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FASTTRACK – CLINICAL RESEARCH
Arrhythmias

Atrial fibrillation in former world-class rowers: role of environmental and genetic factors

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Abstract

Background and Aims Endurance sport has been associated with an increased risk of atrial fibrillation (AF). The aim of this study was to assess the extent to which this is due to exercise burden or genetic predisposition.

Methods Former rowers aged 45–80 years who competed at international championships were compared with a control group extracted from the UK Biobank, matched (1:100) for age and sex. Evaluation included 12-lead and Holter electrocardiograms, cardiac magnetic resonance imaging, and genetic analyses including rare variant evaluation and derivation of a validated AF polygenic risk score (AF-PRS).

Results Of 121 rowers [age 62 years (interquartile range 54–69), 74% male], 26 (21.5%) had AF as compared with 364 of 11 495 control subjects (3.2%), prevalence risk ratio 6.8 [95% confidence interval (CI) 4.7–9.8]. Incident AF over 4-year follow-up was also greater [6 of 95 rowers (6.3%) vs 252 of 11 131 controls (2.3%), hazard ratio 2.8 (95% CI 1.6–5.0)]. Compared with controls, athletes demonstrated greater structural and electrophysiological cardiac remodelling. Athletes had similar cardiovascular risk

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factor profiles but a higher stroke prevalence than controls [3.3% vs 1.1%, risk ratio 3.0 (95% CI 1.1–7.9)]. Rare pathogenic and likely pathogenic variants in cardiomyopathy genes had low prevalence in athletes (2.7%) and were not enriched in those with AF. In contrast, in those subjects with a high AF-PRS (defined by the upper quartile in a healthy reference population) the odds of having AF increased 3.7-fold in athletes (95% CI 1.5–9.4) and 2.0-fold in controls (95% CI 1.7–2.4; $P = .37$ for between-group comparisons).

Conclusions Despite having a favourable cardiovascular risk factor profile compared with controls, elite endurance athletes had a markedly higher prevalence and incidence of AF. These data suggest that exercise-induced cardiac remodelling and genetic susceptibility contribute to AF in endurance athletes.

Structured Graphical Abstract

Key Question

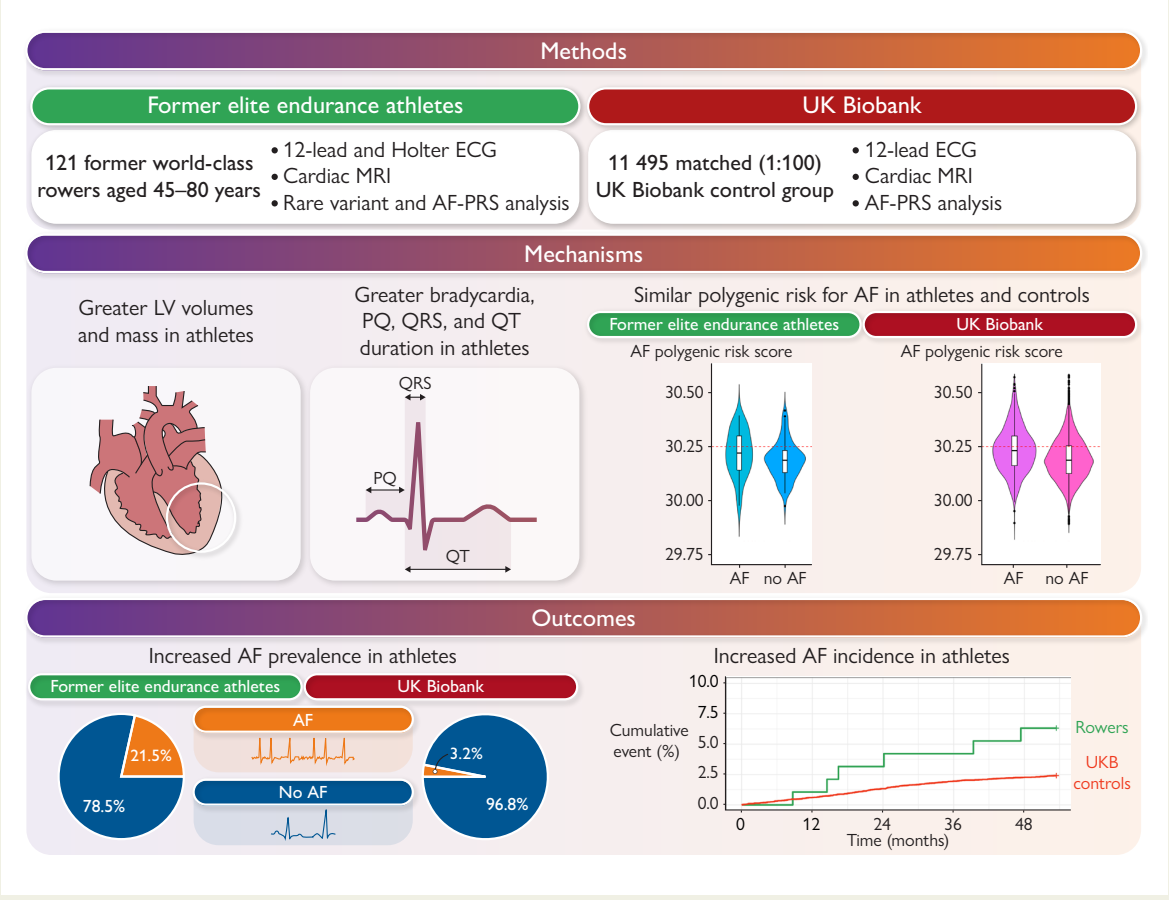
Is atrial fibrillation (AF) more prevalent in former elite rowers than in the general population? Is AF in athletes explained by a greater genetic predisposition?

Key Finding

The prevalence of AF was considerably higher in former elite rowers as compared with non-athletes. Athletes demonstrated greater structural and electrophysiological cardiac remodelling, whilst high polygenic risk increased the odds of AF in athletes and non-athletes alike.

Take Home Message

Exercise-induced cardiac remodelling and genetic susceptibility can help identify athletes at particularly high risk of AF. This may assist in the early diagnosis of AF and prevention of thromboembolic events.



The study compared 121 former elite rowers with 11495 age- and gender-matched subjects from the community (UK biobank). Structural and electrical remodelling was greater in the athletes. Both athletes and controls with atrial fibrillation (AF) were more likely to have a high AF polygenic risk score than those without AF (middle panels). Remarkably, athletes were 7-times more likely to have AF (bottom left). Incident AF over 4-years follow-up was also increased in the athlete cohort as compared with controls (bottom right).

