eating (i.e. vagal stimulation) (80). Supported by animal models, bradycardic
335 responses to blood pressure elevation with phenylephrine (reflecting vagal upregulation),
336 was approximately doubled following 16-weeks of endurance exercise training compared to
337 no change in sedentary controls (66).

338 In addition, early and delayed afterdepolarizations are thought to cause ectopic and re-entry
339 arrhythmic activity, promoted by prolonged repolarization and Ca²⁺ handling abnormalities,
340 respectively. Liu and Nattel (81) suggested that vagal stimulation promoted AF via
341 prolongation of the atrial effective refractory period (ERP; during which a new action
342 potential cannot be initiated, though individual cells/sites can depolarize), which was not
343 seen during sympathetic stimulation. This effect occurs via activation of acetylcholine-
344 dependent potassium currents. Increased vagal tone as a result of endurance exercise has
345 been shown to elicit heterogeneous shortening of the action potential duration (APD) via
346 increased sensitivity to acetylcholine, secondary to a reduction in regulators of G-protein
347 signalling proteins (82). Thus, an increased ERP and a correspondingly reduced APD may be a
348 key mechanism in the development of 'athletic AF'.

349 Despite some existing mechanistic insights highlighted above, further research is needed to
350 elucidate the autonomic and associated molecular characteristics, which contribute to AF in
351 humans (especially endurance athletes), particularly with regard to individual and
352 subpopulation heterogeneity.

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355

3. Summary and future perspectives

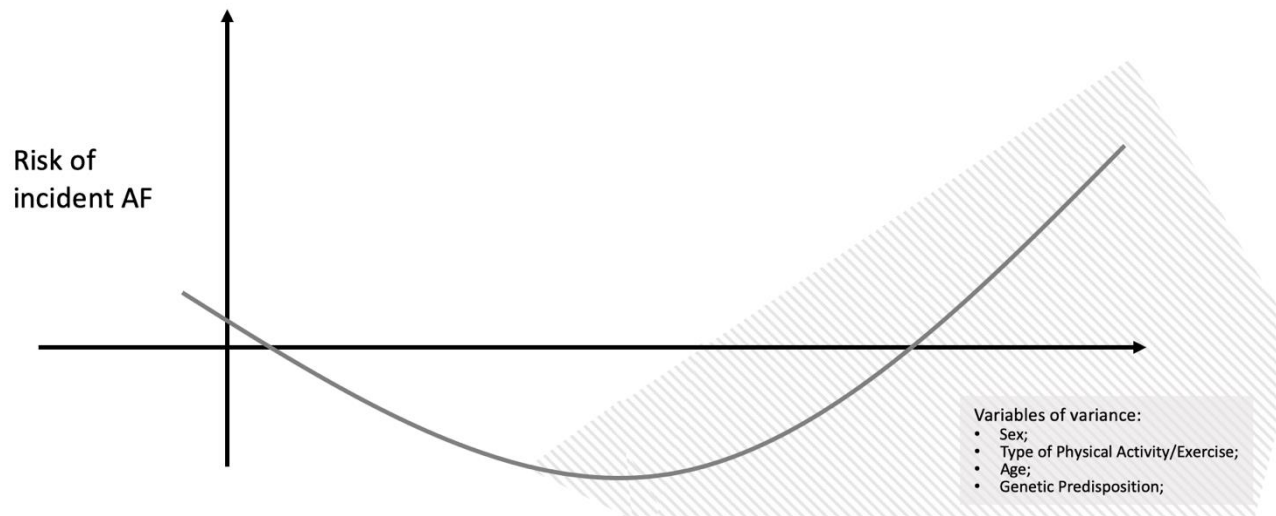
356 Regular PA and exercise training induce a dose-dependent decline in risk of incident AF and
357 secondary cardiovascular events, which may be explained through its effect on traditional
358 cardiovascular risk factors, inflammation, cardiac remodelling, endothelial function, and
359 autonomic balance. As levels of PA and exercise increase beyond that recommended, the
360 protective health impacts on AF development attenuate. In fact, as one moves further to the
361 right of the dose-response curve, e.g. excessive endurance exercise, AF risk returns to normal
362 or may even exceed the risk for incident AF found in inactive cohorts (Figure 1). Potential
363 pathological mechanisms relating to this counterintuitive role of (too much) exercise on AF,
364 include an AF substrate (atrial enlargement, atrial fibrosis, myocardial inflammation) and
365 upregulated vagal tone.

366 Nevertheless, further work is needed to investigate the effects of PA on AF in humans,
367 independent of other target risk factors such as body mass, blood pressure, and lipids, for
368 example. In addition, given the relatively small sample size of the most active study
369 participants, further research is needed to elucidate the seemingly enhanced risk of AF in
370 these cohorts. It is possible components of 'athletic AF' are reversible with detraining, as
371 shown in animal models, though research is needed in humans to confirm the reversibility of
372 underlying mechanisms and indeed how such recommendations are received by athletes.

