PHYSICAL ACTIVITY AND CARDIORESPIRATORY FITNESS IN ATRIAL FIBRILLATION INCIDENCE, PROGNOSIS AND PATOPHYSIOLOGY

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In loving memory

of my Mum

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ABSTRACT

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and its burden is rapidly growing worldwide as a consequence of the ageing population and uncontrolled cardiovascular risk factors. The present thesis presents original work addressing multiple aspects of the relationship between AF, physical activity (PA) and cardiorespiratory fitness (CRF).

While PA is an essential component in the management of cardiovascular risk, its role in AF risk prevention is less clear. Recently published data has emerged from large cohorts to clarify this relationship. Chapter 2 systematically reviews the literature and pools AF risk estimates with self-reported PA as the exposure variable. We found an overall AF risk reduction with higher PA with important gender differences. We also observed a non-linear dose-response relationship between PA and AF risk.

Multiple studies demonstrate that obesity results in electrical and structural remodelling ultimately leading to initiation and maintenance of AF. Recent studies have suggested that this association may be mediated by lean mass. Chapter 3 analyses the relationship between AF, ventricular arrhythmias and bradyarrhythmia risk and both lean and fat mass in the UK Biobank cohort. Significant risk of AF was associated with higher lean and fat mass in both men and women. Higher fat mass was associated with higher bradyarrhythmia risk in both men and women with only men having a higher risk with higher lean mass but not women. Furthermore, significant risk of ventricular arrhythmias was associated with higher lean and fat mass with no sex interaction. Importantly, PA did not modify the risk associated with these anthropometric measurements and any of these outcomes.

Patients with established AF have a higher mortality compared with no AF. Chapter 4 shows the associations between weekly total and vigorous PA dose and both all-cause and cardiovascular mortality among participants of the UK Biobank with established AF at

enrolment. Total PA was associated with lower all-cause mortality in women, but not men, although the association between vigorous PA and all-cause mortality persisted across the entire cohort. Total PA was no associated with lower cardiovascular mortality while lower cardiovascular mortality was observed with up to 2000 Metabolic equivalents of task (MET)-minutes/week of vigorous PA.

AF is associated with a profound electrical remodelling of the left atrium (LA) with includes reduced LA voltage, conduction abnormalities and electrogram fractionation. Chapter 5 compares total and regional LA electroanatomical characteristics across CRF levels among patients undergoing AF catheter ablation. Significantly lower voltages were found among those in the lowest CRF category, particularly in the posterior wall, with higher global and regional electrogram fractionation.

LA remodelling is not only limited to electrical but also structural remodelling. LA strain (LAS) is a novel echocardiographic parameter which allows LA mechanical function. Chapter 6 looks at LAS in relation to CRF among patients with a history of AF in sinus rhythm referred for a treadmill test. We found lower LAS (reservoir, booster and conduit) as well as higher LA stiffness in association with lower CRF. Importantly, we found no differences among normal, overweight and obese.

DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Ricardo S. Mishima

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List of abbreviations

AF Atrial fibrillation

AV Atrioventricular

BMI. Body mass index

BSA Body surface area

CAD Coronary artery disease

CFE Complex fractionated electrogram

CI Confidence interval

CIED Cardiac implantable electronic device

CRF Cardiorespiratory fitness

CV Conduction velocity

CVD Cardiovascular disease

DALY Disability-adjusted life-year

DM Diabetes mellitus

ECG Electrocardiogram

ESUS Embolic stroke of unknown origin

EST Exercise stress test

HF Heart failure

HFpEF Heart failure with preserved ejection fraction

HFrEF Heart failure with reduced ejection fraction

HR Hazard ratio

HRQOL Health-related quality of life

IHD Ischaemic heart disease

IPAQ International physical activity questionnaire

IPAQ-SF International physical activity questionnaire – Short Form

IQR Interquartile range

IVSd Interventricular septal thickness in diastole

LA Left atrium/atrial

LAEF Left atrial ejection fraction

LAH Left atrial hypertension

LAVI Left atrial volume index

LAmax Maximal left atrial volume index

LAmin Minimum left atrial volume index

LAS Left atrial strain

LASr Reservoir left atrial strain

LASb Booster left atrial strain

LASc Conduit left atrial strain

LV Left ventricular

LVA Low voltage areas

LVEF Left ventricular ejection fraction

LVEDD Left ventricular end diastolic diameter

MET Metabolic equivalent of task

NOS Newcastle-Ottawa Scale

OR Odds ratio

OSA Obstructive sleep apnoea

PA Physical activity

PCI Percutaneous intervention

PWd Posterior wall thickness in diastole

RFM Risk factor modification

SE Standard Error

SD Standard deviation

TOE Transoesophageal echocardiogram

TTE Transthoracic echocardiogram

WHO World Health Organization

Chapter 1: Review of the literature

1.1 - CARDIOVASCULAR DIASEASE BURDEN

The last century has witnessed a shift in disease burden, with non-communicable diseases being the most prevalent worldwide[1] and their reduction being a priority as reported by the World Health Organization (WHO) in 2013[2]. In this context, cardiovascular disease (CVD) rank among the world's top causes of death and disability, mainly because of an increase in the total population and the improvement of life expectancy[1,2].

Epidemiological studies show that global deaths from CVD have risen by 41% from 1990 to 2013 despite a decrease in age-specific death rates due to an aging population and population growth[3]. More recently, data published by the Global Burden of Disease for the period between 2007 and 2017 demonstrated similar results, with an overall increase in the total number and percent deaths attributed to CVD, with ischaemic heart disease (IHD), stroke, heart failure (HF) and atrial fibrillation (AF) among the most important contributing causes[4]. Furthermore, CVD such as stroke, IHD and AF are associated with significant disability[1,2] and rising economic costs. The direct and indirect cost of CVD was 555 billion US dollars and is predicted to increase to 1.1 trillion in 2035, along with a doubling cost in so-called 'informal' care[5].

1.1.1 - Cardiovascular risk factors

Cardiovascular risk factors such as hypertension and diabetes play a major role in the development of cardiovascular disease. A meta-analysis of 18 cohort studies[6] including

257,384 participants showed that a higher burden of risk factors (including diabetes and high blood pressure) was associated with a 38 to 49% higher lifetime risk of death from CVD. In addition, those with an optimal risk factor profile had a lower risk of fatal and non-fatal myocardial infarction and stroke. These differences were consistent across races and age groups. Additionally, and consistent with the rise in CVD burden, the burden of cardiometabolic risk factors has increased over the last decade[1]. For example, disability-adjusted life-years (DALYs) for hypertension rose by just over a quarter from 1990 to 2010, while DALYs for high body mass index (BMI) almost doubled in the same period.

1.1.1.1 - Hypertension

High blood pressure is the biggest single contributor to global burden of disease, with a prevalence that is predicted to rise in the coming decades[7]. In 2010, high blood pressure was responsible for 9.4 million deaths and 7% of global DALYs, mainly mediated by IHD and stroke[8]. Furthermore, the estimated total number of hypertensive individuals is predicted to grow by approximately 60% from 972 million in 2000 to an alarming figure of 1.56 billion by 2025[9], primarily as a result of both an aging population and environmental influences such as diet and obesity.

1.1.1.2 - Overweight and Obesity

The increasing burden of excess body mass and obesity are a global concern as a result of positive energy balance and sedentarism[10]. In 2010, high BMI accounted for 3.4 million deaths and 3.8% of global DALYs[8]. In 2015, 107.7 million children and 603.7 adults were considered obese, showing a dramatic rise compared with figures from 1980[11]. Furthermore, in that same year, high BMI accounted for 4 million deaths worldwide, with more than two-thirds of them caused by cardiovascular disease[11].

1.1.1.3 - Impaired fasting glucose and diabetes mellitus (DM)

Diabetes Mellitus (DM) has become a major health issue in the last century, with a prevalence that has continued to grow as a result of poor dietary habits and sedentary lifestyle, [12]. In 2010, impaired glucose tolerance accounted for 3.4 million deaths as 3.6% of DALYs[8]. In a meta-analysis that included just under 700,000 individuals from 102 prospective studies, DM was associated with a two-fold higher risk of cardiovascular events independently of other risk factors[13].

1.1.1.4 - Obstructive sleep apnoea

OSA is characterized by episodic airway collapse during sleep that results in reduced or absent ventilation, hypoxia, hypercapnia and sleep arousal. Obesity is considered a primary risk factor for the development of OSA [14]. In data from the United States, the estimated prevalence of sleep-disordered breathing was 17% for men and 9% in women aged 50-70 years, a substantial rise compared to previous decades, that occurs in parallel with growth in population BMI[15]. Additionally, OSA is associated with a higher risk of cardiovascular events if left untreated, while treatment with continuous positive airway pressure devices has shown to offset this risk in some studies, although poor patient adherence makes interpretation difficult [16].

1.1.1.5 - Sedentary Behaviour and Physical Activity

Sedentary behaviour is defined as any waking activity with an energy expenditure 1 to 1.5 metabolic equivalents of task (MET)[17]. This energy expenditure is equivalent to an oxygen consumption level of approximately 3.5 mL of oxygen per kilogram of body mass[18]. Objectively measured data shows that sedentary behaviour is highly prevalent in Western countries[19,20]. From the United States, data from 6,329 participants in the National Health and Nutrition Examination Survey showed that overall, participants spent almost 55% of their waking time in sedentary activities[20]. In contrast, data from Australia shows that adults spent

57% of their day in sedentary state[19]. Furthermore, there has been a substantial trend towards increasing sedentary time and a reduction in energy expenditure across the globe in the last decades[21]. Epidemiological data shows that sedentary behaviour is associated with the development of cardiovascular risk factors and CVD outcomes. Lee et al reported that physical inactivity was the cause of 7% of cases of type 2 DM and 6% of coronary heart disease[22]. Sedentary habits have also been linked to a higher risk of hypertension[23] and both cardiovascular and all-cause mortality[24]. On the contrary, physical activity is associated with a lower burden of CVD. The PURE study is a prospective cohort study that included 130,000 participants from 17 countries who were followed up for just under 7 years and showed that both recreational and non-recreational physical activity (PA) was associated with a lower risk of all-cause death and a composite outcome of major cardiovascular events which included CVD mortality plus myocardial infarction, stroke and heart failure[25]. These results are consistent with other studies[26-28] where improved CVD outcomes were observed among more active participants.

PA is defined by the WHO as any bodily movement that results in energy expenditure[29] being beneficial when it involves rhythmic contractions of large muscles capable of transporting the body over distance or against gravity at a moderate intensity relative to capacity for extended periods of time during which 200 to 400 kilocalories (or 4 kilocalories per kilogram of body weight) are expended[30]. More specifically, exercise refers to physical activities that are planned, structured, repetitive, and aim at improvement or maintenance of physical fitness which is the set of attributes to perform a given physical task[29]. Moreover, one of the components of physical fitness is cardiorespiratory fitness (CRF) which refers to the capacity to utilize oxygen and can be measured by an exercise test[31]. Although the definitions of these terms are different, they are closely related[32]. In fact, abundant evidence indicates that PA improves both CRF as well as health outcomes in multiple diseases and chronic conditions[32]. However, the health benefits of PA appear to be mediated by

improvements in CRF[33]. While PA and exercise habits have been measured using questionnaires in various studies, the use of devices such as accelerometers allows for a more accurate measurement[34]. Current guidelines recommend a minimum of 150 to 300 minutes a week of moderate intensity PA or 75 to 150 minutes a week of vigorous intensity PA or an equivalent combination, plus 2 or more weekly sessions of muscle strengthening activities[35]. Examples of moderate-intensity activities include a brisk walk at around 4 to 6 kilometres per hour, playing volleyball, or raking the yard. Examples of vigorous-intensity activities are jogging or running, carrying heavy weights, or a strenuous fitness class[35]. Moderate and vigorous PA are associated with lower mortality compared to light PA at the same total PA volume[33] with an additional mortality benefit associated with vigorous PA compared to moderate PA[36].

1.2 - ATRIAL FIBRILLATION

1.2.1 - Atrial Fibrillation prevalence and incidence

AF is the most common chronic arrhythmia characterised by dyssynchronous atrial contraction and irregular ventricular activation as a result of high atrial rate[37]. The prevalence and incidence of AF have risen substantially in the last decades. Schnabel et al[38] compared the prevalence and incidence of AF in the Framingham Heart Study cohort at 10-year intervals over 50 years (from 1958 until 2007), reporting a substantial increase in age-adjusted prevalence amongst both men and women (from 20.4 to 96.2, and from 13.7 to 49.4 cases per 1000 person-years, respectively) while its age-adjusted incidence went up from 3.7 to 13.4 cases per 1000 person-years in men and 2.5 to 8.6 cases per 1000 person-years in women. Between 1990 and 2010, Chugh et al[39] worldwide estimated prevalence rates went from 569.5 to 596.2 per 100 000 habitants while the figure for women rose from 359.9 to 373.1 per 100 000 habitants. In addition, they also reported an increase in incidence rate in the same period, from 60.7 to 77.5 per 100 000 habitants in men and from 43.8 to 59.5 per 100

000 habitants in women. In Australia, the estimated prevalence of AF in 2014 was 5.35% among people ≥ 55 years old and it was projected to rise to 6.39% in 2034[40].

Importantly, there is additional evidence that the estimates of AF prevalence may be underestimated. The detection of paroxysmal AF can be improved by the use of frequent screening or ambulatory monitoring. The ASSERT study showed that among 2580 patients with a cardiac implantable electronic device (CIED) and no history of AF, subclinical AF was identified in 10.1% at 3 months and it was a predictor of both clinical AF and stroke[41].

1.2.2 - Atrial Fibrillation mortality

Multiple studies have reported the association between AF and all-cause, cardiovascular and non-cardiovascular mortality. In a meta-analysis of 104 cohort studies, those with AF carried a 46% higher risk of all-cause mortality compared to those without documented AF[42]. Other subsequent studies showed similar results, with AF being associated with a higher risk of all-cause mortality[43,44]. Gender differences in all-cause mortality have also been described. While Chapa et al[45] reported no gender differences in all-cause mortality between males and females, a wider meta-analysis by Emdin et al[46] showed different results, with a significantly higher risk of all-cause mortality in women compared to men (HR 1.12, 95% confidence interval 1.07 to 1.17).

For disease-specific mortality, Odutayo et al[42] reported a higher risk of cardiovascular mortality associated with AF (relative risk 2.03, 95% confidence interval 1.79 to 2.30). Lee et al[43] reported that 38% of deaths occurring in patients with AF were accounted for by cardiovascular causes in a Korean cohort of 15 411 participants.

1.2.3 - Atrial Fibrillation diagnosis, natural history, and classification

The diagnosis of AF has been traditionally made upon detection of the arrhythmia on a 12-lead electrocardiogram (ECG) or ambulatory monitoring regardless of its duration or associated symptoms[47]. Its clinical manifestations are varied, ranging from asymptomatic[48] to overt HF[49]. In recent years, CIEDs have allowed the detection of atrial high rate events which require careful examination to ascertain whether the recording corresponds with AF[48]. There is evidence that the detection of paroxysmal AF can be improved by the use of ambulatory monitoring. The ASSERT study[50] showed that among 2580 patients with a CIED and no history of AF, subclinical AF was identified in 10.1% at 3 months and it was a predictor of both clinical AF and stroke. Moreover, the diagnostic yield of continuous ambulatory monitoring appears to be even higher in high stroke risk population. The ASSERT-II study[51] included 256 patients with a mean CHA_2DS_2-VASc score of 4.1 out of which 48% had had a prior stroke showed that the detection rate of subclinical AF was 34.4% per year using loop recorders.