Keywords Athlete • Atrial fibrillation • Genomics • Polygenic • Arrhythmia

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia and is associated with significant morbidity and mortality, including increased risk of stroke, heart failure, and death.[1–3] Atrial fibrillation is commonly associated with risk factors including advancing age, hypertension, obstructive sleep apnoea, obesity, structural heart disease, and alcohol use.[4–7] In this context, it seems counter-intuitive that endurance athletes appear to be at increased risk of developing AF. Most endurance athletes have few of the aforementioned risk factors; yet, studies suggest that male[8–17] and female[18,19] athletes have a greater propensity for developing AF as compared with non-athletes.

The mechanisms, predictors, and extent of AF risk in athletes remain unclear. There are several proposed mechanisms for atrial arrhythmogenesis including exercise-induced haemodynamic stretch, inflammation, and intercurrent illnesses.[20,21] Furthermore, it has been proposed that athletic training may unmask a genetic predisposition to AF.[22] Numerous rare variants have been associated with early-onset AF, with truncating variants in the *TTN* gene being the most frequently identified.[23–27] The cumulative effect of common variants (quantified in polygenic risk scores, PRS) explains a larger proportion of AF heritability,[24] especially in younger individuals with no other risk factors for AF.[26] A recently published Heart Rhythm Society expert consensus statement concluded that it was reasonable to consider genetic testing in young athletes with AF.[28] However, the role of genetic susceptibility to AF in athletes has not yet been assessed.

Although there is relative concordance between studies in the association between endurance exercise and AF, there is variability in the estimates of relative risk. This is due to difficulties in accurately identifying all cases of AF (the 'numerator') from an at-risk athletic population (the 'denominator'). Drawing inference from multiple studies of varied methodology, it seems that AF risk is greatest in athletes who have performed at more elite levels over longer careers.[8–16] An additional factor is that, as for non-athletes, AF prevalence increases with age.[29] Therefore, the highest rates of AF might be expected in elite endurance athletes years after retirement from competition.

In the ProAFHeart study, we sought to (i) provide an estimate of AF prevalence and incidence among elite retired rowers as compared with age and gender matched population referents and (ii) assess the degree to which any excess risk could be explained by genetic predisposition. We hypothesized that we would identify an excess of AF that was explained predominantly by environmental factors (such as a career of intense sports training) rather than genetic factors.

Methods

Study population

We recruited former elite rowers aged 45–80 years who competed at a national, world championship or Olympic level. A minimum of 10-year participation was required for enrolment. Participants were recruited from individual boat clubs and word-of-mouth with the assistance of Australian Rowing History (www.rowinghistory-aus.info) who had compiled a complete list of all 322 athletes in the Australian state of Victoria who had rowed at World Championships or at the Olympic games between 1960 and 1992 inclusive. The study was advertised on the Rowing Australia website and via group emails from Rowing Australia and rowing clubs. The stated purpose of the study in all advertisements and correspondence was to assess the cardiovascular effects of past participation in elite rowing. There were no specific exclusion criteria.

A matched control group at a ratio of 1:100 was extracted from the UK Biobank.[30] Participants were matched for gender, ethnicity, and an age within 5 years of the corresponding athlete age and randomly selected from a subset of 25 140 UK Biobank participants who had undertaken the imaging assessment which includes repeat medical history, electrocardiogram (ECG), dual-energy X-ray absorptiometry (DEXA), and cardiac magnetic resonance imaging (CMR).[31] Unique controls were randomly selected for each athlete and investigators were blinded to AF status at the time of selection. Ages for the UK Biobank participants were calculated based on the date of the imaging assessment. Atrial fibrillation risk factors were identified by extracting specific fields. Prevalent AF was defined as AF, which had been identified by the date of CMR on the baseline UK Biobank evaluation (inclusive of ECG). During follow-up, participants were considered to have incident AF if it was self-reported, diagnosed as a hospital inpatient or recorded in primary care databases with data censored at 4 years to match the follow-up period of the athlete cohort.

Exercise history

All participants completed a questionnaire detailing the frequency, duration, and intensity of exercise training during the years of international competitive rowing and after retirement. Each sport was assigned a metabolic equivalent task (MET) score from the Compendium of Physical Activities[32] but using the reported level of performance (e.g. recreational vs. national competition) and intensity (low, moderate or high) to choose the appropriate MET score from the Compendium since multiple options were available. Exercise volume (MET hrs/week) during active exercise years was calculated by multiplying the MET score by the reported weekly exercise hours as reported previously.[33,34] The population was dichotomized into those athletes who continued to exercise vigorously after their rowing career (termed 'Lifelong Athletes') and were defined as those who engaged in ≥5 cumulative hours per week of high-intensity exercise in the 5 years preceding enrolment and had a maximal oxygen uptake >120% of age-predicted norms (using the FRIEND registry nomogram.[35]) Retired athletes were those who did not meet both of these criteria.

Baseline investigations

Baseline evaluation included medical history, alcohol use survey, ECG, cardiopulmonary exercise testing (CPET), 3-day Holter monitoring, blood sampling for genetic testing, DEXA and CMR for the measurement of left ventricular volumes and ejection fraction. Prevalent AF was identified via ECG and medical history. If there was any uncertainty regarding the diagnosis of AF, additional medical records were sought with participant consent. Participants underwent annual follow-up with a repeat medical questionnaire and 24-h Holter monitoring to identify incident AF.

Genetic analyses

Peripheral blood samples were collected and deoxyribonucleic acid (DNA) was extracted following standard protocols[36] and sequenced using a custom gene array (TWIST Bioscience, San Francisco, CA, USA) comprised of protein-coding sequences of 24 genes that have strong evidence of association with inherited cardiomyopathies. Following quality control metrics, sequencing data were aligned to the hg38 reference human genome, analyzed using a Genome Analysis Toolkit best practices analysis pipeline and annotated using a Variant Prioritizing Ordering tool, a customizable variant prioritization ordering tool.[37] Single nucleotide variants were evaluated further if they were protein-altering (stop gain, splice donor or acceptor site loss, small frame-shifting insertions or deletions, missense) and rare [defined as minor allele frequency (MAF) <0.1% in the gnomAD population database (v2.1.1; accessed May 2022)]. Variants were classified as pathogenic, likely pathogenic (LP), of uncertain significance (VUS), likely benign, benign, according to recommendations for clinical reporting from the American College of Medical Genetics and Genomics (ACMG).[38]

DNA samples were also genotyped using the Axiom Precision Medicine Diversity Array (v2.0; ThermoFisher Scientific, CA, USA). Quality metrics

and variant calling were performed using in-house pipelines aligned to the human reference genome hg38. Atrial fibrillation polygenic risk scores (AF-PRS) were calculated using the Khera *et al* method.[39] To define a high AF-PRS, we used a reference population of 12 031 individuals of European descent aged ≥70 years with no history of diagnosed cardiovascular disease events of AF enrolled into the Aspirin in Reducing Events in the Elderly trial (ASPREE; NCT01038583).[40] The ASPREE study population was genotyped using the same array and methods as the ProAFHeart study.[41] A high AF-PRS was defined by the top quartile of scores in ASPREE participants.