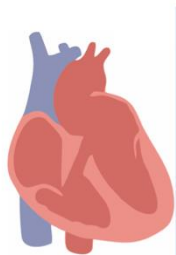
373 Although there remains uncertainty as to the upper 'safe' threshold of exercise and incident
374 AF, there is no evidence to suggest that exercise training within current guidelines causes or
375 exacerbates AF. Conversely, recent evidence suggests three times the recommended PA
376 levels (and even beyond for females) is AF protective (23). It is only at exceptionally high levels
377 of vigorous endurance training do we see an increased risk of AF (e.g. >5000 vigorous MET-
378 mins/week). This increased risk of AF appears to be more pronounced in males than females
379 and research is therefore needed to confirm sex-specific, safe upper levels of PA for AF
380 protection. In addition, further work is needed to determine the effect of different PA modes
381 (e.g. continuous endurance training, high-intensity interval training, and habitual PA) on AF
382 risk.

383 Better understanding of the mechanisms underpinning PA, exercise and AF will contribute to
384 optimal prescription of exercise for AF patients and improve understanding of AF in athletes.
385 Such insight may relate to optimisation (e.g. type, dose, mode of exercise) and wider
386 prescription of regular PA in the primary and secondary prevention of AF. Moreover, research
387 should also consider the wider benefits of regular PA in these populations, especially since AF

388 patients are of increased risk for cerebrovascular complications and cognitive decline. Finally,
389 better insight is required to guide and treat the most active AF patients where excessive
390 amounts of PA have contributed to the development of AF. Nonetheless, the key message
391 remains that exercise should be regarded as medicine for patients with AF, demonstrating a
392 dose-dependent relationship, with excessive amounts corresponding to an “overdose” in the
393 treatment of AF.

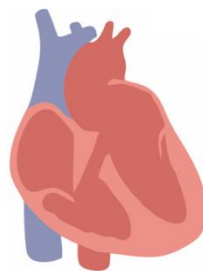


Not Meeting Physical Activity Guidelines Meeting Physical Activity Guidelines Excessive Exercise Levels*

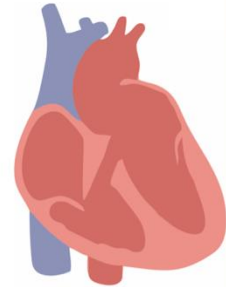


- ↑ **Cardiovascular Risk Factors**
- ↓ Physiological Cardiac Remodelling
- ↓ **Endothelial Function**
- ↓ Vagal Tone
- ↑ **Inflammation**
- Virchow's Triad**
- ↑ Abnormal Blood Flow
- ↑ Abnormal Vessel Wall
- ↑ Blood Constituent Abnormalities

Bold text denotes pro-AF variable



- ↓ Cardiovascular Risk Factors
- ↑ Physiological Cardiac Remodelling
- ↑ Endothelial Function
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- ↓ Inflammation
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- ↓ Abnormal Vessel Wall
- ↓ Blood Constituent Abnormalities



- ↓↓ Cardiovascular Risk Factors
- ↑↑ Physiological Cardiac Remodelling
- ↑ **Pathological Cardiac Remodelling (AF Substrate)**
- ↑ Endothelial Function
- ↑↑ **Vagal Tone**
- ↑ **Inflammation**
- Virchow's Triad**
- ↓ Abnormal Blood Flow
- ↓ Abnormal Vessel Wall
- ↓ Blood Constituent Abnormalities

Bold text denotes pro-AF variable

*Excessive exercise levels refers to that of a training load that far surpasses the recommended guidelines of 150-minutes of moderate-intensity or 75-minutes of vigorous-intensity physical activity per week. Further research is however required to determine an upper 'safe' level, though up to three-fold the recommended physical activity levels (and even beyond for females) seems to confer AF-specific cardio-protection.

Figure 1. Central illustration presenting a J-shaped dose-response curve with reduced incident AF as physical activity levels increase from inactive (below guideline amounts) up to guideline levels of physical activity. Beyond guideline amounts, excessive exercise levels (e.g. long-term high-intensity endurance training) may result in an increased risk of incident AF. The proposed physiological mechanisms of beneficial effects of guideline levels of physical activity on AF and pathological mechanisms of inactivity (left) and excessive levels of exercise (right) are also presented. The shaded area of interest, which increases in size towards the right of the x-axis, denotes the proposed variance in high levels of endurance training and risk of AF. These variables of variance include sex (whereby males seem to be at a higher risk as exercise levels increase), type of physical activity (it is believed vigorous-intensity endurance exercise may increase risk, though the impact of high-intensity interval training on AF risk is unknown), age (as age increases, so does the risk of AF), genetic predisposition (there is a genetic risk of AF, independent of training response). It is also important to note research caveats relating to a variety of trial designs, sample size, and small participant numbers at the highest of activity levels (far right of the curve).

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