Implantable devices have also helped in the characterization of the natural history of AF. Among 590 high risk individuals without history of AF included in the Atrial Fibrillation Detected by Continuous ECG Monitoring Using Implantable Loop Recorder to Prevent Stroke in High-risk Individuals (LOOP) study, AF was diagnosed in 205 (35%). Although progression to 24h episodes occurred in 16%, the vast majority remained asymptomatic after a median follow-up of 40.2 months[52]. Furthermore, among 415 patients with subclinical AF with episodes between 6 minutes and 24 hours from ASSERT, 65 (15.7%) progressed to episodes longer than 24 hours or clinical AF after a mean follow-up of two years[53]. Furthermore, this study identified older age, higher BMI and longer subclinical AF episodes as independent predictors of HF hospitalization.

There are a range of devices that allow identification of subclinical AF using wearable devices such as smartwatches[48]. These devices use photoplethysmography for the detection of the heartbeat or a single-lead ECG. In combination with a Kardiaband, Apple devices

showed a high sensitivity for the detection of AF although specificity was low[54] whereas other devices showed a high sensitivity and specificity for AF diagnosis[55]. Preliminary data indicates that, although wearable technology to diagnose and detect AF is promising[56-58], further research is required to clarify its use.

From a clinical perspective, AF is typically classified on the basis of episode duration in paroxysmal (<7 days), persistent (>7 days) and long-standing persistent (>12 months)[49]. In addition, the term 'permanent AF' refers to a situation where both clinician and patient have agreed in stop pursuing restoration or maintenance of sinus rhythm[49]. These subtypes have prognostic as well as pathophysiological implications. Among 1,291 participants with paroxysmal AF enrolled in the Euro Heart Survey on AF, 15% showed progression after 1 year of follow up, which was associated with a higher cardiovascular hospitalization rate and higher incidence of ischemic stroke[59]. Additionally, the Phenotyping Young-Onset Atrial Fibrillation Patients study (YOUNG-AF), a cohort study that included younger patients with paroxysmal AF, showed higher mortality and HF hospitalizations among those with progressive AF[60].

1.2.4 - Atrial Fibrillation symptoms and quality of life

Health-related quality of life (HRQOL) is a term that refers to a person's functionality and wellbeing in the social, mental and physical domains taking into account only health related aspects[61]. The clinical manifestations of AF are varied and include fatigue, dyspnea, palpitations and syncope and AF management is determined by the presence of these symptoms[62]. The main goal of frontline therapies for AF is to reduce symptom burden and improve patients' outcomes and HRQOL [63].

Multiple studies have demonstrated that Individuals with AF have reduced HRQOL compared to the general population and that their HRQOL is determined by multiple factors. A meta-analysis by Thrall et al[64]showed that patients with AF have a significantly reduced HRQOL compared to general population, which can be improved by both rate and rhythm control strategies. Furthermore, data from the ORBIT-AF registry shows that female sex, younger age, new onset AF, higher heart rate, obstructive sleep apnea, symptomatic HF, chronic obstructive pulmonary disease and coronary artery disease were independently associated with reduced HRQOL[65]. In the Reasons for Variations in Health Related Quality of Life and Symptom Burden in Patients With Atrial Fibrillation (SMURF) study, anxiety, depression and low-grade inflammation were identified as the most important determinants of HRQOL among 192 AF patients referred for radiofrequency ablation[66]. In addition, left atrial (LA) dilation significantly predicted the presence of symptoms. In this same cohort, LA volume, diabetes, HF, AF attack frequency before ablation and recurrence were significant predictors of post ablation symptoms and HRQOL[67].

1.2.5 - Atrial Fibrillation and associated conditions

1.2.5.1 - Atrial Fibrillation and Heart Failure

Given the frequent coexistence of AF and heart HF, the combination of these two entities has been extensively studied. In fact, both conditions have common risk factors which can cause both AF and/or HF via multiple physiopathological mechanisms[68] and their simultaneous presence is associated with worse outcomes[69].

Firstly, there is strong evidence that the presence of AF increases the risk of HF. A meta-analysis of 15 cohort studies showed that the risk of HF in AF patients was more than 4 times higher compared to no AF[44]. Among the included studies, the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study, which included 8265 patients followed-up for almost 10 years, showed a high incidence of both HF with preserved (HFpEF) and

reduced ejection fraction (HFrEF). However, Ho et al[70] showed that among 6340 participants of the FHS, AF was predictive of HFpEF only along with high BMI and smoking, with similar results reported by Lee at al[71] among Medicare beneficiaries.

Similarly, HF significantly increases the risk of AF. In the FHS, the presence of HF was associated with a 6-fold increased risk of AF[72] with other epidemiological studies showing similar results[37,73]. Moreover, large HF trials have demonstrated that the risk of AF is even higher when HF is more severe[68], with the likelihood of AF going from 10% in those with New York Heart Association (NYHA) class I to 50% in those with NYHA class IV. Furthermore, a retrospective analysis of the Studies of Left Ventricular Dysfunction (SOLVD) Prevention and Treatment Trials showed that in patients with LV systolic dysfunction, those with AF had a worse prognosis as evidenced by a higher risk of all-cause mortality, death attributed to pump-failure and a composite endpoint of death or hospitalization for HF[74]. In regards HF phenotype, Pellicori et al[75] showed that while the prevalence of AF was higher among patients with HFpEF (40% vs 26%), the incidence was similar in both groups after just over 4 years of follow up.

1.2.5.1.1 - Pathophysiological mechanisms in Atrial Fibrillation and Heart Failure

There are multiple mechanisms involved in the pathophysiology of both diseases. Mechanisms involved in the development of HF in the context of AF are loss of atrial contraction, tachycardia and irregularity. From a mechanical point of view, LA systole contributes with 25% of the ventricular end-diastolic volume which in turns increases end-diastolic pressure and stroke volume in sinus rhythm[68]. Electrical cardioversion of AF to sinus rhythm results in immediate improvement of both LVEF and LV longitudinal strain[76].

Firstly, the deleterious effects of rapid heart rate on the myocardium have been thoroughly described. Animal models have shown that fast heart rates result in myocyte deformation and

reduced attachment to extracellular matrix[77], myocyte loss and hypertrophy[78] and T-tubule calcium depletion[79]. Furthermore, an in vitro experiment with LV human samples, Selby et al[80] showed that impaired myocyte relaxation is associated with higher LV mass and LA volume.

Secondly, irregularity itself appears to contribute to impaired ventricular function. In vitro studies suggest that irregularity alters gene expression and activity of key proteins involved in intracellular calcium handling[81]. This is further supported by observations from the Cardiac Resynchronization Therapy in Atrial Fibrillation Patients Multinational Registry (CERTIFY) study where patients with LV dysfunction and a cardiac resynchronization therapy device and AF treated with atrio-ventricular node ablation had a greater LV ejection fraction (LVEF) improvement along with lower risk of death compared to those on rate control medication[82]. Irregularity has also been associated with higher pulmonary capillary wedge pressures, right atrial pressures and reduced cardiac output[83].

Conversely, HF can induce AF via LA electrical remodelling, LA dilation by increased filling pressures and adrenergic and neurohumoral activation. Li et al showed that HF-related arrhythmogenic substrate was characterized by higher conduction heterogeneity and fibrosis in ventricular pacing induced HF compared to rapid atrial pace[84]. Furthermore, these alterations persisted after recovery of ventricular function despite reduced AF duration[85]. Sridhar et al[86] showed that HF dogs had molecular (altered ion channel function), electrical (lower atrial action potential duration), mechanical (reduced LA contractility) and structural (higher fibrosis) remodelling compared to controls, partially mediated by oxidative stress. Moreover, there is preclinical and clinical evidence of the electrical and structural atrial remodelling induced by renin-angiotensin system activation which is a key mediator of HF pathogenesis[87-91]. In an AF canine model, increased expression of profibrotic pathways as well as increased atrial fibrosis and AF inducibility and duration were demonstrated[89]. These phenomena were partially attenuated by RAA system blockade. In humans, RAA system dependent increase in kinases involved in profibrotic molecular pathways was demonstrated

in atrial tissue[91], and its expression was reduced in those treated with angiotensin-converting enzyme inhibitors. In the Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure (EMPHASIS-HF), eplerenone reduced the risk of AF by 42% compared to placebo[87]. Atrial wall stress and LA stretching are also implicated in LA electrical and structural remodelling. Using a computerized model, Hunter et al[90] showed that peaks in LA wall stress (measured in kPa) were consistent with low voltage areas which in turn suggest fibrosis. Molecular changes at the level of ion channels induced by mechanical atrial stretching which may contribute to AF in HF have also been described[88].

Additionally, phenomena such as LV stiffening, regional fat accumulation and systemic inflammation can act synergistically and predispose or worsen to both conditions simultaneously. Uetake et al showed that ventricular stiffening is not only associated with the presence of AF, but also with the progression from paroxysmal to persistent AF[92,93]. Patients with signs and symptoms of heart failure but normal LVEF had significantly higher LV stiffness[94] which is due to abnormalities at cellular and extracellular levels in the myocardium[95]. Furthermore, epicardial fat is associated with higher fibrosis and electroanatomical changes in the atria[96,97] along with deleterious cardio-mechanical effects with increasing diastolic dysfunction in the ventricle[98]. These effects appear to be at least partially mediated by local inflammation. Oxidative stress also promotes interstitial fibrosis which is a key feature in both AF and HF(99-101).

1.2.5.2 - Atrial Fibrillation and Coronary Artery Disease

AF and CAD have multiple risk factors in common, thus the relationship between these two conditions is not surprising and often coexist. The incidence of CAD in AF varies from 18[102] to 38%[103] while its prevalence has been reported between 18 and 46.5%[104]. Moreover, while the prevalence of AF in CAD patients is relatively low[104,105], its incidence grows considerably to 50% at 10 years after myocardial infarction or coronary revascularization[106].

The occurrence of AF after an acute coronary event entails serious prognostic implications. In fact, in a large database of 120,566 patients after an acute coronary syndrome, new-onset AF was associated with a higher risk of death, myocardial infarction and stroke[107] despite a low incidence. Similarly, the presence of AF is associated with a higher risk of a coronary event[44].

1.2.5.2.1 - Pathophysiological mechanisms in Atrial Fibrillation and Coronary Artery Disease

AF and CAD share common risk factors such as obesity and hypertension and there may be some overlapping pathophysiology. In a sheep model, Alasady et al[108] showed that with an occlusion of the circumflex coronary artery resulted in LA infarction and fibrosis along with conduction abnormalities and higher AF vulnerability compared to controls and LAD occlusion model. In another study, Ye et al[109] demonstrated that ligation of the left anterior descendent coronary artery resulted in higher sympathetic tone, lower parasympathetic activity and increased LA inflammation and fibrosis and AF inducibility. Consistent with these results, Miyaguchi et al[110] demonstrated multisite LA wave breaks of paced wavefronts using epicardial mapping along with higher AF inducibility in a dog chronic ventricular infarction model.

1.2.5.3 - Atrial Fibrillation and stroke

Ischaemic stroke is a serious complication of AF. AF not only increases the risk of stroke, but also AF-related strokes convey a higher risk of long-term disability and mortality. A five-fold higher risk of ischaemic stroke was reported in the FHS cohort[111]. The risk of stroke among AF patients depends on the presence of other well stablished risk factors such as age, gender, previous transient ischemic attack/stroke/thromboembolism, vascular disease, HF, hypertension and diabetes mellitus and well-known risk calculators have been developed[112-

[115]. Furthermore, data from the Copenhagen Heart Study shows that AF-related strokes have higher mortality, longer hospital stay and worse neurological and functional outcomes. Similar results were reported in the FHS[116]. Although the risk of ischemic stroke is significantly reduced with oral anticoagulation[117], this therapy still entails some risk of bleeding with potential catastrophic consequences[118].

While AF type is not usually considered when estimating stroke risk, there is some evidence that it could influence stroke risk in AF. Post hoc adjusted analysis of Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation(ARISTOTLE)[119], Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation(ENGAGE-AF)[120], and Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF)[121] trials have all shown consistently lower stroke risk for patients with paroxysmal AF compared with those with persistent AF. A systematic review and meta-analysis of randomized controlled trials, cohort studies and case-series showed results consistent with this observation[122]. However, some registry data have not found any association between AF type and stroke risk, which is possibly due to the complex nature of these two conditions[123]. In addition, although evidence is scarce, non-paroxysmal AF appears to be associated to more severe strokes and a higher risk of recurrence[123].

Embolic stroke of unknown source (ESUS) is a clinical entity which involves multiple possible causes, and subclinical AF is often discovered after these events. The EMBRACE trial[124] randomized 572 patients with ischaemic cryptogenic stroke without known AF to either continuous 30-day ECG monitoring (intervention group) or standard 24-hour monitoring (control group). The intervention resulted in a significantly higher detection rate of AF. These results were further supported by a meta-analysis where longer ECG monitoring was associated with higher diagnostic yield for AF[125]. Although mechanisms of clot formation and subsequent brain embolism in the context of AF are not fully understood, they may include endothelial dysfunction, blood stasis and hypercoagulability as suggested by

clinical and in vitro studies[37]. In recent years, the structural changes observed in the atria and referred to as 'atrial myopathy' have been associated with the risk of stroke regardless of the presence of AF and could potentially explain the lack of temporal relationship between AF episodes and stroke occurrence[126].

Recent evidence suggests that the relationship between AF and embolic stroke is mediated not only by the rhythm disturbance in AF but also by the atrial cardiomyopathy associated with it[127]. Different LA structural and mechanical characteristics have been associated with higher risk of AF[128]. Both LA size and left atrial appendage morphology have been associated with a higher risk of stroke[129,130]. Higher LA fibrosis as per magnetic resonance measurements was associated with spontaneous echocardiographic contrast and LAA thrombus[131]. In addition, higher LA fibrosis was independently associated with clinical cerebrovascular events[132]. Moreover, LA strain, an echocardiographic parameter of myocardial deformation, has been associated with cryptogenic stroke[133]. Collectively, this data indicates that the LA structural remodelling underlies the pathogenesis of both disease processes.

1.2.6 - Cardiovascular risk factors and Atrial Fibrillation pathophysiology

Recent data demonstrates that cardiovascular risk factors are linked not only to the risk of AF, but also to its associated risk of stroke[114]. In fact, both the preventive and therapeutic role of risk factor management has gained more attention[134]. Data from the Framingham Heart Study shows that prevalence of modifiable risk factors increased over the last decades along with a constant association with AF risk over time. In the latest period analysed by this study (from 1998 to 2007), hypertension and obesity had the greatest population-attributable risk of AF[38]. Additionally, data from the Atherosclerosis Risk in Communities (ARIC) study cohort reported that just over 50% of AF cases could be attributed to at least one uncontrolled risk factor[135]. In this same cohort, AF risk was higher among those participants meeting the

criteria for metabolic syndrome, with significant associations with high blood pressure, elevated waist circumference, low high-density lipoprotein cholesterol and impaired fasting glucose[136]. Cardiovascular risk factors are not only implicated in AF incidence, but also in AF progression. Among 2869 AF patients who were followed up for 3 years, traditional cardiovascular risk factors were predictors of a new rhythm control intervention[137].

The presence of risk factors has been associated with LA structural and electrical remodelling, thus creating a favourable substrate for AF. Preclinical models have demonstrated that cardiovascular risk factors increase both AF vulnerability and duration via multiple mechanisms including but not limited to LA stretching, dilation and fatty infiltration[138,139], fibrosis[140] and autonomic remodelling[141]. In humans, data from electroanatomical maps shows that the presence of cardiovascular risk factors is associated with reduced bipolar voltages and conduction velocities along with higher electrogram fractionation[96,142,143].

From a mechanistic perspective, while multiple studies have described specific deleterious effects of each risk factor in the development of a pathological LA substrate that predisposes to AF, LA hypertension (LAH) has been proposed as a unifying factor and a major determinant of LA remodelling[144]. LAH has been defined as atrial pressures higher than 15 mmHg[145]. Among 240 patients with normal LVEF and non-valvular AF undergoing catheter ablation, the prevalence of LAH was 15%[146]. In addition, using a handgrip protocol, the authors were able to unmask LAH in 23% of those who had normal LA pressure at rest. The presence of LAH was associated with a higher prevalence of cardiovascular risk factors, higher LV systolic dysfunction, LA stiffness and wall stress, more extensive areas of low voltage in electroanatomical maps and lower contractility and distensibility. Also, although systolic blood pressure was one of the strongest variables linked to LAH, no significant correlation was observed between increase in the blood pressure and increase in the LA pressure in response to exercise.