Statistical analysis

The primary outcome was prevalence of AF in both groups. Secondary outcomes included incident AF, high AF-PRS, prevalence of AF risk factors and cardiac volumes on CMR.

Data were assessed for normal distribution using the Kolmogorov–Smirnov test. Normally distributed data are expressed as mean ± standard deviation, and variables were compared using an independent samples *t*-test. Non-normally distributed data are expressed as median (interquartile range, IQR) and compared using a Welch two sample *t*-test. Categorical values were compared using Pearson's chi-square or Fisher's exact test for comparisons involving fewer than 5 cases. A sensitivity analysis was performed to assess the prevalence of AF if none of the non-recruited athletes had been diagnosed with AF.

The study was initially planned to recruit 220 former elite rowers and 220 control subjects. This sample size provided 80% power of identifying a 4-fold greater prevalence among athletes (alpha = 0.05), assuming a 2.5% prevalence of AF in male control subjects and 0.5% of female subjects (20% of total cohort). Recruitment difficulties, particularly of control subjects and exacerbated by the COVID-19 pandemic, resulted in a change of design in which the UK Biobank was utilized as a control population. Harnessing the additional power of matching 100 controls to each elite athlete resulted in greater power with a smaller athlete cohort. Using the same gender assumptions, cohorts of 104 and 10 400 subjects, respectively, provided 90% power of detecting a 4-fold difference in AF prevalence.

Results

Over a 4-year period, 121 former elite rowers were recruited and followed for a median of 4.4 years (IQR: 3.6–5.1 years). The mean age was 62 ± 9 years, 74% were male, and all were white ethnicity. Baseline demographics are presented in *Table 1*. The athletes were an elite cohort with 23 being former Olympians. Between them, they won nine Olympic gold medals, ten silver medals and two bronze medals.

As might be expected, even in retirement, athletes performed more exercise, were taller, leaner, and had greater bone mineral density than controls (*Table 1*). There were few differences between the athlete group and controls in regard to cardiometabolic disease, with similar rates of ischaemic heart disease, diabetes, and hypertension, although athletes had slightly lower systolic and diastolic blood pressures. The athletes were less likely to have ever smoked compared with controls (25% vs. 38%), and no athletes were current smokers as compared with 4% of controls. There was a difference in the pattern of alcohol consumption with athletes being more likely to drink at either extreme (seldom or frequently), whereas control subjects were more likely to drink intermittently. Strokes were uncommon, but three times more prevalent [95% confidence interval (CI) 1.1–7.9] in the athletes as compared with controls.

The cardiac volumes of the athletes as measured on CMR were significantly larger than those measured in the control group, but there was no difference in left ventricular ejection fraction. There were also significant differences in the ECG parameters between the two groups. The athletes had lower heart rates, longer PQ intervals, longer QRS durations, and longer QT intervals than the control participants (*Table 1*).

The primary outcome of AF prevalence was higher among former elite athletes (26 of 121, 21.5%) than control subjects (364 of 11495, 3.2%, $P < .001$) [prevalence risk ratio (PRR) 6.8, 95% CI 4.7–9.8] (*Figure 1*). The proportion of women with prevalent AF was similar in athletes (1 of 31, 3.2%) compared to controls (122 of 2823. 4.3%) (PRR 0.75, 95% CI 0.1–5.2). Considering the potential for a selection bias, a sensitivity analysis was performed assuming 100% selection bias, i.e. that none of the 201 eligible athletes that did not volunteer to participate had AF. In that scenario, the prevalence of AF in the rowers remained greater than in the controls (8.1% vs. 3.2%; PRR 2.5, 95% CI 1.7–3.7). The corollary, that all of the eligible but non-enrolled athletes had AF, would have resulted in a maximal potential AF prevalence of 70.5% and a 22-fold greater prevalence (19.3–25.7). Therefore, considering the sensitivity analysis, the prevalence comparison between athletes and non-athletes could be expressed as 21.5% (8.1%–70.5%) vs. 3.2% and a PRR between 2.5 and 22.3 (95% CI 1.7–25.7).

Follow-up data revealed a significant difference in the incidence of AF between the two groups (*Figure 2*). Six of 95 (6.3%) rowers with no prior AF experienced a first episode of AF during follow-up as compared to 252 of 11 131 (2.3%) of the control group. This represents an incidence of 16.0 vs. 5.7 AF cases per 1000 person-years. Survival analysis demonstrated that in those without AF at baseline, the athletes were 2.8 times likely to develop incident AF (hazard ratio 2.80, 95% CI 1.6–5.0).

As documented in Supplementary data online, *Table S1*, retired and lifelong athletes performed similar amounts of exercise during their competitive years (104 vs. 96 MET hrs/week, $P = .51$). As expected, lifelong athletes continued regular exercise training for longer than the retired athletes such that the total years of exposure were greater (43 vs. 38 years, $P < .001$). Atrial fibrillation was more prevalent among retired athletes (22 of 80, 27.5%) than lifelong athletes (4 of 41, 9.8%; PRR 2.8, 95% CI 1.01–7.7), whereas incident AF tended to be less [5.1% in retired athletes vs 8.1% in lifelong athletes; risk ratio 0.64, 95% CI 0.14–3.0)]. Overall rates of AF (prevalent and incident) were not significantly different (31.3% vs. 17.1% in retired vs. lifelong athletes; risk ratio 1.8, 95% CI 0.85–3.9).

Within group analysis of the UK Biobank control group demonstrated that participants with prevalent or incident AF were more likely to be older and male (*Table 2*). In an unadjusted descriptive analysis, they were also significantly more likely to have hypertension, ischaemic heart disease, diabetes, and prior stroke. The participants with AF also had higher body mass index (BMI) and higher systolic blood pressures than those without AF but had lower diastolic blood pressures. Those without AF were more likely to have never smoked than those with AF. Alcohol use was also associated with prevalent AF, with AF subjects more likely to drink daily or almost daily, although differences were modest between those with and without AF. Participation in vigorous exercise was slightly less in the AF cohort.

The control group participants with AF also had significantly lower stroke volumes and slightly lower left ventricular ejection fractions. Regarding ECG measurements, heart rates were slower while PQ intervals, QRS durations, and QT intervals were all longer in the AF cohort (*Table 2*).

Athletes with prevalent or incident AF were also more likely to be male and older (*Table 3*). In analyses without adjustment for these differences in age and sex, athletes with AF performed less daily vigorous activity, had higher blood pressure and had a trend toward higher prior stroke, although the prevalence was low. Cardiac structure and electrocardiographic measures were similar in those with and without AF.

Table 1 Baseline demographics

	UKB Cohort $n = 11\,495$	Athletes $n = 121$	*P*-value
Female, *n* (%)	2945 (25.6)	31 (25.6)	
Age, years, median (IQR)	62 (56–68)	62 (54–69)	.68
Ethnicity, White, *n* (%)	11 495 (100)	121 (100)	
Height, cm	174 ± 10	180 ± 9	<.001
Weight, kg	79.5 ± 14.3	84.9 ± 15.1	<.001
BMI, kg/m^2	26.1 ± 4.0	25.9 ± 3.2	.58
Total tissue fat percentage (%)	32 ± 8	27 ± 7	<.001
Bone mineral density, Z-score	1.26 ± 0.13	1.34 ± 0.13	<.001
Smoking, *n* (%)			.005
Never	7152 (62.2)	91 (75.2)	
Current	451 (3.9)	0 (0.0)	
Daily moderate activity, min, median (IQR)	30.0 (20.0–60.0)	38.0 (24.3–64.3)	<.001
Daily vigorous activity, min, median (IQR)	20.0 (0.0–45.0)	64.3 (4.3–128.6)	<.001
Alcohol intake, *n* (%)			.009
Never	545 (4.7)	8 (6.6)	
Special occasions only	919 (8.0)	14 (11.6)	
One to three times a month	1204 (10.5)	0 (0.0)	
Once or twice a week	3162 (27.5)	15 (12.4)	
Three or four times a week	3527 (30.7)	50 (41.3)	
Diabetes, *n* (%)	653 (5.7)	4 (3.3)	.26
Hypertension, *n* (%)	2702 (23.5)	25 (20.7)	.53
Systolic blood pressure, mmHg	138 ± 18	133 ± 19	.001
Diastolic blood pressure, mmHg	80 ± 10	75 ± 11	<.001
Myocardial infarction, *n* (%)	220 (1.9)	0 (0.0)	.23
Angina, *n* (%)	249 (2.2)	1 (0.8)	.49
Stroke, *n* (%)	128 (1.1)	4 (3.3)	.049
Cardiac magnetic resonance measures			
LVEDVi, mL/m^2, median (IQR)	76 (67–86)	90 (81–97)	<.001
LVESVi, mL/m^2, median (IQR)	33 (29–39)	40 (34–45)	<.001
LVEF, %, median (IQR)	56 (52–59)	55 (52–59)	.47
LVSVi, mL/m^2 median (IQR)	42 (37–48)	50 (44–54)	<.001
Electrocardiogram parameters			
Ventricular rate, bpm	60 ± 10	55 ± 10	<.001
PQ interval, ms	165 ± 28	192 ± 44	.017
QRS duration, ms	90 ± 13	102 ± 15	<.001
QT interval, ms	419 ± 32	434 ± 32	<.001
R axis, degrees	28 ± 37	40 ± 55	.025

BMI, body mass index; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LVSV, left ventricular stroke volume.

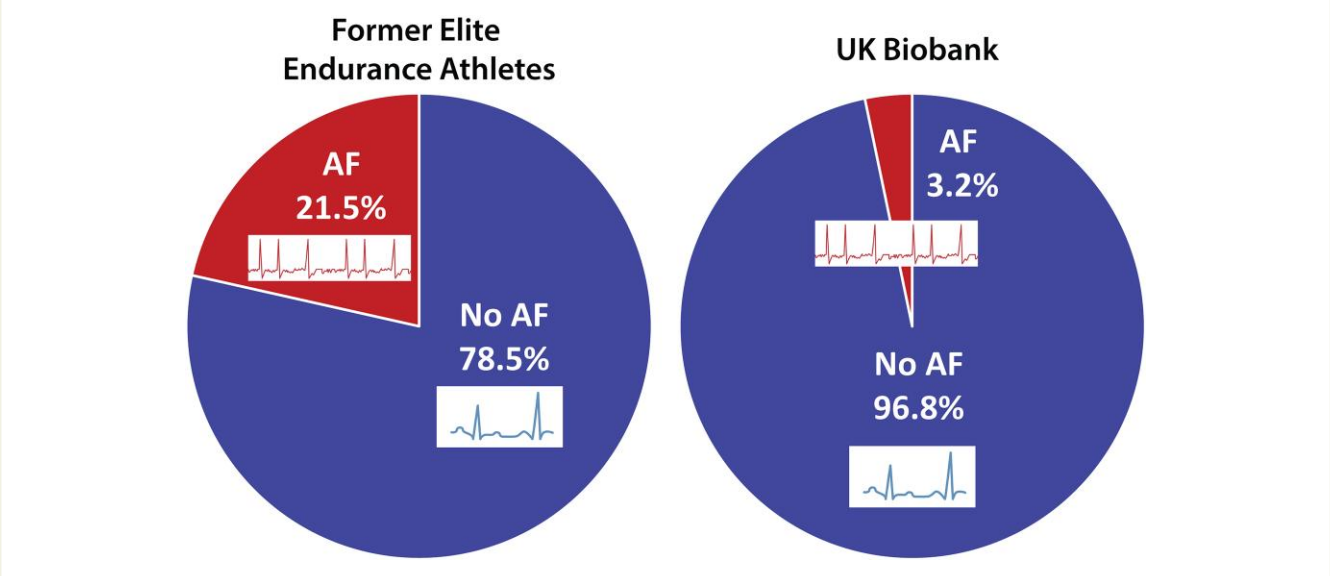


Figure 1 Atrial fibrillation in former elite rowers vs a matched general population. Pie charts demonstrating a marked increase in prevalence of AF (21.5% vs 3.2%, $P < .0001$) in former elite rowers than in the large community-based UK Biobank population