Consistent with data demonstrating the deleterious effects of modifiable risk factors in AF, a large body of evidence supports the benefits of risk factor modification (RFM) in AF management. Consequently, RFM has been postulated as the fourth pillar in AF management along with antithrombotic therapy, rhythm control and rate control[147]. RFM has been associated not only with AF risk reduction, but also with improved outcomes in stablished AF such as reduced AF burden, symptom improvement, reduced thromboembolic risk and lower AF recurrence after catheter ablation.

1.2.6.1 - Hypertension

Multiple studies have highlighted the relationship of hypertension with incident AF. Among 14,546 subjects from the Atherosclerosis Risk In Communities cohort, hypertensive participants had a significantly higher risk of new-onset AF compared to normotensive[148] with other population-based studies showing similar results[149,150]. Furthermore, hypertension has also associated with AF progression. Among 1219 participants of the Euro Heart Survey on AF, hypertension was identified as a significant predictor of AF progression in adjusted analysis[59]. These results were reproduced in a cohort with young-onset AF[60].

There is evidence that blood pressure reduction reduces the risk of new –onset AF. The Cardio-Sis study is an open-label multicentre randomized clinical trial (RCT) that allocated 1111 non-diabetic patients with systolic blood pressure (BP) >150mmHg to usual (<140 mmHg) or tight (<130 mmHg) BP control[151]. After a follow-up duration of 2 years, patients in the tight control arm showed a 66% lower risk of AF along with a significant reduction in electrocardiographic left ventricular (LV) hypertrophy. In a large population-based study that included 45,530 individuals, achieved systolic BP >140 mmHg was associated with a significantly higher odds of new-onset AF after a mean follow up of 3.5 years[152]. Hypertension was also associated with AF progression from paroxysmal to persistent[59,60].

In established AF, blood pressure reduction could also reduce the risk of stroke. In fact, hypertension is a well-known risk factor for stroke in the AF population and is included in validated models of stroke prediction in AF[153]. Hypertensive patients not only have larger LA which is in turn associated with a higher risk of stroke[153,154], but also with a higher degree of LA appendage stasis[155]. In general population, a meta-analysis of cohort studies and randomized clinical trials showed a 34% reduction in the risk of stroke with a 5 mmHg reduction in diastolic blood pressure[156].

1.2.6.2 - Overweight, obesity and body composition

The association between excess body weight and atrial fibrillation is well-established. Obesity not only increases the risk of new onset as well as post-operative AF[157], but also contributes to its progression from paroxysmal to persistent AF[158]. Other measurements of adiposity have also been associated with a higher risk of AF. A Danish cohort that included over 55,000 patients with a mean follow up of over 10 years reported a 29% rise in AF risk per 1 sex-specific standard deviation increment in body fat measured by bioelectrical impedance[159]. A dose-response meta-analysis from 2017 reported that AF risk increased 9% per 5 kg of body fat mass and 32% per 10 centimetres of hip circumference(160). Furthermore, the specific location of adiposity appears to be important. Pericardial fat (defined as regions of high signal intensity between the myocardium and parietal pericardium) was not only associated with the presence of AF, but also with AF severity and poorer outcomes after catheter ablation[161].

In line with these observations, there is evidence that weight loss results in AF burden and symptoms severity reductions along with improved risk factor profile and arrhythmia free survival after AF ablation procedures. The LEGACY-AF study (Long-Term Effect of Goal Directed Weight Management on Atrial Fibrillation Cohort: A 5 Year Follow-Up Study) looked at the effect of weight loss in AF burden and symptoms[162]. Those who lost ≥10% of body weight showed a significant decrease in AF burden and symptom severity and lower

recurrence of AF without rhythm control strategies. Similarly, the ARREST-AF study (Aggressive Risk factor Reduction Study or Arial Fibrillation and implications for the outcome of ablation) demonstrated that patients with RFM had a significantly higher weight loss and AF frequency, duration and symptom severity improvement along with better AF ablation outcomes[163]. Risk factor targeted interventions also resulted in a favourable cardiac remodelling with significant interseptal ventricular thickness and LA area reductions[164]. Weight loss can reverse the natural progression of AF. The PREVEntion and regReSsive Effect of weight-loss and risk factor modification on Atrial Fibrillation (REVERSE-AF) study showed that weight reduction ≥ 10% was associated with a significantly lower progression from paroxysmal to persistent AF and even a reversal from persistent to paroxysmal or no AF[165].

Recent evidence suggests that components of body mass beyond adiposity may be important in the development of AF. Data from the Danish Diet, Cancer and Health cohort reported that among more than 55,000 patients, lean body mass significantly increased the risk of atrial fibrillation even after adjustment for adiposity measurements and comorbidities after a median follow-up of 17 years, whereas the association with body adiposity measurements was attenuated after adjustment for lean mass[166]. Similar results were reported by Azarbal et al[167] who found a significant association of lean body mass with AF even after adjustment for fat mass with no significant association of fat mass and AF risk after adjustment for lean mass among 8832 postmenopausal women. However, data from the UK biobank that included just under 500,000 participants, both lean and fat mass were associated with a higher risk of AF[168] with similar results reported by Karas et al[169]among 4276 participants of the Cardiovascular Health Study. A meta-analysis from 2017 showed that BMI, waist circumference, hip circumference, waist to hip ratio and total fat mass were significantly associated with AF risk but not fat percentage although statistical heterogeneity was high[160]. When estimates for lean body mass were pooled together, lean body mass showed a

significant association with AF incidence although with significant statistical heterogeneity[170]. From a mechanistic perspective, there is abundant evidence that obesity is associated with haemodynamic, structural and electroanatomical remodelling.

1.2.6.2.1 - Pathophysiological mechanisms in overweight & obesity

In addition to mechanistic links between obesity and AF mediated by obesity comorbidities such as hypertension[171], preclinical and clinical studies have described specific pathogenic mechanisms for obesity.

In a sheep model, Abed et al[139] demonstrated that progressive weight gain was associated with in higher LA fibrosis, inflammatory and fatty infiltration and increased expression of profibrotic mediators, namely transforming growth factor ß1 and platelet derived growth factor. This study also showed that weight gain resulted in lower conduction velocity and higher conduction heterogeneity. Using the same sheep model, Mahajan et al[138] showed that obese sheep had higher LA pressures, LA volumes and electrogram fractionation along with lower posterior wall voltages, higher epicardial fat infiltration in this wall and higher AF frequency and duration. In addition, weight loss was associated with lower LA pressure and atrial fibrosis along with higher LA refractoriness, faster conduction velocity and lower AF inducibility[172].

Consistent with these results, in a cohort of 63 AF patients who underwent AF ablation, Munger et al[173] showed higher LA pressures and volumes in the obese group compared to normal BMI patients along with shorter effective refractory periods. Mahajan et al[96] demonstrated that obesity was associated with lower conduction velocities and electrogram fractionation along with higher low voltage areas in the posterior and inferior walls which were consistent with epicardial fat location.

1.2.6.3 Impaired fasting glucose and Diabetes Mellitus

Impaired glucose metabolism is associated with AF. In the ARIC cohort, age adjusted incidence rate of AF was double for those with diabetes, which resulted in a significantly higher adjusted risk (HR 1.35, 95% CI 1.14-1.6)[174]. Among those with DM, those with a poor glycaemic control had an even higher risk. Similar results were reported in the Framingham Heart Study[72]. In addition, data from ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) registry demonstrated that the presence of DM was not only associated with higher mortality and hospitalizations but also with worse quality of life and symptoms[175].

From a mechanistic standpoint, the relationship between AF and diabetes seems to be mediated by oxidative stress, ion channel remodelling and abnormal intracellular lipid metabolism. Reactive oxygen species production is increased in diabetic individuals as well as animal models[176,177], and antioxidant systems are impaired in atria of diabetic humans[178]. Oxidative stress observed in diabetes leads to electrical remodelling that facilitates both initiation and maintenance of AF[100]. Preclinical models demonstrate that antidiabetic drugs with antioxidant properties such as dipeptidyl peptidase inhibitors reduce atrial remodelling[179,180]. In addition, metformin reduces ion channel remodelling and abnormal intracellular lipid metabolism in preclinical models[181,182]. The protective role of metformin is further supported by epidemiological data[183] showing that metformin use was associated with a 19% AF risk reduction.

1.2.6.4 - Obstructive Sleep Apnoea

Epidemiological data shows that obstructive sleep apnoea is strongly linked to AF risk. In the Sleep Heart Health Study, those with sleep disordered breathing the prevalence of AF was 4

times higher compared to controls[184]. Likewise, a meta-analysis of 5 prospective cohort studies showed that OSA increased the odds of AF post coronary artery bypass graft surgery by 2-fold[185]. Moreover, among 10,132 AF patients enrolled in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF), patients with OSA were more symptomatic and had a higher risk of death, myocardial infarction, stroke, major bleeding and AF progression after adjustment for confounders[186]. Continuous airway positive pressure (CPAP) had no effect on these outcomes except for AF progression. Among patients with AF, the VARIOSA AF[187] study showed considerable night to night variation in sleep disordered breathing which is undetectable with a single overnight sleep study. This study also showed that patients with more severe OSA had a significantly higher AF burden. Fein et al[188] showing higher AF-free survival after catheter ablation among CPAP users in a cohort of AF patients with confirmed OSA diagnosis.

Multiple mechanisms have been proposed to explain the relationship between sleep apnea and AF. In a rat model of OSA[189], AF was more inducible and AF episodes were longer. This was accompanied by substantial atrial conduction slowing, connexin-43 downregulation and higher atrial fibrous tissue content. Higher atrial fibrosis was also found in a canine model of OSA along with changes in ion channel protein expression, atrial effective refractory period (AERP) shortening and autonomic remodelling[141]. Using a pig OSA model, Linz et al[190,191] showed that OSA episodes were associated with BP raises, higher plasma renin activity and aldosterone concentrations, shorter AERP and higher AF vulnerability which were attenuated by renal denervation.

Extensive LA remodelling was also demonstrated in humans. Among patients undergoing AF ablation, those with OSA had larger atria, lower atrial voltages and more widespread complex fractionated electrograms[142]. Electroanatomical disturbances were also reported by Nalliah et

al[192] in a study which included 66 AF patients who underwent catheter ablation. In this study, apnea-hypopnea index was associated with lower LA voltages and more low-voltage areas along with higher voltage and conduction heterogeneity more fractionated points, particularly in paroxysmal AF. Both CPAP therapy and renal denervation improve outcomes after catheter ablation[193,194].

1.2.7 - Physical Activity, Cardiorespiratory Fitness, Atrial Fibrillation and cardiovascular risk factors

1.2.7.1 Physical Activity and Atrial Fibrillation risk

Abundant epidemiological evidence has highlighted the mortality benefit associated with regular physical activity in healthy populations as well as people with prevalent cardiovascular disease[195-197] with current guidelines recommending a minimum of 500–1000 metabolic equivalent task (MET)-minutes per week of regular physical activity[198,199]. However, a large share of the population is still below that threshold[200]. In response to the high prevalence of physical inactivity, the American College of Sports Medicine has proposed the Exercise is Medicine® initiative[201], a program that characterizes exercise as a drug with a specific minimum dose to achieve benefit and a maximum dose above which exercise could be potentially toxic[202] given the evidence suggesting that physical activity at extreme doses could be deleterious[203,204].

In particular, large cohort studies have described a dose-response relationship between PA and AF risk. While Jin et al[205] described a U-shape curve with the highest risk reduction achieved at a PA level between 500 to 1000 MET-minutes per week among just over 500,000 participants, Lee et al[206] found no relationship between PA dose and AF risk in adjusted models. Moreover, Elliott et al[207] described a differential effect in women compared to men, with females achieving a lower risk reduction compared to men. Perhaps the main criticisms

in all the studies conducted so far is that all of them assess PA using questionnaires, and that AF was diagnosed by medical records review, self-report or routine ECG in most of them. Palmisano et al[208] also reported that among 770 patients with HF and a transvenous implantable cardioverter defibrillator a lower device-reported physical activity was associated with higher arrhythmia incidence, mortality and HF hospitalization. More recently, Khurshid et al[209] showed that among 93 669 participants of the UK Biobank free of AF with 1-week wrist accelerometer data, those who met guideline recommendations had a lower risk of AF.

To this date, it has been difficult to assess the presence of any PA thresholds within which AF risk is lower. It is important to clarify that the above-mentioned studies differ in multiple aspects. Firstly, the mean age of the participants varied from 37 to 72 years old with an also variable percentage of females thus reflecting heterogeneous populations despite presenting adjusted risk estimates. Secondly, in all these studies, PA was measured with questionnaires, which in most cases where specific questionnaires for the study. Thirdly, AF diagnosis was mainly based on medical records reviews potentially missing subclinical cases of AF.

Regarding the relationship between CRF and AF risk, the evidence available is more consistent. In general, most studies show an AF risk reduction associated with higher CRF[210-215]. In addition, Quareshi et al[210] showed that at CRF levels lower than around 10 METs, AF risk is significantly higher in obese compared to non-obese, with similar risk beyond that threshold while Kamil-Rosemberg et al(210) showed a consistent risk reduction within BMI categories with higher CRF. Additionally, a study including 5692 veterans who were followed up for a median of 8.3 years showed that risk reduction associated with high CRF was similar in those 65 years old or older compared to younger than 65 years old. Hussain et al[213] showed that the risk reduction in AF with higher CRF was also associated with lower mortality and lower stroke incidence whereas Tikkanen et al[214] showed that AF incidence

was consistently lower among those at low, intermediate and high genetic risk with higher CRF. Nevertheless, other studies[216,217] reported a U-shape association of CRF and AF risk with the maximal risk reduction at around 8-10 METs while Crump et al[218] reported a higher risk of AF associated with higher CRF in a cohort that included 1 547 478 individuals.

There are a number of aspects to be considered from these studies. Firstly, the risk of AF is based on baseline CRF with no mention of CRF change during the follow-up period. Similar to PA, CRF is a dynamic metric which is likely to change over the follow up period of all these studies. Secondly, CRF was assessed using different methods and protocols across studies. Thirdly, AF diagnosis was ascertained using medical record thus there may be cases of subclinical AF which may have not been identified.

1.2.7.1.1 - Endurance exercise and Atrial Fibrillation risk

The first evidence of a link between endurance sports and increased risk of AF was reported in the late 1990s. In a case-control study, Karjalainen[219] reported a significant prevalence of AF among 300 top rank orienteers compared to controls. After that, multiple studies looking at this relationship have been published. Four case-control studies by the same group showed AF patients had a higher proportion of 'sportsmen' and where more active than controls[220-223]. A cross-sectional study by Baldesberger et al[224] reported that AF was more common in former professional cyclists compared to matched golfers (10% vs 0%) with much more narrow difference among cross-country skiers reported by Myrstad et al[225]. A retrospective study by Molina et al[226] reported a higher AF incidence among marathon runners while a prospective study by Andersen et al[227] showed that AF risk among cross-country skiers was associated with the number of completed races and shorter finishing times. More recently, Svedberg et al[228] compared the risk of AF, stroke and death in 208 654 cross-country skiers with 527 448 non-skiers. The study showed that female skiers had lower risk whereas male

skiers had similar risk of AF compared to their non-skier counterparts, with those with the highest number of completed races or fastest times at the highest risk among the skiers. In addition, while skiers with AF had a higher risk of stroke compared to skiers and non-skiers without AF, the overall risk among skiers was lower compared to nonskiers. Importantly, following AF diagnosis skiers had a lower incidence of stroke and mortality compared to skiers.