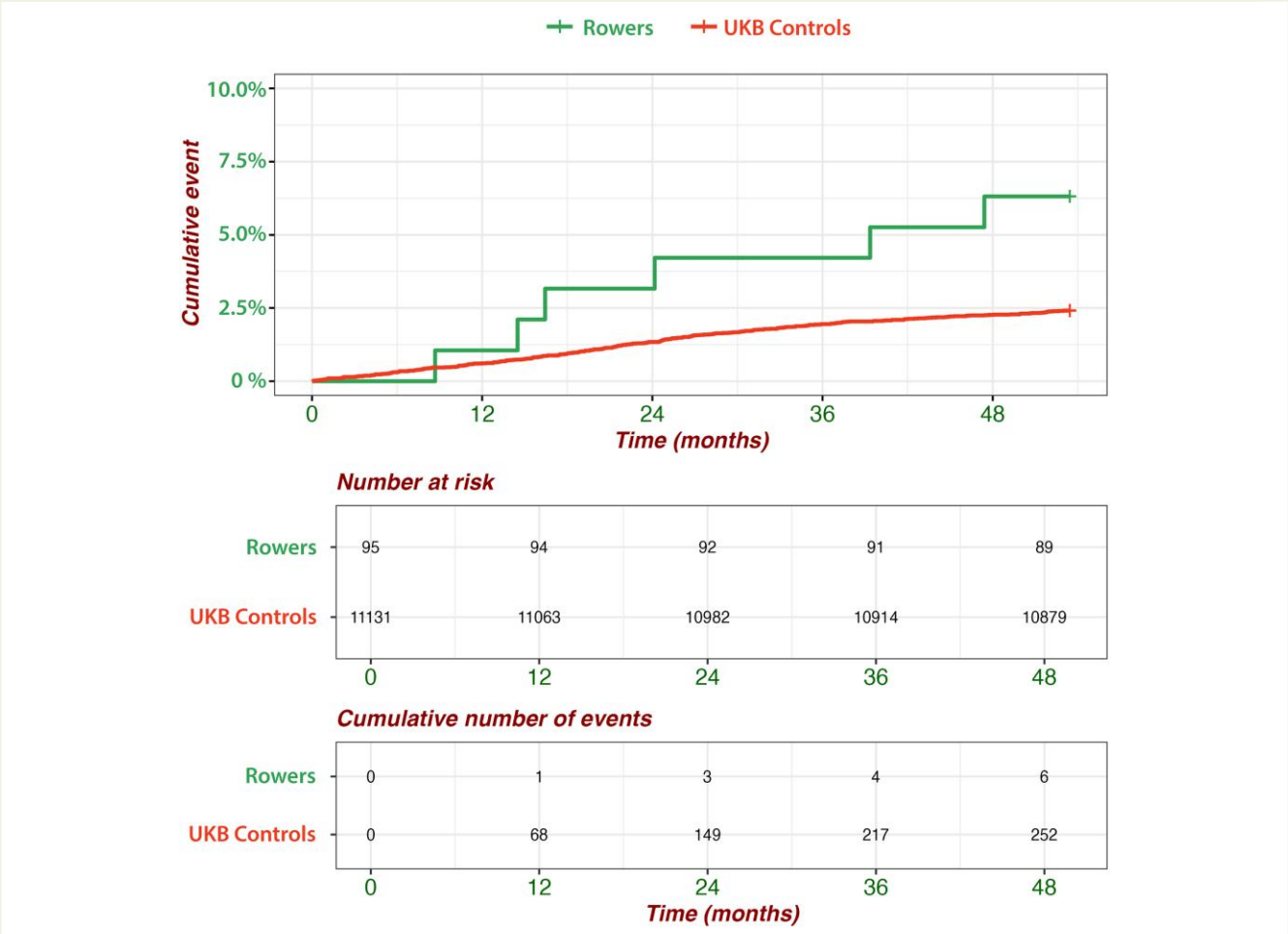


Figure 2 Atrial fibrillation incidence in former elite rowers vs a matched general population. Survival analysis demonstrating a 2.8-fold greater incidence in AF among former elite rowers as compared with the UK Biobank population [hazard ratio 2.8 (95% CI 1.6–5.0)]

Table 2 UK Biobank demographics by AF status

	No AF $n = 10\,863$	AF $n = 632$	*P*-value
Female, *n* (%)	2823 (26.0)	122 (19.3)	<.001
Age, years	61.7 ± 7.6	67.2 ± 7.3	<.001
BMI, kg/m^2	26.1 ± 4.0	26.8 ± 4.4	<.001
Smoking, *n* (%)			<.001
Never	6808 (62.7)	344 (54.4)	
Current	434 (4.0)	17 (2.6)	
Daily vigorous activity (mins), median (IQR)	20.0 (0.0–45.0)	15.0 (0.0–41.2)	.023
Alcohol intake, *n* (%)			.04
Never	508 (4.7)	37 (5.9)	
Special occasions only	871 (8.0)	48 (7.6)	
One to three times a month	1150 (10.6)	54 (8.5)	
Once or twice a week	2999 (27.6)	163 (25.8)	
Three or four times a week	3340 (30.7)	187 (29.6)	
Daily or almost daily	1995 (18.4)	143 (22.6)	
Diabetes, *n* (%)	594 (5.5)	59 (9.3)	<.001
Hypertension, *n* (%)	2460 (22.6)	242 (38.3)	<.001
Systolic blood pressure, mmHg	138 ± 18	142 ± 19	<.001
Diastolic blood pressure, mmHg	80 ± 10	79 ± 11	<.001
Myocardial infarction, *n* (%)	183 (1.7)	37 (5.9)	<.001
Angina, *n* (%)	208 (1.9)	41 (6.5)	<.001
Stroke, *n* (%)	111 (1.0)	17 (2.7)	<.001
Cardiac magnetic resonance measures			
LVEDVi, mL/m^2, median (IQR)	76 (67–86)	78 (67–88)	.0743
LVESVi, mL/m^2, median (IQR)	33 (29–39)	36 (30–44)	.01
LVEF, %, median (IQR)	56 (52–59)	54 (48–59)	<.001
LVSVi, mL/m^2, median (IQR)	42 (37–48)	41 (34–48)	.002
Electrocardiogram parameters			
Ventricular rate, bpm	60 ± 10	61 ± 10	<.001
PQ interval, ms	165 ± 27	181 ± 41	<.001
QRS duration, ms	90 ± 12	93 ± 14	<.001
QT interval, ms	418 ± 32	430 ± 39	<.001
R axis, degrees	29 ± 37	24 ± 37	<.001

BMI, body mass index; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LVSV, left ventricular stroke volume.