Although collectively this data clearly suggests a higher risk of AF associated with sports practice, there are aspects that need to be considered. Most of these studies are case-control studies with a relatively low number of patients. Secondly, in most of them PA is measured with questionnaires which is not the best way to measure PA. O'Neal et al[229] showed that objectively measured time doing moderate to vigorous PA using accelerometers was associated with a lower AF risk. However, the PA reported in this study were certainly below the training volumes of professional athletes. Thirdly, in most studies AF diagnosis was either self-reported, based on medical records reviews of those who presented symptoms only, or not thoroughly investigated in case-control studies.

1.2.7.2 – Physical activity and cardiorespiratory fitness in established Atrial Fibrillation

Multiple studies have looked at the association between PA or CRF in patients with established AF. Among 2442 patients enrolled in the EURObservational Research Programme on AF (EORP-AF) Pilot Survey, self-reported physical activity was associated with a lower all-cause and cardiovascular death, thromboembolism and bleeding at 1 year, but not with AF progression at 1 year[230]. In addition, data from the 'Discerning Symptomatic and Asymptomatic Episodes Pre and Post Radiofrequency Ablation of Atrial Fibrillation' (DISCERN AF) study[231] which included 50 patients with implantable monitors showed that daily activity is inversely correlated with patient activity that starts decreasing at 500 AF

minutes/day and drops even more beyond 1000 daily AF minutes. In a cohort or 591 patients who underwent AF ablation, Donnellan et al[232] showed that higher CRF is significantly associated with a lower AF recurrence and mortality after a mean follow up of 32 months. A mortality and morbidity benefit associated with CRF as well as self-reported PA was also demonstrated by Garnvik et al[233] in a cohort of 1117 AF patients from the HUNT3 study, where both PA and estimated CRF were associated with a lower all-cause mortality, cardiovascular mortality and a composite endpoint of myocardial infarction, HF and stroke.

Furthermore, other studies have looked at the effect of exercise-based interventions in patients with AF. All studies randomized patients to interventions of 8[234] to 16 weeks[235] of two[235] to three[234,236-238] weekly sessions. In relation to outcomes, all the studies reported significant increases in exercise capacity[234-238] while the majority reported improvements in QOL[234,236,237] except Risom et al[238] although this study reported a low adherence rate (51%) with no difference in the total exercise dose between groups assessed with the a questionnaire after the intervention. Malmo et al[237] reported lower AF burden measured with implantable monitors and lower AF symptom frequency and severity. In particular, Zeren et al[239] demonstrated that a 12-week inspiratory muscle training program resulted in improved spirometry parameters as well as 6-minute walk test.

1.2.7.3 - Pathophysiological mechanisms

Mechanistically, preclinical and clinical studies have proposed multiple mechanisms which could explain the propensity to AF conferred by PA despite its overall protective role in cardiovascular disease in general.

Firstly, increased vagal tone shortens the effective refractory period and sympatho-vagal shifts precede AF onset in humans. Among 25 patients who showed vagal excitation during AF catheter ablation, fibrillatory cycle length increased significantly during vagal

stimulation(240). In another study, analysis of Holter monitors from 77 unselected consecutive patients revealed that episodes of paroxysmal AF are preceded by a sequence of sympathetic activation followed by a sudden increase in vagal activity just before the onset of the episode[241]. In fact, vagal hyperactivity and sympatho-vagal shifts are observed in athletes in response to increasing training loads[242].

Secondly, besides autonomic changes, atrial inflammation and fibrosis have been implicated in the pathogenesis of exercise-induced AF. Aschar-Sobbi et al[243] showed in a mice model that levels of exercise exceeding 70% on VO2max (equivalent to professional training programs) resulted in increased vagal tone, atrial hypertrophy, inflammation, fibrosis and AF vulnerability. Moreover, inhibition of Tumor Necrosis Factor alpha resulted in prevention of atrial inflammation and fibrosis. However, while detraining abolished AF inducibility, atrial fibrosis was only partially reduced, indicating that other mechanisms besides fibrosis are required to initiate AF in athletes. In addition, increased LA pressures can result in LA stretch and consequently stimulate fibrous tissue accumulation[126,244].

On the contrary, mechanisms which could mediate AF risk reduction are not only improved risk factor profile but also direct mechanisms in the LV. Among 454 participants of the Hypertension and Ambulatory Recording VEnetia STudy (HARVEST)[245], active patients with stage I hypertension were less likely to develop LV hypertrophy independently from blood pressure control. In a large study which included 57 449 participants with a mean age of 40 years old, Ryu et al[246] showed that physical activity was associated with improved diastolic parameters after adjustment for risk factors and blood pressure. In addition, Sarma et al[247] demonstrated that higher myocardial lipid content was associated with higher diastolic dysfunction and lower LA compliance. In this study, BMI was positively associated with lipid content while CRF was inversely associated. Bhella et al[248] showed that LV stiffening

process associated with ageing could be prevented by a relatively high exercise dose (4 to 5 sessions a week). Furthermore, Florido et al[249] reported that low doses of PA are associated with higher myocardial damage after adjustment for risk factors. Even in sedentary middle-aged subjects, an exercise program of 2 years increased CRF and reduced LV stiffness[250], thus it is likely that it reduces the risk of both HFpEF and AF.

Particularly in the LA, acute and chronic responses to exercise have been described although the evidence is more limited. Schnell et al[251] compared acute responses of right and LA volumes and emptying functions in athletes, non-athletes and patients with chronic thromboembolic pulmonary hypertension (CTEPH). They found that both athletes and non-athletes had a significant rise in both right and LA emptying function along with left and right reservoir strain increase in response to exercise. These mechanisms were blunted in patients with CTEPH. Furthermore, among 22 rheumatoid arthritis patients, a 2-year exercise intervention resulted in a significant improvement in LA global strain, with no significant modifications in the LV[252] which may suggest that exercise could prevent LA structural remodelling. However, the low number of patients in this study may limit the interpretation of this finding. Moreover, Peritz et al[253] reported higher amounts of fibrosis quantified by cardiac MRI in endurance masters athletes compared to controls. Further studies are required to clarify the effect of different exercise-based interventions in the LA structure and function.

1.2.7.3.1 - Physical Activity, Cardiorespiratory Fitness and hypertension

Multiple studies have addressed the role of physical activity in primary prevention of hypertension. In a meta-analysis of prospective cohort studies reporting risk of high and moderate PA vs low PA, active individuals had a significantly lower risk of hypertension compared to the least active ones (RR 0.81, 95% CI 0.76-0.85 and RR 0.89, 95% CI 0.85-0.94, respectively)[254]. After that, a dose-response analysis by Liu et al found a linear inverse

relationship between both leisure-time PA and total PA and incidental hypertension[255]. More recently, similar results have been reported in a Chinese cohort[256]. Mechanisms involved in the preventive effect of exercise are unclear but may include reduced sympathetic and renin-angiotensin system activity, lower vascular resistance and reduced endothelial dysfunction[257].

The incidence of hypertension has also been studied in relation to cardiorespiratory fitness (CRF). Among 22,109 participants included in the The Henry Ford ExercIse Testing (FIT) Project, 8053 developed hypertension after a median follow up of 4.4 years. After adjustments, those who were able achieve ≥12 METs in a treadmill exercise test at baseline had a 20% reduced risk of hypertension compared to those achieving <6 METs[258]. Other cohort studies have obtained similar results[259-262]. Given that cardiorespiratory fitness is a modifiable variable which can vary significantly over time, other studies have also looked at the relationship between CRF change and incident hypertension. Among just under 5000 participants from the ACLS study, with a mean follow up of 10 years and at least 4 treadmill tests performed over that period, those who showed an increasing pattern of CRF had the lowest risk of hypertension in comparison to those with a decreasing CRF pattern[263]. Other studies where CRF was measured using expired gas analysis support this finding[264,265].

Physical activity has also been proved to be of significant utility to treat high blood pressure. In the EXERDIET-HTA, one-hundred and seventy-five overweight/obese hypertensive individuals were randomized to three different exercise interventions in addition to a hypocaloric diet. After 16 weeks, exercise interventions resulted in systolic and diastolic blood pressure reductions of up to 11.6 mmHg and 4.9 mmHg respectively, with no significant differences across type of exercise programme[266]. Furthermore, a meta-analysis of 391 randomized controlled trials of antihypertensive medications and exercise interventions found that although antihypertensive medications tended to be more effective

than exercise in blood pressure reduction, the effect of exercise was more profound at higher levels of systolic blood pressure[267]. Exercise interventions were not as extensively studied as antihypertensive drugs.

1.2.7.3.2 – Physical Activity, Cardiorespiratory Fitness and Glucose Metabolism Disorders

There is a large body of evidence on the relationship between PA, CRF and glucose metabolism disorders. A comprehensive systematic review and meta-analysis by Aune et al found that both PA and CRF are inversely associated with a lower risk of type 2 DM[268]. In addition, recently published cohort studies have also demonstrated that PA reduces both the risk of IFG and the progression from IFG to overt DM[269,270]. When DM is already present, physical activity improves glycaemic control[271] and diabetic foot-related outcomes[272]. Furthermore, a Swiss study showed that the incidence of major cardiovascular events was significantly higher among those unable to achieve 6 METs in an exercise stress test after a mean follow up of 2 years[273].

The role of exercise in glucose metabolism has been intensively investigated in the last decades. In fact, exercise can stimulate glucose uptake in insulin-resistant skeletal muscles and improve insulin sensitivity for up to 48 hours after a 60 minute-session[274]. Exercise intensity and duration are fundamental determinants of skeletal muscle glucose uptake[275].

1.2.7.3.3 - Physical Activity, Cardiorespiratory Fitness and Overweight and Obesity

Exercise is a key component in obesity management. A randomized clinical trial conducted by Villareal et al allocated 107 obese adults of 65 years of age or older to either a control group, a diet group an exercise group or a diet-plus-exercise group[276]. The exercise intervention consisted of three group sessions per week lead by a physical therapist which

consisted of a combination of aerobic, resistance, flexibility and balance training with an initial intensity of 65% of peak HR which was progressively increased to 70 to 85%. After 1 year, body weight was reduced by 10% and 9% in the diet group and diet-plus-exercise group respectively compared to the control group, with no significant reductions in the exercise group. Importantly, combined diet and exercise reduced lean mass and bone mineral density loss while improving strength and balance. A second trial by the same group evaluated the impact of three different exercise programmes (aerobic, resistance or combined aerobic and resistance exercise) in addition to diet[277]. Out of these three groups, the combined exercise regime showed improved peak oxygen consumption without significant lean body mass and bone mineral density reduction.

More specifically, there is evidence showing the potential effect of PA in modifying body fat. A cross sectional study by Larsen et al[278] examined the relationship of both sitting time and physical activity with different body fat deposits in a multiethnic cohort of 519 individuals. With regards sitting time, they found a significant association with pericardial fat even after adjustment for demographics, cardiovascular risk factors, BMI and inflammatory markers, with a marginally significant association with visceral fat in unadjusted analysis which disappeared after adjustment. In relation to PA, it was associated with visceral fat even in fully adjusted models while the association with pericardial fat was significant when adjusted for demographics and cardiovascular risk factors but failed to reach significance with further adjustment for BMI and inflammatory markers. More recently, Christiansen et al[279] randomized 50 sedentary obese patients to either an endurance or resistance training programme for 12 weeks. The endurance programme consisted of high intensity interval exercise on an ergometer bicycle while the resistance training programme involved 45-minute sessions where participants performed exercises high volume exercises at a medium load (60% of 1 maximum repetition, progressively increased to 80%). In both arms, the frequency of the sessions was 3 times a week. At the end of the 12 weeks, both endurance and resistance

training groups showed a significant reduction in epicardial fat mass while the resistance training group showed further significant reductions in pericardial fat mass compared to endurance and control groups. There was no significant change in BMI, total fat mass or lean body mass in the experimental groups compared to controls. However, there was a significant increase in peak VO2 in both exercise groups compared to controls, with further strength gains in the resistance group.

1.2.7.3.4 - Physical Activity, Cardiorespiratory Fitness and Obstructive Sleep Apnoea

Multiple studies have addressed the relationship between PA, CRF and OSA which seems to be bidirectional. While physical inactivity increases the risk of OSA, sleep disordered breathing cause daytime sleepiness and fatigue which in turn reduces activity levels[280]. Cross-sectional studies show that prevalence of OSA is lower among more physically active individuals, even after adjustment for BMI and other measures of body habitus[281,282] . Physical activity is also inversely related to OSA severity[283].

Furthermore, physical inactivity increases the risk of OSA. In the Wisconsin Sleep Cohort which included 1521 middle-age adults, who were followed up for 8 ± 2 years, baseline exercise was associated with lower incidence of both mild and moderate OSA[284]. This study also showed that lower activity levels were inversely associated with higher OSA severity as measured by apnoea-hypopnea index.

Other studies have looked at the therapeutic role of exercise in OSA. In 2009, a small feasibility study by Barnes et al[285] showed that a combined dietary and exercise intervention of 16 weeks in obese individuals with OSA resulted in significant weight loss and a significant correlation with AHI. Later on, randomized clinical trials showed that exercise

interventions resulted in significant AHI and oxygen desaturation index reductions and improved quality of life, sleep quality and exercise capacity with no significant weight loss[286,287]. On the contrary, data about the effect of CPAP in PA is less conclusive[280]. More recently, a systematic review and meta-analysis showed that exercise training is associated with a significant decrease in apnoea-hypopnea index (mean decrease of 8.9 events/h; 95% CI: −13.4 to −4.3; $p < 0.01$) along with reduction in daytime sleepiness, higher CRF as per VO2peak measurement with no change in BMI[288].

In relation to physical fitness, a large population-based study showed that lower CRF was associated with incidental OSA in adjusted models, particularly among people with normal BMI, while muscular strength showed no significant differences[289]. Additionally, OSA was associated with poor LV response to exercise compared to controls as measured by cardiac output and stroke volume increments[290]. This abnormal response was improved with CPAP treatment. In another study, twenty patients with OSA showed abnormal oxygen consumption which was reversed by nasal CPAP[291].

The mechanisms explaining how PA reduces OSA severity are not well defined. Besides weight loss, other mechanisms include upper airway muscle inflammatory and neural changes[292] along with higher strength and fatigue resistance[286], reduced rostral fluid shift[293], decreased nasal resistance and improved respiratory stability during sleep[286]. Body composition changes induced by exercise may also be implicated in this process[294].

1.2.7.3.5- Physical Activity and Cardiorespiratory Fitness in Atrial Fibrillation-related conditions

1.2.7.3.5.1 - Physical activity, Cardiorespiratory Fitness and Heart Failure

PA and CRF have profound implications in primary prevention of HF as well as prognostic and therapeutic aspects.

Firstly, PA has been linked to a significant risk reduction of HF. A comprehensive meta-analysis of 12 prospective cohort studies (including 370,460 subjects, 20,203 HF events over a median follow up of 13 years) shows that there is a dose-dependent linear inverse relationship between PA and HF risk which is consistent across subgroups and regions[(295)]. This study also showed that minimum PA guideline recommendations are only associated with a marginal benefit in terms of HF risk reductions, thus suggesting that more PA is required to obtain a more robust benefit in terms of primary prevention. The cardioprotective effect of exercise appears to be mediated by adaptations at a structural, functional, cellular and molecular level in the heart in response to exercise[(296)].

Secondly, the importance of physical activity and exercise in HF management has been increasingly recognized over the last decades. In 1988, a seminal paper by Sullivan et al[(297)] demonstrated for the first time that HF patients could not only perform exercise safely, but also the positive impact in their physical fitness. In this study, 12 ambulatory HF patients with an LVEF of 24 ± 10 undertook an exercise program which consisted of 4 to 6 hours a week of exercise performed at 75% of their peak VO_2. This resulted in significant increases in aerobic capacity and improved leg blood flow. In 2009 results from Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION)[(298)] were published. In this randomized controlled trial, 2331 HF patients with a median age of 59 years and a median LVEF of 25 were enrolled in either an exercise group or a control group. The intervention

was a group-based, supervised exercise program, with a goal of 3 sessions per week for a total of 36 sessions in 3 months, where intensity was increased over 6 sessions to a target intensity of 70% of heart rate reserve. Patients in the intervention group patients in the exercise training group had a significant improvement in distance in the 6-minute walk test (median, 20 vs 5 meters; P<0.001), in exercise time on the cardiopulmonary exercise test (1.5 minutes vs 0.3 minutes; P<0.001), and in peak VO_2 (0.6 vs 0.2 mL/min/kg; P<0.001). However, reductions in the primary endpoint (all-cause death or hospitalization) were modest and only statistically significant after adjustment for highly predicting variables.

1.2.7.3.5.2 - Physical Activity and Cardiorespiratory Fitness in Coronary Artery Disease

There is a wealth of data assessing the role of PA and exercise in coronary artery disease. This includes epidemiological as well as mechanistic studies.

Firstly, PA is involved in the prevention of coronary artery disease. In 1973, Morris et al[299] reported that individuals who performed vigorous physical activity at least twice a week had a lower incidence of coronary events in a cohort of 16,882 participants. This resulted in an increasing interest in the role of PA in the prevention of CAD. More recently, among 12,516 middle aged persons included in the Harvard Alumni Study, risk was consistently reduced with increasing PA, even in the those with cardiovascular risk factors[300]. Other studies suggest that this risk reduction is even independent from genetic risk[301]. Sattelmair et al[302] conducted a meta-analysis of prospective cohort studies where they found that those who met the activity levels recommended by guidelines had a 20% lower risk of CAD with modest risk reductions beyond that level. They also found that even at lower levels, significant risk reduction was still present, supporting the hypothesis that ‘some physical activity is better than none’. Mechanistic studies suggest that CAD risk reduction conferred by PA is due to its

effects in risk factor management and its effects in the endothelial dysfunction, which can precede coronary atherosclerosis by years[301].

Secondly, it is important to highlight the differences between PA and CRF in terms of risk prediction of CAD. A systematic review and meta-analysis of 16 cohort studies analysed the dose-response of PA or CRF in the risk of CAD or cardiovascular disease (which included CAD and stroke)[303]. This study showed that a) the risk of CAD decreased linearly with increasing PA, b) on the contrary, there was a sharp decrease in the risk of CAD beyond the 25th percentile of fitness distribution, with a further decrease beyond the 75th percentile and c) relative to the most unfit or inactive percentile, risk was significantly more reduced in the fitter than in the more active. The conclusion of this study was that a PA guideline based solely on PA recommendations could be inappropriately misleading given the more powerful effect of higher CRF in the reduction of CAD risk.

Thirdly, PA confers benefits in secondary prevention of CAD. A randomized controlled trial assigned 101 patients with stable CAD to either percutaneous intervention (PCI) or exercise[304]. The exercise intervention consisted of daily sessions of 20 minutes each on a bicycle at 70% of the maximum heart rate achieved on a symptom-limited exercise test in addition to one extra 60-minute session per week. After 12 months, the exercise group had better event-free survival (stroke, target vessel revascularization, PCI of a de novo lesion, or coronary artery by-pass graft surgery). Exercise intervention was also less costly and resulted in significant improvement in exercise capacity. After 2 years of follow up, event-free survival was still lower in the exercise group, which also had a significant reduction in systemic inflammatory markers[305]. A systematic review and meta-analysis of 63 studies including 14,486 individuals with CAD concluded that exercise-based rehabilitation programs resulted in significant reductions of cardiovascular mortality and hospital admissions along

with significant improvements of HRQOL. Mechanisms proposed include reduced platelet activation, increased vasculogenesis with formation of collateral vessels, regression of coronary atherosclerotic plaques and partial correction of endothelial dysfunction[301].

1.2.7.3.5.3 - Physical Activity and Cardiorespiratory Fitness in stroke

The relationship between physical activity and stroke has been reported in multiple studies. While the FHS and ARIC cohort failed to demonstrate a clear relationship between PA and stroke risk[306,307]. Lee et al described a U-shape curve in the Harvard University alumni cohort[308] which was consistent with other two earlier studies[309,310]. A systematic review and meta-analysis that searched publications from 1966 to 2002 in one medical database reported a 27% reduction in the risk of stroke or death among highly active individuals compared with low-active individuals, including both ischemic and haemorrhagic strokes[311]. More recently, the Northern Manhattan Study reported a significantly lower risk of ischemic stroke among those who performed moderate to heavy PA compared to light or none PA even after adjustment for risk factors[312]. Furthermore, a recent cohort study compared the incidence of both AF and stroke among long distance cross-country skiers[228]. Skiers of either sex had a lower incidence of stroke than non-skiers regardless of the number of races completed and finishing time.

Particularly in the context of AF, PA and CRF appear to be associated with stroke incidence. The risk of stroke is significantly lower among physically fitter participants[213]. Additionally, a cross sectional Spanish study which included 443 non-valvular AF patients showed that those with a healthy lifestyle (defined as adherence to Mediterranean diet and >3000 MET-minutes per week as per a validated questionnaire) had a lower risk of ischemic brain lesions on magnetic resonance imaging regardless of symptoms[313].

PA is also fundamental after an index stroke for secondary prevention, rehabilitation and prognosis and both aerobic as well as strength training are strongly supported by current guidelines[314]. In fact, the majority of stroke survivors suffer from a sequelae, with 40% having difficulties with daily activities such as personal hygiene and dressing[315]. Randomized clinical trials have evaluated the usefulness of different exercise-based interventions showing positive results in walking ability, cognitive tasks and muscle strength[316] although data is still scarce.

There are multiple mechanisms that have been proposed to explain stroke risk reduction among more active individuals which include improvement in blood pressure control and lipid metabolism, enhanced vasodilation and vasomotor function in the vessels due to better endothelial function, enhanced fibrinolysis and reduced blood viscosity, fibrinogen levels and platelet aggregability[311].

In summary, the present literature review has described the available evidence on AF from epidemiological data to pathophysiological mechanisms. This first chapter highlights the importance of AF as a major health issue worldwide due to its rising burden. Furthermore, it also explores the pathophysiological links between traditional cardiovascular risk factors, AF and associated conditions. The following chapters of this thesis will address aspects of the epidemiology and pathophysiology of AF in relation to PA and CRF that remain poorly understood: a) chapters 2 and 3 will explore the relationship between PA, body composition and AF risk, b) chapter 4 will describe the associations between PA and mortality once AF is established and c) chapters 5 and 6 will describe the electroanatomical as well as mechanical LA features in patients with AF in relation to their exercise capacity.

Chapter 2: Self-reported Physical Activity and Atrial Fibrillation Risk: A Systematic Review and Meta-analysis

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Manuscript: **Mishima RS**, Verdicchio CV, Noubiap JJ, Ariyaratnam JP, Gallagher C, Jones D, Malik V, Agbaedeng TA, Middeldorp ME, Lau DH, Sanders P, Elliott AD. Self-reported physical activity and atrial fibrillation risk: A systematic review and meta-analysis. *Heart Rhythm 2021; 4:520-528*.

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2.1 - INTRODUCTION

Atrial fibrillation is a growing public health problem globally, owing to its rising prevalence and associated high morbidity and mortality[39]. Although catheter ablation success rates are

fairly high, it remains associated with significant recurrence and the potential for serious complications.

A large body of evidence demonstrates that cardiovascular risk factors such as hypertension, diabetes, obstructive sleep apnoea and obesity increase the risk of AF[134]. New onset AF is frequently the consequence of left atrial electrical and structural remodelling induced by the development of these risk factors, a complex pathogenic process that includes atrial inflammation and fibrosis, conduction abnormalities and autonomic dysfunction[134].

PA is an essential component in the management of cardiovascular risk. Moreover, current guidelines recommend at least 150 minutes a week of moderate intensity PA or 75 minutes a week of vigorous intensity PA, equivalent to 450 metabolic equivalent of task (MET)-minutes per week of PA for significant health benefits[35]. However, the association between PA and AF risk is less clear. Although the main challenges in evaluating the relationship of PA and AF are the subjectivity and time-varying nature of the PA, the emergence of recent data presents the opportunity for more detailed analyses.

The aim of this study is to systematically summarize the evidence pertaining to the association between PA and risk of AF. Therefore, we conducted a systematic review and meta-analysis to evaluate the overall association between physical activity and incident AF. We hypothesize that physical activity as per guideline recommendation is associated with lower risk of incident AF.

2.2 - METHODS

This review is reported in accordance with the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines[317] and has been registered in the PROSPERO (registration number CRD42020197228).

2.2.1 - Search Strategy

Embase and MEDLINE databases were searched to identify studies reporting primary data on the relationship between PA and AF risk, published in these databases up until March 9, 2020. Search strategy was developed using terms related to atrial fibrillation and physical activity (Supplement table 1).

2.2.2 - Study Eligibility

We included prospective cohort studies, with a minimum follow-up of 4 years, reporting the association between PA and incident AF. We excluded case reports, case series, cross-sectional and case-control studies, studies not reporting primary data, animal, ex vivo and in vitro studies. PA units were transformed to MET-minutes per week (details below). Where multiple studies reported results from the same cohort, that with the greatest number of participants was included. Studies reporting on occupational or device-reported PA only were excluded. Furthermore, articles where the outcome variable was included as a composite outcome or was assumed based on antiarrhythmic prescription and postoperative AF were excluded.

2.2.3 - Data extraction

Data was extracted using a preconceived and standardised data abstraction form, by two investigators (RM and DJ), with discrepancies resolved by consensus. These data included the

first author, year of publication, number of participants and distributions of co-morbidities, duration of follow-up, method of AF diagnosis, method of PA assessment, maximally adjusted risk estimates with the 95% confidence interval (CI). For each PA group, we used the reported data on PA quantity to determine MET-minutes per week, according to the following assumptions: PA was assumed to be of moderate intensity unless reported otherwise. Moderate PA was assigned a value of 4.5 METs according to the mid-point of standardized guidelines for moderate intensity exercise (3-6 METs). PA specifically reported as 'vigorous' activity was assigned a MET value of 7.5 METs, which was calculated as the lowest value within this category (6 METs) plus the difference from the lowest range of the closest adjacent category to its mid-point (i.e. 1.5 METs). Where PA was reported as Kcal/week, we used a standardised conversion factor of 1.39 Kcal = 1 MET-minute based on accepted calculations[318]. In instances where PA was reported in days per week, we assumed a typical duration of 30 minutes activity per day. Finally, where PA for each group was reported as a range, we used the mid-point of that range as the assigned PA value. To reduce the potential confounding effect of these assumptions, a sensitivity analysis was conducted, excluding those studies where PA was estimated from a non-validated questionnaire or where PA was assumed of moderate intensity. Sensitivity analysis was also conducted excluding the studies where risk estimates were not adjusted for BMI.

2.2.4 - Assessment of Methodological Quality

The methodological quality of studies was independently assessed by two investigators (RM and CV) using the Newcastle-Ottawa Scale (NOS) for cohort studies. Discrepancies were resolved by a consensus.

2.2.5 - Statistical Analysis

All extracted data were analysed using R Version 1.0.143. We performed a random-effects meta-analysis using the generic inverse variance method for pooled odds ratios. Data was entered as (Log) OR and standard error (SE), based on the multivariate adjusted values shown in each study. Heterogeneity was assessed by the χ^2 test on Cochrane's Q statistic which was quantified by I^2 values, assuming I^2 values of 25, 50, and 75% respectively representing low, medium, and high heterogeneity. Publication bias was assessed using funnel plots of effect size against standard error. A two tailed p-value of <0.05 was considered statistically significant.

For our primary analysis, we included studies where the risk of AF could be extracted among patients grouped by their PA levels. In this primary analysis, we included the group with a mean or median PA that was above the minimum recommended PA (450 MET-minutes per week). Where multiple groups were within this range, we took the lowest of the two. In a secondary analysis, we sought to create a dose-response analysis whereby all groups were included in the analysis. To do so, we extracted the multivariate adjusted risk, number of cases and total sample size, where available, for each level of PA and calculated the risk for every 500 MET-minutes per week of PA compared to inactive. The 'DosResMeta' package was used to estimate a dose-response relation from multiple summarized data, taking into account the correlation among set of log relative risks. The covariances were approximated according to the method proposed by Greenland et al[319] study-specific estimates were combined according to principles of multivariate random-effects meta-analysis.

2.3 - RESULTS

A total of 24,205 records were identified from the initial searches. After screening of titles and abstracts, 26 articles were selected for full-text review, out of which 15 were finally included **(Figure 1)**.

2.3.1 - Study Population

The total number of participants was 1,464,539 (51.7% females) with 36,917 cases (2.5%) of incident AF. Baseline characteristics are shown in **Table 1** and supplementary table 2.

2.3.2 - Physical Activity and Atrial Fibrillation assessment

All the studies assessed PA using questionnaires, one of which[320] has not been validated with either accelerometer, exercise test, test-retest or energy consumption methods. Activity volume was reported in different units across studies.

Diagnosis of AF was ascertained by self-report and medical records review in three studies[320-322], linkage to medical records in eight[205,323-329], routine ECG in one[206] and routine ECG combined with medical record review in three[330-332].

2.3.3 - Categorical data meta-analysis

In the primary analysis, we first compared patients meeting current PA guidelines (Median 720 MET-minutes per week, IQR 540-1004) with inactive individuals as reported within each study. Compared to inactive individuals, pooled estimates indicate a lower risk of incident AF amongst those participants broadly meeting current PA guidelines (HR 0.94, 95% CI 0.90-0.97, p=0.001) with evidence of moderate statistical heterogeneity (I^2 = 44%, p=0.034) (**Figure 2A**).

In a subsequent analysis that compared the group with the highest PA (Median 1485 MET-min/week, IQR 1221-1960) within each study with the inactive group, the pooled estimates showed an 8% lower risk of AF (HR 0.92, 95% CI 0.85-0.98, p=0.02, **Figure 2B**) with evidence of moderate to high heterogeneity (I^2 = 73%, p<0.001).

2.3.4 - Sensitivity Analyses

In sensitivity analysis, when studies where the implemented questionnaire was not validated or PA was assumed of moderate intensity were excluded, results did not differ. Both guideline recommended PA (HR 0.92, 95% CI 0.88–0.96, p=0.0001) and highest PA (HR 0.88, 95% CI 0.800.96, p=0.006) remained associated with a significantly lower risk of AF (**Supplemental figure 1A and 1B**, respectively).

Adjustment for BMI was not performed in Mozzafarian et al[331], Huxley et al[330], Albrecht et al[327] and Ogunmoroti et al[320]. When these studies were excluded from the analysis, results remained significant for inactive vs guideline PA (HR 0.94, 95% CI 0.91-0.98, p=0.003) (**Supplement figure 2A**). Risk among high PA remained lower than the inactive group (HR 0.93, 95% CI 0.87-1.00, p=0.05) (**Supplement figure 2B**).

In sex-specific subgroup analysis, PA above the guideline-recommended level was associated with lower risk of incident AF in both women (HR 0.91, 95% CI 0.88-0.95, p<0.0001, I^2 = 0%, 5 studies) and men (HR 0.96, 95% CI 0.93 – 1.00, p=0.03, I^2 = 0%, 4 studies) (**Figures 3A and 4A**). Highest PA was associated with lower risk of AF in women (HR 0.88, 95% CI 0.83 – 0.92, p<0.00001, I^2 = 15%, 5 studies), but not in men (HR 1.03, 95% CI 0.94 – 1.12, p = 0.12, I^2 = 48%, 4 studies), compared to inactive (**Figures 3B and 4B**).

2.3.5 - Dose response meta-analysis

When all studies were pooled together in a dose response analysis **(Figure 5)**, we observed a significant association between PA dose and AF risk (χ^2=9.7, p=0.008). Specifically, the upper confidence bounds indicated a lower risk of incident AF at all levels of physical activity from 500-1900 MET-minutes per week. The hazard for incident AF was 0.94 (95% CI: 0.90-0.98), 0.89 (95% CI: 0.83-0.96) and 0.94 (95% CI: 0.78-1.13) at 500, 1500 and 2500 MET-minutes per week, respectively.