Sequencing of 24-cardiomyopathy genes identified likely pathogenic variants in 3 of 113 athletes (2.7%) in whom genetic testing was performed. One of these athletes, who carried a likely pathogenic variant in the *JUP* (plakoglobin) gene, had prevalent AF whereas neither of the two athletes with likely pathogenic variants in the *PKP2* (plakophilin-2) and *DSP* (desmoplakin) genes had prevalent or incident AF. In the three genotype-positive athletes, there were no overt phenotypic features of cardiomyopathy, and none reported any suspicious family history.

Importantly, identification of these potentially disease-causing rare variants has healthcare implications for the 3 athletes involved and their families. Appropriate testing and surveillance have been arranged. However, the overall yield of rare variants was low and did not differ between athletes with and without AF.

Table 3 Athletic demographics by AF status

	No AF $n = 89$	AF $n = 32$	*P*-value
Female, *n* (%)	30 (33.7)	1 (3.1)	.002
Age, years	60.0 ± 8.6	66.5 ± 8.6	<.001
BMI, kg/m^2	25.6 ± 3.2	26.9 ± 3.3	.057
Smoking, *n* (%)			.72
Never	68 (76.4)	22 (69.0)	
Current	0 (0.0)	0 (0.0)	
Daily vigorous activity (mins), median (IQR)	64.3 (30.0–128.6)	48.0 (4.3–112.5)	.022
Alcohol intake, *n* (%)			.61
Never	5 (5.6)	3 (9.4)	
Special occasions only	10 (11.2)	4 (12.5)	
One to three times a month	0 (0.0)	0 (0.0)	
Once or twice a week	9 (10.1)	6 (18.8)	
Three or four times a week	27 (30.3)	7 (21.9)	
Daily or almost daily	38 (42.7)	12 (37.5)	
Diabetes, *n* (%)	2 (2.2)	2 (7.7)	.13
Hypertension, *n* (%)	16 (18.0)	9 (28.1)	.34
Systolic blood pressure, mmHg	130 ± 16	141 ± 23	.017
Diastolic blood pressure, mmHg	74 ± 10	78 ± 12	.17
Myocardial infarction, *n* (%)	0 (0.0)	0 (0.0)	1.0
Angina, *n* (%)	1 (1.1)	0 (0.0)	.9
Stroke, *n* (%)	1 (1.1)	3 (9.4)	.096
Cardiac magnetic resonance measures			
LVEDVi, mL/m^2	91 ± 15	86 ± 14	.13
LVESVi, mL/m^2	40 ± 9	39 ± 7	.49
LVEF, %	56 ± 5	54 ± 6	.26
LVSVi, mL/m^2	51 ± 8	47 ± 10	.11
Electrocardiogram parameters			
Ventricular rate, bpm	54 ± 10	55 ± 9	.89
PQ interval, ms	184 ± 37	167 ± 111	.42
QRS duration, ms	102 ± 16	104 ± 12	.49
QT interval, ms	432 ± 32	438 ± 32	.43
R axis, degrees	41 ± 46	39 ± 77	.90

BMI, body mass index; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LVSV, left ventricular stroke volume.

In contrast to these rare variant findings, evaluation of background genetic susceptibility using AF-PRS revealed significant differences between groups (*Figure 3*). A high polygenic risk score was associated with a nearly 4-fold risk of AF in the athlete cohort (OR 3.7, 95% CI 1.5–9.4, $P = .008$) and a 2-fold risk in the UK Biobank population (OR 2.0, 95% CI 1.7–2.4, $P < .0001$). The proportion of subjects with a high AF-PRS did not differ between athletes and UK Biobank subjects ($P = .37$).

Discussion

We observed a remarkably high prevalence of AF (21.5%, with a lowest possible estimate of 8.1%) in former world-class rowers several decades after retirement from elite competition (*Structured Graphical Abstract*). At a median age of 62 years, this represents one of the highest rates of prevalent AF in any population to date and validates

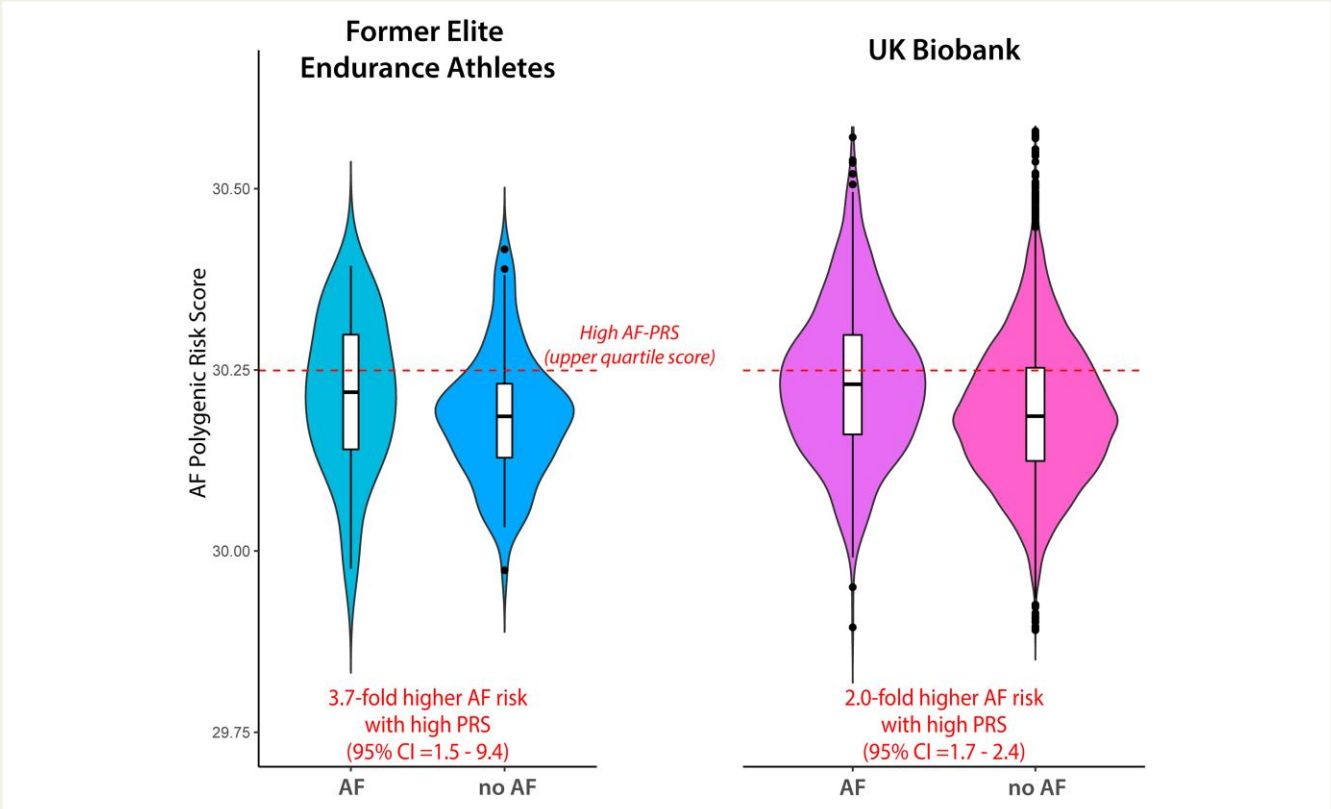


Figure 3 AF polygenic risk score in former elite rowers vs a matched general population. Violin plots demonstrating the distribution of AF polygenic risk scores in former eliter rowers and the UK Biobank population comparing those with and without prevalent AF. In both populations, a high AF-PRS (defined as the upper quartile scores from the healthy ASPREE cohort) was associated with a greater likelihood of AF (2.0 and 3.7 times more likely in the UK Biobank and rowers, respectively)

previous observations of a strong association between AF and intense endurance sports participation. For the first time in an athletic cohort, we report that there is also a measurable genetic contribution to AF.

To accurately define the excess risk of AF in endurance athletes, we studied a group of athletes that had competed at an elite level for at least 10 years. Former elite rowers were recruited from a well-defined population that could be cross-referenced against a Rowing Australia database thereby enabling us to estimate any potential selection bias. This is not trivial as it could be anticipated that athletes with cardiac symptoms (such as known AF or palpitations) may be more likely to volunteer for a study with the stated aim of assessing cardiovascular health. We sought to minimize any potential selection bias by providing ambiguous advertisements to potential volunteers and by making repeated efforts to recruit as many eligible athletes as possible. Furthermore, any potential bias was addressed with a sensitivity analysis that considered the possibility of a 100% selection bias such that all athletes with AF volunteered and none of the remainder had AF. Even in that unlikely scenario, the rowers were more than 2.5 times (95% CI 1.7–3.7) more likely to have AF than matched volunteers from the UK Biobank. Finally, not only was prevalent AF more common, but we observed a 2.8-fold (95% CI 1.6–5.0) greater AF incidence in athletes as compared with population controls. Incident AF is less easily explained by selection bias given that there are seldom prodromal symptoms or signs that would serve as a likely trigger to seek a medical check.

Rowers have been comprehensively evaluated and have amongst the highest training loads, aerobic capacities and greatest cardiac remodelling of any endurance sport.[42–44] Despite the well-defined association between endurance exercise and AF,[8–16,18,19] and rowers being an exemplar for athletic cardiac remodelling, the prevalence of AF had not been previously described in rowers. In our cohort of former world-class rowers with a median age of 62 (IQR 54–69) years, the prevalence estimate of paroxysmal, sustained or chronic AF of between 8.1% and 21.5% is second only to mitral stenosis[45] and similar to that of hypertrophic cardiomyopathy,[46] two conditions in which regular screening for AF is recommended. It could be argued that modern personalized devices with efficacy in the detection of AF may be a prudent investment for older rowers, especially those with risk factors for thrombo-embolism in whom the identification of sub-clinical AF may serve as a trigger for initiating anticoagulation for stroke prevention. Although few events, it is interesting to note that there was a slight excess of strokes among the rowers as compared with the matched UK Biobank population.

It is challenging to identify the ideal cohort when seeking to assess the association between intense exercise and AF. It would seem important to identify a cohort of endurance athletes who submit to the highest loads of training over a prolonged period and then assess this group of athletes at an age when AF becomes prevalent. Prior studies have assessed amateur and recreational athletes[13,15,17,47] or large populations of endurance ski race entrants[10,11] in which the level of athleticism cannot be readily estimated. As far as we are aware, only one prior study has assessed former 'professional' endurance athletes competing at the highest international standard. Baldesberger *et al.*[48] studied 62 former

Tour De Suisse cyclists and compared them with 62 non-athletes (golfing enthusiasts). At an age of 66 ± 7 years, Baldesberger *et al*. observed a 10% prevalence of AF in the former professional cyclists as compared with 0% among the golfers ($P = .028$). The two studies raise the question as to whether the tendency to AF is due to the decades of intense training at younger ages or the tendency for athletes to remain highly active throughout life. In both our study and that of Baldesberger *et al*., there was only a relatively modest excess in the cross-sectional estimates of exercise training among the former athletes as compared with the controls. With the limitations inherent in self-reported exercise history, we sought to interrogate whether AF prevalence differed between lifelong athletes and those who had discontinued intense exercise training. Interestingly, AF seemed to be at least as prevalent among the 'retired' athletes as those still actively training (27.5% vs. 9.8%; PRR 2.8, 95% CI 1.0–7.7). The comparison was greatly confounded in that the retired athletes were slightly older, more frequently male, and the development of AF may have precipitated sport discontinuation in some. However, despite these confounders, it may be reasonable to conclude that the excess AF prevalence is not confined to those who continue to train and that a lifetime of intense exercise is not requisite to the development of AF. Rather, the increased prevalence in the former elite rowers may be attributed to the training and competition as young adults.

The mechanisms underpinning AF predisposition in athletes remains uncertain, although animal studies have linked repeated intense exercise exposure to fibro-inflammatory infiltrates of the myocardium and an increase in vagal tone that modulates arrhythmia inducibility.[21,47,49] Several clinical risk factors have been associated with AF,[7] but this cohort of relatively young athletes and matched referents had relatively low prevalence of comorbidities such as hypertension, smoking, and diabetes. Greater alcohol intake has been associated with AF burden[50] and interestingly athletes were more likely to drink most days than control subjects. The taller stature and lower body fat of the rowers constitute additional modest AF risk factors.[51,52] However, other potential AF risk factors such as the lower blood pressure observed in the athletes would favour a lower expected AF prevalence in rowers. Overall, the differences in comorbidities and lifestyle factors seem modest and somewhat balanced. Certainly, they would not be expected to explain the 7-fold difference in AF prevalence. The history of elite endurance sports training and competition remains the dominant difference between the groups and is further evidenced by the differences in structural and electrophysiological remodelling. On average, the cardiac volumes in the athletic cohort were 15%–20% greater than controls. The athletes had lower heart rates and prolonged conduction and repolarization times. These are well described features of exercise-induced cardiac remodelling ('athlete's heart'),[53] but it is interesting to note that many of these former elite athletes retired decades earlier and yet the changes persist. The amount of structural and electrical remodelling was not different between the athletes with and without AF, again pointing to the intriguing possibility that AF risk persists well after high level training has ceased. This has potential clinical relevance given that many clinicians are cognisant of the association between athletic training and AF, but perhaps less likely to inquire about exercise training several decades prior.