2.4 - DISCUSSION

2.4.1 - Major Findings

This analysis presents the most comprehensive findings to date regarding the relationship between PA and incident AF. First, performing PA as per recommended by current guidelines is associated with a lower risk of AF. Second, although PA as per recommended by guidelines was significantly associated with a lower risk of AF compared to inactive, the lowest AF risk appears to occur at a higher range of approximately 1500 MET-minutes per week. Third, beyond this level of PA, there is less certainty regarding the effect of PA on AF risk. Finally, in women, higher PA was associated with a lower risk of AF compared to men.

These results are in contrast to previous meta-analyses reporting no significant association between PA and AF risk[333,334]. This may be explained because these include studies that report work-related or poorly defined PA, and case-control studies. Moreover, the present analysis includes large prospective cohort studies that were published recently[205-207,320,326-328,332]. In the vast majority of the studies, risk has been adjusted for age, gender, BMI and comorbidities. In synthesising this evidence, we have included the maximally adjusted risk estimates from each study. However, this meta-analysis of observation studies prohibits us making inferences about potential mechanisms.

The results of this study are consistent with extensive data showing that regular physical activity is associated with lower cardiovascular disease, including incident heart failure and coronary disease. A meta-analysis of prospective cohort studies investigating the association between leisure time PA and coronary artery disease risk[302], demonstrated an attenuation of risk up to leisure-time PA levels of 2750 kcal/week which corresponds to 1978 MET-minutes per week. Similarly, Pandey et al[295] explored the association between dose of PA and incident heart failure events in a meta-analysis including 370,460 participants. They found a substantial lower risk with 1000 and 2000 MET-minutes per week of PA. The data presented here shows that the benefits of a PA should be extended to AF. Regular physical activity improves exercise capacity, cardiac function, symptom burden and quality of life in the context of stablished AF[335]. In addition, Donnellan et al[232] demonstrated a lower mortality and arrhythmia recurrence associated with higher CRF after AF ablation.

The lower incident AF amongst physically active participants is supported by data that shows a higher AF risk amongst patients with low exercise capacity, as assessed using exercise stress testing. In a cohort of over 60,000 participants referred for exercise testing, each 1-MET improvement of cardiorespiratory fitness (CRF) was associated with a 7% lower risk of incident AF[210]. Furthermore, a recently published study by O'Neal et al[229] that quantified PA using accelerometer data showed that while some AF prevention might be achieved at the minimum level of guideline recommended PA, significantly lower risk is associated with higher levels, a finding that is consistent with our results.

Although there is consistent evidence demonstrating an elevation of AF risk amongst endurance athletes, we found that PA up to 1900 MET-minutes per week appears to be associated with a significantly lower risk of AF. Training volumes in endurance sports competitors are frequently

much higher than that covered in this analysis and sustained over long periods of time[336]. As a result, there is notable atrial remodelling alongside heightened vagal activity that converge to create an arrhythmogenic substrate[244]. The risk of AF associated with this high training volume is beyond the scope of this meta-analysis, particularly given that there are few prospective studies of participants in this range of exercise. Further studies are required to explore whether there is a threshold of exercise volume or intensity, above which the risk of AF appears to increase.

There is a large body of evidence describing the causal role of cardiovascular risk factors on the AF substrate and subsequent risk and burden of AF[134]. It is known that PA is associated with a reduction of cardiovascular risk factors in sedentary individuals. It is likely that most of the lower risk observed in these studies may be mediated by the enhanced control of cardiovascular risk factors. Nevertheless, most studies present analyses adjusted prevalent risk factors, suggesting that PA may be independently associated with lower risk of AF. Data from population studies show that leisure time PA is associated with improved diastolic parameters along with reduced LV hypertrophy and myocardial damage[337].

There appears to be a stronger association between PA and AF risk for females, compared to males. In the female-only cohorts, the lower AF risk amongst physically active individuals was maintained whereas amongst male-only cohorts no overall associated was observed. There is evidence for marked gender differences in the pathophysiology of AF, with women having a higher prevalence of hypertension, more fibrosis despite lower LA volumes and different clinical presentation with more atypical symptoms[338]. This data further suggests that the association between lifestyle behaviours and risk factors may differ for women.

This study has several limitations that warrant consideration. Firstly, methods regarding PA and AF ascertainment across studies were variable. Some questionnaires have shown limited correlation with accelerometer data. In addition, PA levels were assumed based on subjective reports of PA. Furthermore, most studies use medical records and annual electrocardiograms to diagnose AF. In fact, a large proportion of high-risk patients are asymptomatic[339], which may suggest that AF could have been present at baseline, especially among high-risk participants. Secondly, PA habits may change over time. Only three studies take this into account. None of the studies reported risk associated with quantitative modifications of PA volume. Similarly, while most of the studies present results adjusted for baseline BMI, variations of BMI over time can affect the risk of AF in a cumulative manner[340]. Thirdly, while there are multiple potential direct and indirect mechanisms that could explain the variation in AF risk observed at different PA levels, we cannot stablish a cause-effect relationship between PA and AF. More research regarding PA, LA arrhythmogenic substrate and AF incidence is required.

2.5 - CONCLUSION

PA exhibits a dose-dependent relationship with AF risk with higher levels of PA associated with lower risk of incident AF. Regular PA should therefore be recommended to those at risk of developing AF, highlighting its role as a primary preventative strategy in AF development. Further studies looking at AF risk at higher volumes of PA are required to define optimal levels of benefit.

This chapter has systematically reviewed the available evidence in relation to PA and AF risk. Chapter 3 will explore the relationship between PA, body composition and AF risk in a large cohort of participants from the UK Biobank.

2.6 - TABLES AND FIGURES

TABLE 1. Baseline characteristics.

FIGURE 1. Consort diagram.

FIGURE 2. PA-AF risk in people performing PA according to guidelines (2A) and above guidelines (2B).

FIGURE 3. PA-AF risk in women performing PA guidelines (3A) and above guidelines (3B).

FIGURE 4. PA-AF risk in men performing PA according to guidelines (3A) and above guidelines (3B).

FIGURE 5. PA-AF risk dose response analysis.

Study	Participants	Age	Gender (% female)	PA measurement	Follow up	AF diagnosis	Adjustment
Mozzafarian et al[331]	5446	72.8 ± 5.6	58	Modified Minnesota Leisure-Time Activities questionnaire	12 years	(i) Annual 12-lead ECG (ii) Discharge diagnoses	Age, gender, enrolment site, education, smoking, CHD, COPD, DM, alcohol use and BB use
Aizer et al[321]	16921	51.7	0	Tailored questionnaire	12 years	Self-reported	Age, treatment, BMI, DM, hypertension, hyperlipidaemia, parental history of premature MI, alcohol use, smoking status, fish consumption, vitamin intake, LVH, CHF, evidence of CVD
Everett et a[322]	34759	53	100	Tailored questionnaire	14.4 years	Self-reported, hospital record	Age, randomized treatment, cholesterol, current smoking, past smoking, alcohol use, DM, race, hypertension, BMI
Huxley et al[330]	12646	54.2 ± 5.7	61.5	Baecke questionnaire	20.4 years	(i) Triennial 12-lead ECG (ii) Hospital records	Age, race, sex, study site, education, income, prior CVD, cigarette smoking, height, and alcohol use
Azarbal et al[323]	81317	63.4	100	Tailored questionnaire	11.5 years	Hospital records	Age, race, education, BMI, hypertension, DM, hyperlipidaemia, CHD, CHF, PAD, smoking
Drca et al (male)[324]	44410	57-63	0	Tailored questionnaire	12 years	Medical records	Age, education, smoking status, BMI, DM, hypertension, CHD or CHF, family history of MI, aspirin use, alcohol intake
Drca et al (female)[325]	36513	60-64	100	Tailored questionnaire	12 years	Medical records	Age, education, smoking status, BMI, DM, hypertension, CHD or CHF, family history of MI, aspirin use, alcohol use
Morseth et al[326]	20494	36-39	49.7	Tailored questionnaire	20 years	Medical records	Age, sex, BMI, height, daily smoking, CVD, systolic blood pressure, diastolic blood pressure, diabetes, hypertension treatment, and RHR
Skielboe et al[332]	15818	48.1	54	Copenhagen City Heart Study Physical Activity Questionnaire	20.3 years	ECG on follow up visits	Age, height, BMI, sex, smoking, alcohol use, school education, blood pressure, RHR, spirometry, cardiac medication, DM, CHD and enrolment number
Garnvik et al[328]	43602	52.1 ± 15	54.1	Tailored questionnaire	8.1 years	Medical records	Sex, age, current smoking, alcohol use, self-reported CVD, occupational status, BMI
Albrecht et al[327]	7018	67.3–71.9	58.2	Zutphen Physical Activity Questionnaire (adapted)	12.3 years	Medical records	Age, sex, PA types, smoking, previous CVD, alcohol use, diet, education
Ogunmoroti et al[320]	6506	62 ± 10.2	53	MESA Typical Week Physical Activity Questionnaire	11.2 years	(i) Self-reported (ii) Medical records	Age, sex, race/ethnicity, education, income, health insurance
Jin et al[205]	501690	47.6 ± 14.3	50	IPAQ – SF questionnaire	4 years	Medical records with ECG review	Age, sex, BMI, CHF, hypertension, diabetes, previous MI, prior stroke or TIA, CKD, smoking, and alcohol use
Lee et al[206]	211992	37.8 ± 7.8	38.7	IPAQ – SF questionnaire (adapted)	5.6 years	Annual 12-lead ECG	Age, sex, centre, year of screening examination, smoking status, alcohol intake, education level, BMI, hypertension, DM, CVD, hs-CRP
Elliott et al[207]	402406	56.5 ± 8	52.4	IPAQ questionnaire	6.96 years	Medical records	Age, BMI, smoking, alcohol intake, hypertension, DM, OSA, CHF, valvular disease, CHD

TABLE 1. Baseline characteristics. CHD = Coronary heart disease, COPD = Chronic obstructive pulmonary disease, DM = Diabetes mellitus, BB = beta blocker, BMI = Body mass index, LVH = Left ventricular hypertrophy, CHF = Congestive heart failure, CVD = Cardiovascular disease, PAD = Peripheral artery disease, MI = myocardial infarction, RHR =

Resting heat rate, TIA = Transient ischaemic attack, CKD = Chronic kidney disease, hs-CRP = High-sensitivity C reactive protein, OSA = Obstructive sleep apnoea.

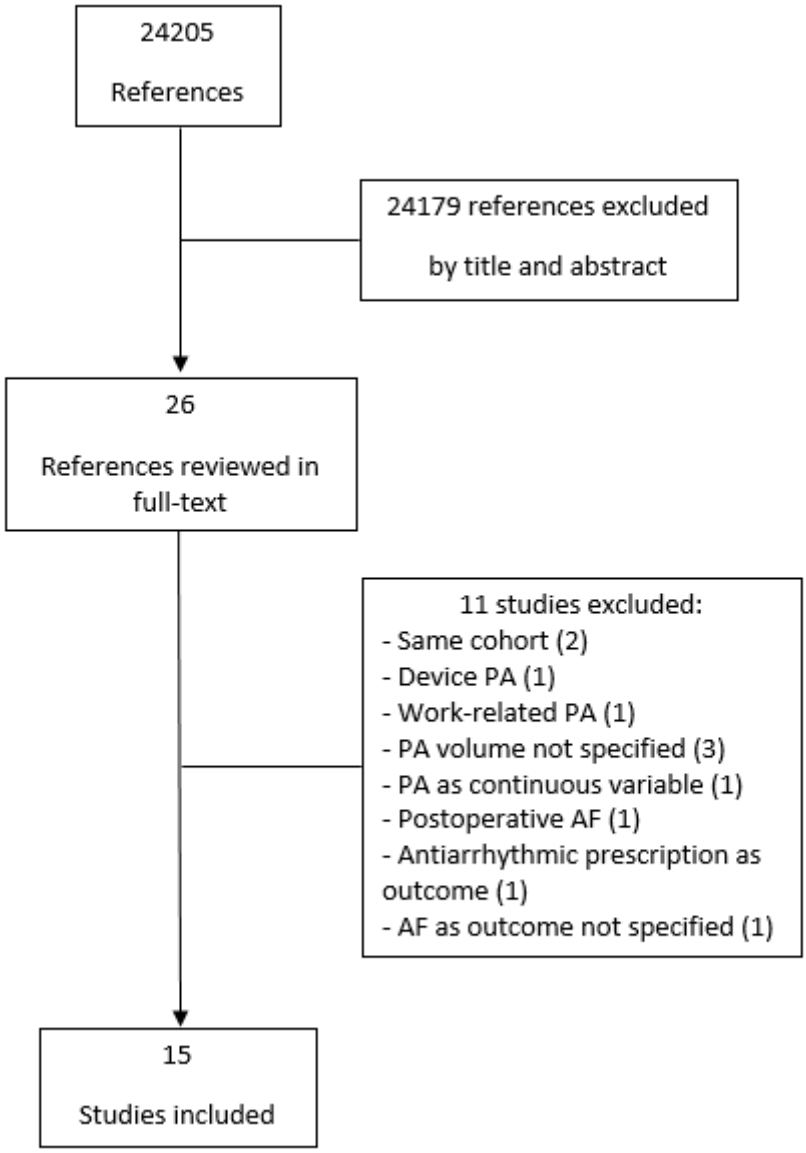

FIGURE 1. Consort diagram.

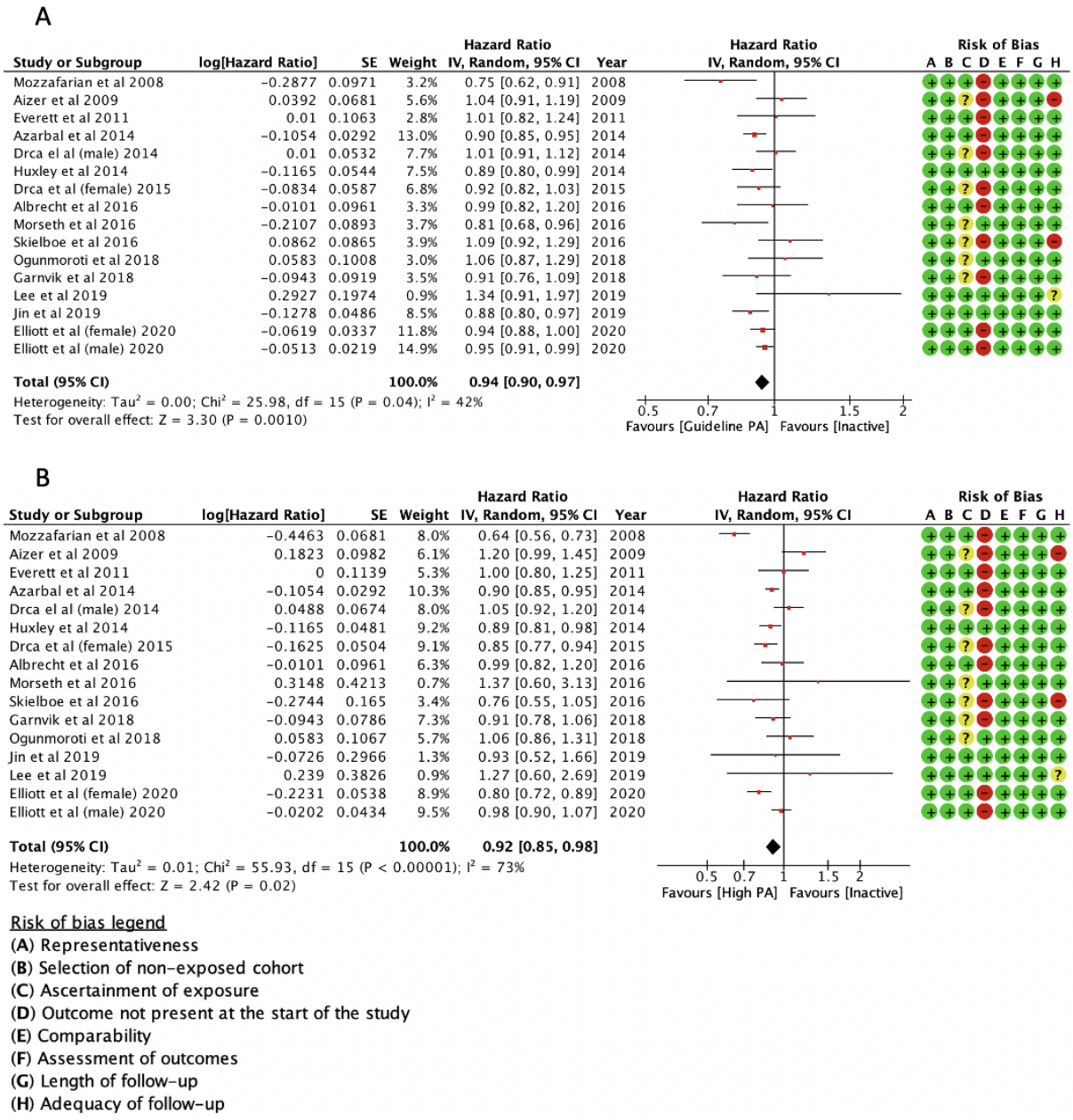

FIGURE 2. Physical activity (PA)–atrial fibrillation risk in people performing PA according to guidelines (A) and above guidelines (B). CI = confidence interval; SE = standard error.

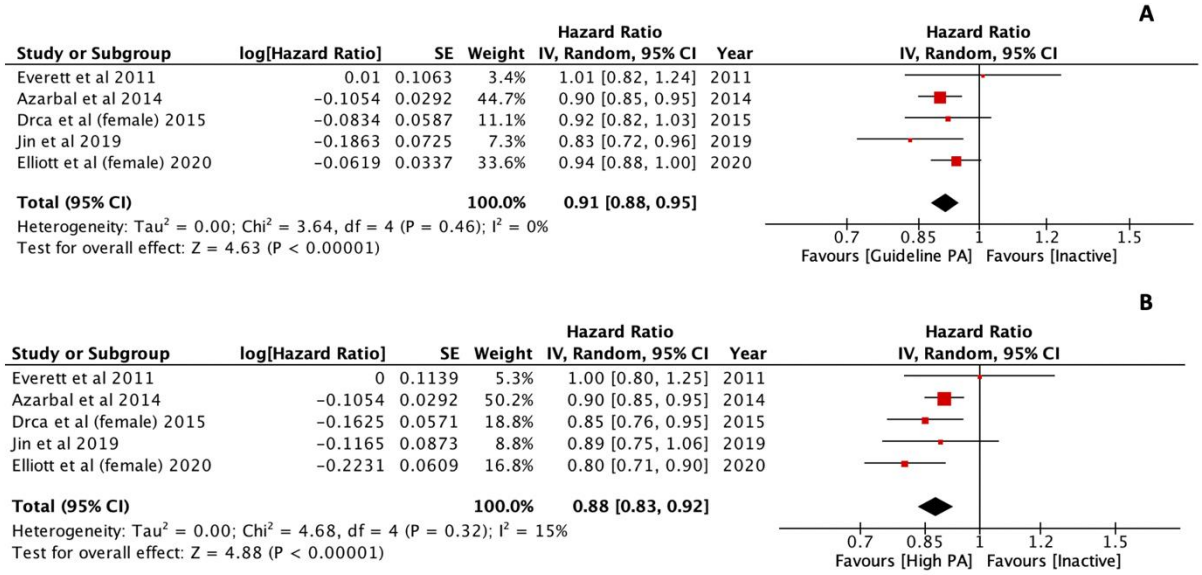

FIGURE 3. PA-AF risk in women performing PA guidelines (3A) and above guidelines (3B).

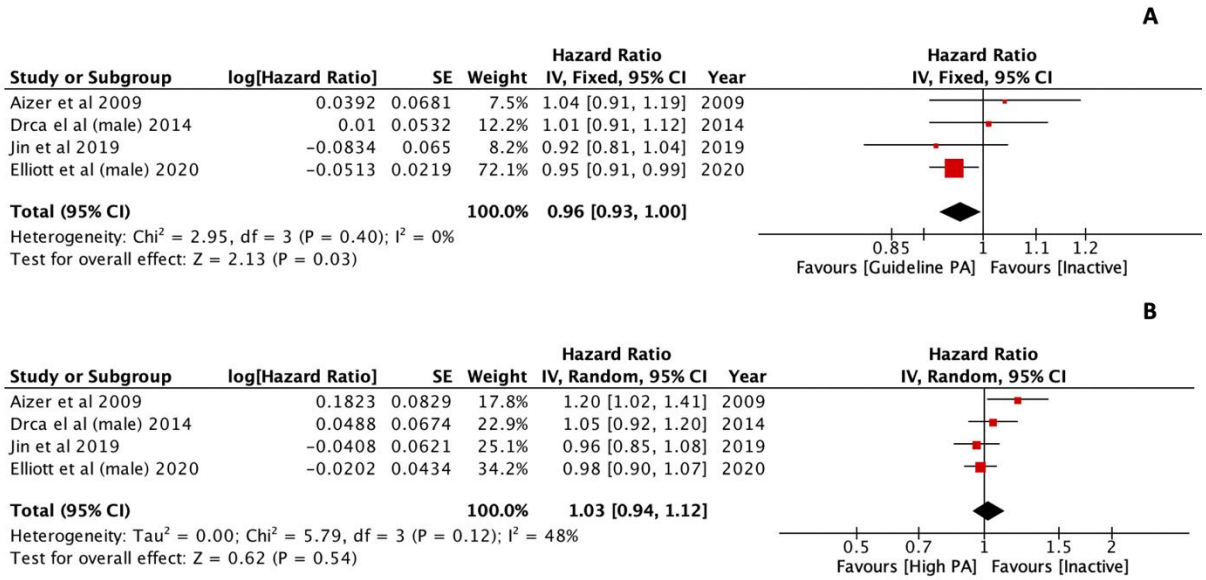

FIGURE 4. PA-AF risk in men performing PA according to guidelines (4A) and above guidelines (4B).

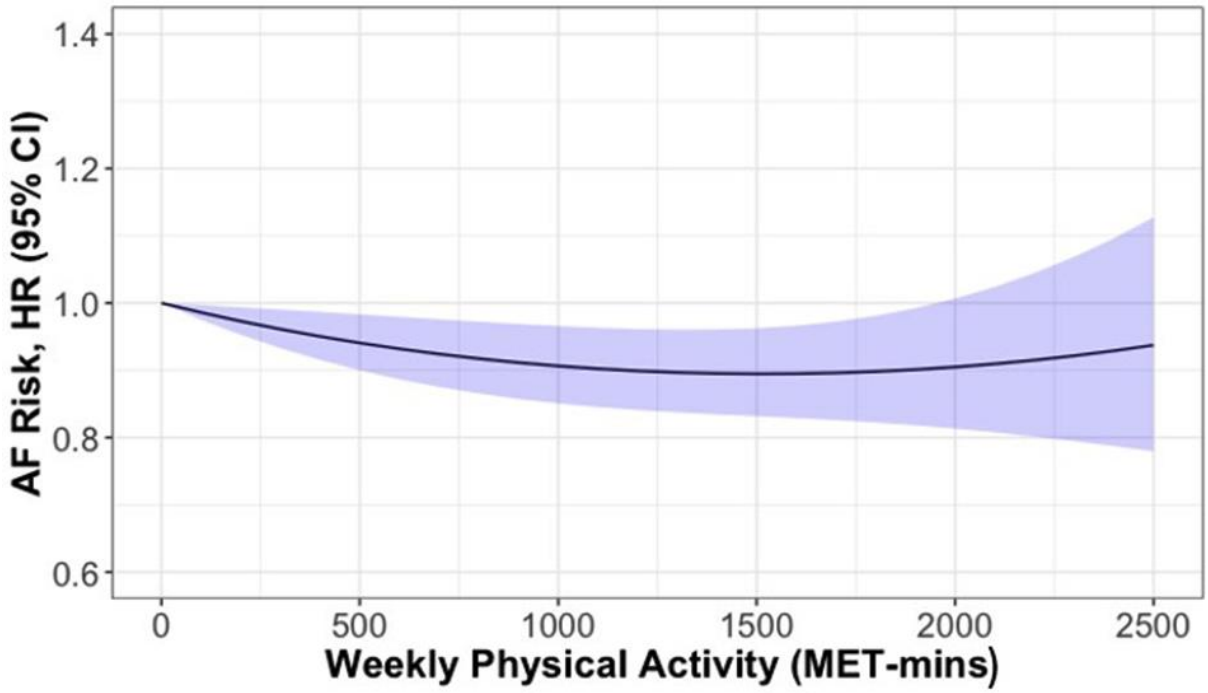

FIGURE 5. PA-AF risk dose response analysis.

Chapter 3: Body Composition and Risk of Cardiac Arrhythmias

i. **<u>Presentation from abstract:</u>** Lean Body Mass and Adiposity Increase the Risk of Atrial Fibrillation. **Mishima RS**, Linz D, Lau DH, Kadhim K, Wong CX, Gallagher C, Emami M, Middeldorp ME, Hendricks J, Sanders P, Elliott AD. Asia Pacific Heart Rhythm Society 2019, Bangkok, Thailand.

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Overall percentage (%)	50%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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INTRODUCTION

The rising incidence of cardiac arrhythmias, including AF presents a serious healthcare challenge[39,341]. A large proportion of atrial arrhythmias are attributable to modifiable risk factors, including obesity[342,343]. There is also a strong association between obesity and sudden cardiac death[344,345]. Therefore, excess body weight and adiposity are important considerations in evaluating the risk of cardiac arrhythmias.

Preclinical and human studies demonstrate that adiposity leads to fat accumulation in proximity to the LA, resulting in conduction disturbances, structural remodelling and vulnerability to AF[138,346]. Beyond the atria, obesity promotes atherosclerotic disease and development of risk factors that increase the risk of ischemic heart disease[347], leading to ventricular arrhythmias. However, recent data suggests that the association between obesity and arrhythmic events may not be solely mediated through increased adiposity.

A growing body of work provides evidence that lean mass promotes AF, potentially to a greater extent than fat mass[348]. However, it is unclear whether findings relating lean mass to AF risk, can be extrapolated to other arrhythmias. Mechanistically, greater lean mass may increase atrial and ventricular size, potentially providing additional substrate for arrhythmias. However, the precise mechanisms have yet to be elucidated. Additionally, whether the association between lean mass and arrhythmias persists in both sexes or is modified by physical activity and fat mass, is still unclear.

The aims of this study were to: (i) quantify the independent association of atrial, ventricular and bradyarrhythmias with lean mass and measures of overall adiposity, and (ii) assess the interaction between sex, habitual physical activity, anthropometric measures and arrhythmia risk.

METHODS

Study Design

Between April 2007 and December 2010, the UK Biobank cohort recruited 502,543 community-dwelling individuals, aged 40-69 years, to attend one of 22 assessment centers around the United Kingdom, where they completed extensive touch screen questionnaires as well as undertaking physical measurements. All participants were followed up for health outcomes through linkage to national electronic health-related data sets. Participants provided written informed consent to participate in this research, which was approved by the UK Biobank Research Ethics Committee (reference number 11/NW/0382).

Exposure Variables

The anthropometric measures of interest were BMI, body composition, lean mass, fat mass, and waist circumference. Trained staff collected anthropometric data during initial study visits, including height, body mass and waist circumference. Body composition analysis was performed using 8-electrode biompedance analysis (Tanita, BC418MA, Tanita Corporation, Tokyo, Japan). Body fat percentage was directly assessed, with fat mass and lean mass subsequently computed. PA habits were assessed at baseline using the validated short form international physical activity questionnaire (IPAQ). The IPAQ questions participants on three types of activity (walking, moderate and vigorous intensity activities). From these questions, total physical activity volume can be computed in metabolic equivalent-minutes per week (MET-minutes/week).

Covariates

Age, sex and lifestyle habits, including smoking status and alcohol intake were evaluated by detailed questionnaire during baseline assessment visits. Frequent alcohol consumption was considered if intake was daily. Prevalent clinical comorbidities were also evaluated through self-reported questionnaire and previous diagnoses, including hypertension, type II diabetes, arrhythmias, heart failure, valvular disease and coronary disease.

Arrhythmia Endpoints and Follow-Up

Hospital admissions were identified through linkage with the Health Episode Statistics records (England and Wales) and to the Scottish Morbidity Records (Scotland). Date and cause of death was obtained from death certificates held by the National Health Service Information Centre for participants from England and Wales, and the NHS Central Register Scotland for participants in Scotland. The primary endpoints were the diagnosis of atrial arrhythmias (fibrillation or flutter, grouped as AF), bradyarrhythmias and ventricular arrhythmias. Incident arrhythmias were classified by at least 1 ICD-10 code for the condition listed as a primary diagnosis, secondary diagnosis or cause of death for a linked medical encounter. Incident AF included hospital diagnosis or death due to atrial fibrillation or flutter, and operative procedures relating to AF including catheter ablation. The diagnosis of bradyarrhythmias included second-degree atrioventricular (AV) block, complete AV block, sick sinus syndrome and operative procedures relating to bradyarrhythmias including pacemaker implantation. Ventricular arrhythmias included ventricular tachycardia, ventricular fibrillation, cardiac arrest and catheter ablation of the ventricular wall. For the analysis of AF incidence, we excluded participants who self-reported prevalent AF at baseline. For the analysis of ventricular and bradyarrhythmias, participants who reported having a cardiac implantable electronic device at baseline were excluded. Person-time for each participant was taken from the date of first assessment and censored at the date associated with the development of arrhythmia, death or last follow-up, whichever occurred earliest.

Statistical Analysis

Baseline variables were reported as mean and standard deviation (SD) for normally distributed variables, median and interquartile range for skewed data and proportions for categorical variables. Anthropometric measures were normalized to gender-specific values and presented as z scores. We first used Cox proportional hazards to assess the influence of association between anthropometric measures and AF independently. Interactions between sex, physical activity, and body composition were considered as significant where $p<0.1$ for the interaction. We subsequently repeated all analyses with mutual adjustment for other anthropometric variables. All models included confounding variables selected a priori for their association with arrhythmias, including age, sex, smoking, alcohol intake, hypertension, type II diabetes, sleep apnoea and prevalent comorbidities (ischemic heart disease, heart failure, valvular disease). For all continuous exposure and confounding variables, we used restricted cubic splines with knots placed at the 5^{th}, 35^{th}, 65^{th} and 95^{th} percentiles to account for potential non-linearity. We assessed the proportional hazards assumption by inspecting log-log plots for all endpoints. We then performed general contrasts of regression coefficients for anthropometric variables to estimate hazards for z scores of -2, -1, 0 (referent), +1 and +2. All statistical analyses were performed using R Version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Population

Of 502,543 participants in the UK Biobank, 492,116 had measurement of body composition. Of these, 54.5% were female, with a mean age of 57±8 years. The baseline characteristics of participants are shown in **Table 1**. Lean mass was 64±8kg and 45±5Kg for men and women, respectively. Mean fat mass was 22±8Kg for men and 27±10Kg for women **(Figure 1)**. Overall, 6 897 participants had a history of AF, whilst 1 571 participants had an existing cardiac

implantable device. For the analysis of incident AF, 485 372 participants were included. For the analysis of incident ventricular and bradyarrhythmias, 491 618 participants were included. Over a mean follow-up of 6.9±1.2 years, 10 564 participants developed AF, 1 589 participants developed a ventricular arrhythmia, and 5 039 participants developed a bradyarrhythmia.