Atrial fibrillation can be an early expression of cardiomyopathy and logic would predict enrichment of inherited heart disease among younger adults with AF. Indeed, a higher prevalence of cardiomyopathic gene variants has been described in younger adults with AF.[23,25,27] However, this same concept cannot necessarily be extrapolated to athletes because it may also be argued that exercise promotes AF via factors such as haemodynamic stressors and remodelling that are sufficiently profound as to promote AF independent of any genetic predisposition. We provide the first data to specifically address these contrasting possibilities and identified a relatively strong association between AF-PRS and AF, thereby suggesting that AF in athletes is not solely attributable to exercise-induced atrial remodelling. Polygenic risk score is a means of quantifying the aggregated genetic risk derived from common genetic variants. By assigning a weighted score to single nucleotide polymorphisms associated with AF derived from whole genome studies in large populations, our study confirms that AF risk is partly determined by a complex interplay of genetic factors that are weak in isolation but moderately influential in combination. We validate this concept in a large non-athletic population and, for the first time, demonstrate that AF in athletes is also associated with the burden of multiple common genetic variants. Those athletes with a high burden of AF-associated polymorphisms (defined by a PRS in the upper quartile of a large healthy community population[40]) were nearly 4-times more likely to develop AF than those athletes with a low burden of AF-associated polymorphisms. The polygenic contribution to AF risk was similar in athletes and non-athletes (odds ratio 3.7 vs. 2.0, $P = .37$) suggesting that complex genetic factors are important in athletes but do not fully explain the markedly heightened prevalence of AF in athletes.

On the other hand, the propensity for AF in endurance athletes was not explained by rare variants in cardiomyopathy-associated genes, which had a very low prevalence overall (2.7%). This approximates, or is lower than, the yield in the general population that has been observed between 6% and 9%.[54,55] Also, the prevalence did not differ between the rowers in our study with or without AF. Expanded genetic testing using larger panels of genes associated with cardiomyopathies and arrhythmias may have resulted in a higher rare variant yield. There are also likely to be subsets of athletes in whom genetic testing may be indicated, such as those with suspicious cardiomyopathic features or a strong family history. Although this cohort of athletes is of modest size, it is the first investigation of cardiomyopathy gene variant prevalence among athletes and the low yield of clinically actionable (likely pathogenic or pathogenic) variants does not provide support for the recent Heart Rhythm Society guidelines that argue that genetic testing in young athletes with AF should be considered.[28] Rather, clinician counselling of athletes with AF should explain that testing is unlikely to identify a significant genetic disorder.

Our data may be an important advance toward refining AF risk stratification and directing targeted care in athletes. Other than increasing age and male gender, we were unable to define many clinical markers that associated with AF in the athletic cohort. Similarly, we have previously demonstrated that imaging markers of atrial myopathy are less predictive in athletic cohorts than in the general population.[56] However, our current data suggest that AF-PRS might be useful for risk stratification. Athletes with a high AF-PRS were four times more likely to have AF than the remaining athletes. It could be argued that male endurance athletes with high AF-PRS represent a cohort in which the risk of AF is markedly increased and in whom further study assessing the efficacy of screening for sub-clinical AF, assessment of thromboembolic risk and targeted anticoagulation is warranted. Furthermore, if evidence evolves suggesting that training modification may attenuate AF risk then AF-PRS may be useful for informing sports choices.

Limitations

This study utilizes two unique populations that are ideal for a comparison of environmental and genetic impacts on AF prevalence. To compare

with a highly refined athletic cohort, we chose a large community-based population of matched demographics and in whom genomic data was available. The 'healthy volunteer' selection bias that characterizes the UK Biobank[57] is likely an excellent comparator for former elite rowers who are generally defined by socio-economic advantage. These two populations were exclusively of white ethnicity thereby aiding comparisons but also limiting generalizability to other ethnicities. Future studies in a more varied sporting demographic will be important in assessing differences in AF prevalence and genetic associations.

It is possible that different selection biases could have impacted comparisons. The methods for determining AF prevalence were similar between the two cohorts, relying upon clinical history and 12-lead ECG at baseline assessment. However, the methods for determining incident AF were not identical. In the athlete cohort, incident AF was determined from an annual Holter monitor and questionnaire whereas, in the UK Biobank, incident AF was determined from linked hospital and family care records and regular on-line questionnaires. It is likely that Holter monitor screening is more sensitive than record linkage and thus incident AF may have been under-estimated in the UK Biobank. It is notable, however, that the incidence of AF in the rowing cohort of 16.0 per 1000 person-years exceeds age-appropriate rates described in the literature and approximates that of populations that are decades older.[58,59] Furthermore, there is a potential for ascertainment bias in that athletes with AF may be more frequently symptomatic than non-athletes.

Our study population was predominantly comprised of men due to the fact that rowing commenced as a world championship and Olympic event for women in 1974 and 1976, respectively. Only one elite female rower had AF making statistical comparisons meaningless. It has recently been reported that AF is more prevalent among athletic women than non-athletic women[18,19] and future studies will be required to assess the extent to which genetic and environmental factors contribute to AF in women.

Conclusions

Former elite endurance sport participation is associated with cardiac remodelling that persists decades after retirement and is associated with a very high prevalence and incidence of AF. Thus, former endurance athletes represent a unique population in which the rate of AF is comparable to other patient groups in which screening for AF may be considered. Contrary to contemporary recommendations, genetic testing to identify variants associated with inherited cardiomyopathies appears to be of low yield. Our data suggest that background genetic variation may be a relatively more important determinant of AF risk. Future incorporation of AF-PRS assessment may be useful in AF risk prediction and could inform AF screening policy and sports choices.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

All authors declare no disclosure of interest for this contribution.

Data Availability

The data relevant to this article will be shared on reasonable request to the corresponding author.

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Ethical Approval

This study was conducted according to the principles outlined by the Declaration of Helsinki and was approved by the local Human Research Ethics Committee (Alfred Hospital HREC/16/Alfred/156).

Pre-registered Clinical Trial Number

The trial has been registered with the ANZ Clinical Trials Registry since commencing in 2018 (ACTRN12618000711213).

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