Incident AF

There was a strong association between BMI, waist circumference, lean and fat mass with incident AF (**Figure 3**). There was evidence supporting a potential interaction between sex and both lean (p=0.08) and fat mass on incident AF (p <0.001), but not BMI or waist circumference. There was a strong association between lean mass and incident AF for men (χ^2=710.6, p<0.001) and women (χ^2=446.4, p<0.001). Similarly, there was a strong association between fat mass and incident AF for men (χ^2=520.1, p<0.001) and women (χ^2=387.5, p<0.001). There was evidence of non-linearity in the association between all anthropometric measures and AF incidence. The association between both lean and fat mass and AF incidence persisted in both sexes after mutual adjustment (**Table 2**).

Association between Lean and Fat Mass and AF Risk

The hazards for a given Z score for both lean and fat mass within both sexes, following mutual adjustment, are shown in **Table 2**. For men and women, elevated lean and fat mass was associated with incident AF. For lean mass, AF incidence was lower across the entire lower range for men, with a 22% (-1SD) and 30% (-2SD) reduction in AF risk. In contrast, for women, AF risk was only statistically lower at -1SD but not -2SD. In men, there was evidence of a U-shape relationship between fat mass and AF risk, with participants -1 and -2 SD carrying an increase in AF risk. However, AF risk in women was slightly lower at -1SD for fat mass and not significantly different at -2SD.

Incident Ventricular Arrhythmias

There was a significant association between incident ventricular arrhythmias and BMI (χ^2=26.2, p<0.001), waist circumference (χ^2=44.6, p<0.001), lean mass (χ^2=30.1, p<0.001) and fat mass (χ^2=25.0, p<0.001) **(Figure 4, Figure 5)**. We did not observe any sex-dependent effects in the relationship between anthropometric measures and ventricular arrhythmias (p>0.1 *for interaction*).

Association Between Lean Mass, Fat Mass and Ventricular Arrhythmias

Both low and high lean mass was associated with elevated risk of ventricular arrhythmias (**Table 2**). There was a 12% increase in risk at both +1SD (HR 1.12, 95% CI: 1.00-1.25) and -1SD (HR 1.12, 95% CI: 1.01-1.24). For fat mass, an increase in ventricular arrhythmias was observed at +2SD (HR 1.23, 95% CI: 1.03-1.47). We did not observe statistical evidence for an increase in ventricular arrhythmias at +1SD or any level below the mean.

Incident Bradyarrhythmias

There was a significant association between incident bradyarrhythmias and BMI, waist circumference, lean mass and fat mass (**Figure 6, Figure 7**). Notably, we observed evidence of statistical interaction between sex and each of BMI (p=0.07), waist circumference (p=0.08) and fat mass (p=0.003). Fat mass was associated with incident bradyarrhythmias in women (χ^2=28.6, p<0.001) but not men (χ^2=1.3, p=0.73). In contrast, lean mass was significantly associated with bradyarrhythmias in men (χ^2=53.7, p<0.001), but not women (χ^2=4.1, p=0.25).

Association Between Lean Mass, Fat Mass and Bradyarrhythmias

In men, there was a strong association between lean mass and bradyarrhythmias. A lean mass of +1SD and +2SD was associated with a 22% (HR 1.22, 95% CI: 1.15-1.30) and 55% (HR 1.55, 95% CI: 1.36-1.76) increase in bradyarrhythmia risk, respectively (**Table 2**). We did not observe any association between fat mass and bradyarrhythmia risk in men. In contrast, amongst women, we observed a significant association between fat mass and bradyarrhythmia risk. A fat mass of +1 and +2SD was associated with a 29% (1.29, 95% CI: 1.16-1.42) and 33% (1.33, 95% CI: 1.13-1.58) increase in incident bradyarrhythmias.

Body Composition and Physical Activity

To assess the potential interaction between body composition and physical activity, we repeated our analysis amongst patients who had completed a baseline physical activity assessment (*n*=389 710). We found no evidence for an interaction between the effects of lean mass and total weekly PA on any of the arrhythmia endpoints. Similarly, we found no evidence towards an interaction between fat mass and total PA on any arrhythmia endpoint.

DISCUSSION

Major Findings

In a cohort of almost half a million adults, we demonstrate that (i) there is a strong association between higher lean mass and both incident AF and ventricular arrhythmias amongst men and women, even after adjustment for measures of adiposity; (ii) fat mass retains a significant association with risk of atrial and ventricular arrhythmias amongst both men and women, following adjustment for lean mass; and (iii) the association between BMI and bradyarrhythmias is driven predominantly via fat mass in women, and lean mass amongst men.

Body Composition and Arrhythmias

A strong association between BMI and both incident AF and sudden cardiac arrest has been described previously[157,344], although the latter is not always observed[349]. This study reinforces the association between BMI and incident cardiac arrhythmias As a result, excess body mass should be widely considered an arrhythmogenic risk factor. However, BMI is a relatively crude measure of obesity. Body composition provides more specific information on adiposity, and the quantity of lean mass, which may provide more sensitive prognostic value.

For AF, recent studies have suggested that the lean component of body mass, including muscle, bone and organ mass, is the primary anthropometric determinant of incident events, rather than fat mass[167,348,350]. The principal findings of this study confirm the strong association between AF risk and lean mass in both men and women, whilst showing a persistent association between measures of adiposity and AF. Critically, we show that both lean and fat mass are associated with ventricular arrhythmia risk. Although previous studies have highlighted an association between BMI and sudden cardiac death, very little information on the association between specific components of body composition and ventricular arrhythmia risk have been presented. The association between adiposity and sudden cardiac death has been confirmed elsewhere[344]. Our findings, expand the association between body composition and ventricular arrhythmias in demonstrating that lean mass is associated with ventricular arrhythmia risk.

A novel finding is that, whilst higher BMI is associated with elevated risk of incident bradyarrhythmic events, the association between body composition and bradyarrhythmias is sex-dependent. Specifically, in women, fat mass is strongly associated with bradyarrhythmias, whilst in men, it is lean mass that carries the stronger association. Although preclinical models have demonstrated the presence of adverse sinus node remodeling in the presence of

obesity[351,352], it is seldom considered a primary risk factor for the development of bradyarrhythmias. Our findings highlight, that excess adiposity, particularly in women may be an important risk factor for these common arrhythmias.

Lean Mass and Arrhythmia Risk

The pathophysiological mechanisms linking arrhythmia risk and lean mass are not immediately clear. Regarding AF, a recent mendelian randomization analysis using this cohort provides evidence for a direct causal link between the two[168]. There is a positive relationship between lean mass and cardiac size[353], as well as both BMI and height with LA size[354,355]. The elevated risk of AF, may be mediated through increased LA size, providing sufficient substrate to maintain AF. However, amongst previous studies[356], inclusion of LA size as a confounder only partially attenuates the relationship between lean mass and AF.

The presence of left ventricular (LV) hypertrophy increases the risk of ventricular arrhythmias and sudden cardiac death[357,358]. Lean mass is more strongly correlated with LV mass[353] than fat mass. Although we don't have data on LV hypertrophy from this cohort, it is feasible that the association between lean mass and ventricular arrhythmias is partially mediated via increased LV mass.

Adiposity and Arrhythmia Risk

The link between obesity and AF is well established[359] based on epidemiological findings that higher BMI raises AF risk, coupled with preclinical data demonstrating the arrhythmogenic effects of obesity[138]. Weight gain in an ovine model promotes epicardial fat accumulation, conduction slowing, atrial fibrosis, and increased propensity for AF[138]. Furthermore, the presence of excess adiposity promotes atherosclerotic disease[360,361],

increasing the likelihood of ventricular arrhythmias and sudden cardiac arrest. Excess adiposity is strongly correlated with adverse cardiac remodeling and increased epicardial fat[362]. The expansion of epicardial fat, even in the absence of cardiovascular disease, is associated with ventricular interstitial fibrosis that may predispose to ventricular arrhythmias[363]. Similarly, the development of obesity in the context of the metabolic syndrome, increases adipose tissue desposition in the region of the sinoatrial node and results in electrical remodeling[351].

Underweight & Arrhythmia Risk

Although low lean mass was associated with reduced AF incidence, we noted increased risk of ventricular arrhythmias amongst participant with low lean mass. Despite adjustment for existing cardiovascular disease, we cannot exclude the possibility that other comorbidities contributing to a cachexic state, may promote the incidence of ventricular arrhythmias. Low lean mass was not associated with the incidence of any other cardiac arrhythmia. Interestingly, we observed a paradoxical increase in AF risk amongst men with low fat mass. This finding supports studies demonstrating heightened AF risk amongst underweight individuals[364]. Uniquely, we demonstrate that low fat mass promotes the risk of AF, rather than low lean mass and that this association is observed in men, but not women. This observation suggests a possible cardioprotective element to adipose tissue, although further experimental studies are required to elucidate the mechanisms promoting AF in men with low adiposity.

Implications for Prevention

These findings should not diminish focus on weight control in the primary or secondary prevention of cardiac arrhythmias, particularly AF. Weight loss, including dietary control and bariatric surgery, frequently elicit parallel reductions in fat and lean mass[277,365]. Moreover, in

the context of secondary prevention, weight reduction strategies amongst AF patients lowers arrhythmia burden, recurrence and symptom severity[162,165]. The findings of this study raises the possibility that at some of these benefits, may be mediated through reduced lean mass as well as fat mass.

Physical Activity and Atrial Fibrillation

PA is associated with reduced incidence of AF[329], although there is a paradoxical increase in AF risk for endurance athletes. Given that exercise training frequently promotes the maintenance, or increase of lean mass, we sought to explore the potential interaction between physical activity and body composition for the association with incident arrhythmias. Interestingly, our findings do not support any interaction between body composition and weekly physical activity habits. This finding has important implications by demonstrating that a physically active lifestyle does not offset the arrhythmogenic effects of high lean mass. Likewise, the absence of any statistical interaction between fat mass and physical activity suggests that physical activity does not modify the association between a adiposity and cardiac arrhythmias, as has been suggested previously in smaller cohorts[328].

Study Limitations

The findings of this study should be considered in the context of several limitations. First, this observational study prevents the assessment of causation. Second, the primary exposure variables of lean mass and fat mass were assessed using bioelectrical impedance, which may not provide the precision offered by alternative methods[167], nor the ability to assess fat depots such as pericardial fat, which may have greater arrhythmogenic properties[346]. However, in a small subset of this cohort, lean mass derived from dual X-ray absorptiometry corrletated closely with that derived from bioimpedance[168]. Additionally, physical activity was assessed using self reported questionnaire. Although this has acceptable validity, it may

lead to potential bias in the assessment of physical activity. Third, there is limited follow-up data available within the UK Biobank to assess the impact of change in exposure variables, over the follow-up period. It is likely that a number of participants may have experienced weight change following baseline assessment, which may have been more prominent for measures with larger temporal variability such as fat mass and physical activity. Finally, although we excluded participants with known AF at baseline, we cannot rule out the possibility of subclinical AF being present prior to enrolment. Likewise, there is a strong likelihood that some participants may experience subclinical eposides of AF during follow-up that did not require hospitalization.

CONCLUSION

This study demonstrates a strong association between lean mass and the incidence of cardiac arrhythmias. These findings advance those demonstrated previously linking AF incidence with greater lean mass, showing that the arrhythmogenic effect of obesity may be promoted through increased lean and fat mass. Importantly, there are non-linear effects seen across all associations and evidence of divergent effects between men and women. The assessment of obesity should consider the role of both lean mass and excess adiposity in considering risk of arrhythmias.

This chapter has explored the association between PA, body composition and arrhythmia incidence. Chapter 4 will describe the associations between PA and mortality once AF is established using data from those with AF at the time of enrolment in the UK biobank.

TABLES AND FIGURES

	Men (*n*=223,402)	**Women** (*n*=267,895)
Age	57±8	56±8
Body Mass Index (Kg/m^2)	27.8±4.2	27.1±5.2
Waist Circumference (cm)	96.9±11.3	84.7±12.5
Body Composition (% Fat)	25.3±5.8	36.6±6.9
Lean Mass (Kg)	64±8	45±5
Fat Mass (Kg)	22±8	27±10
Hypertension (n, %)	69, 471 (31.1)	63,892 (23.8)
Type II Diabetes (n, %)	15,296 (6.8)	10,035 (3.7)
Coronary Artery Disease (n, %)	15,896 (7.1)	6692 (2.5)
Heart Failure (n, %)	472 (0.2)	254 (0.1)
Valvular Disease (n, %)	1,583 (0.7)	2,303 (0.9)
Frequent Alcohol Consumption (n, %)	56,760 (25.4)	43,186 (16.1)
Smoker (n, %)	27,762 (12.4)	23,850 (8.9)

TABLE 1. Patients' baseline characteristics

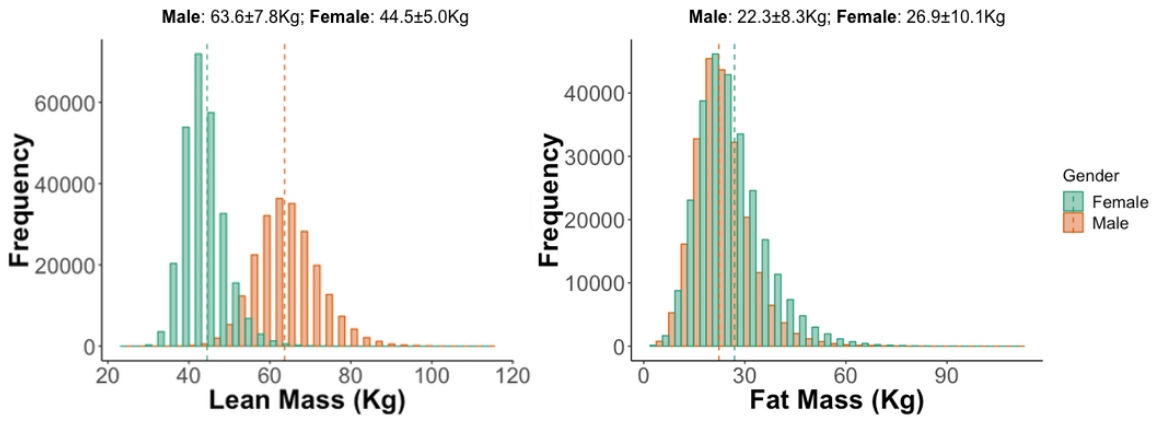

FIGURE 1. Mean lean and fat mass for men and women

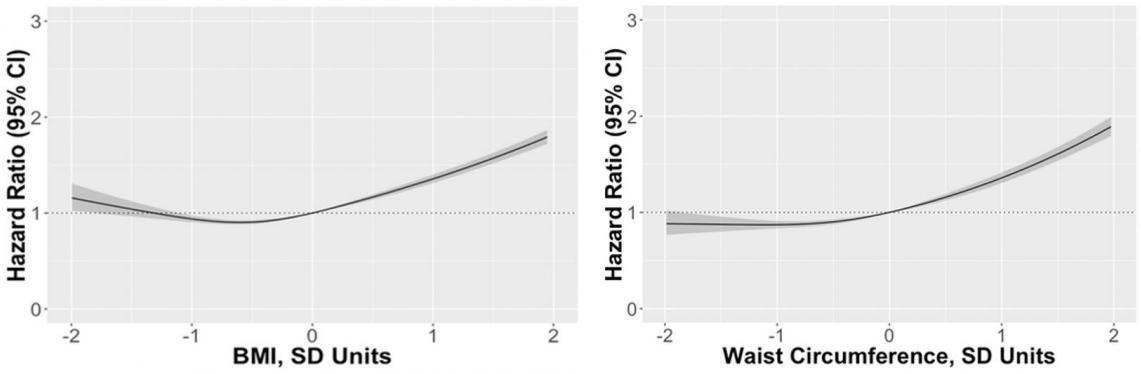

FIGURE 2. Association of BMI and waist circumference with AF risk

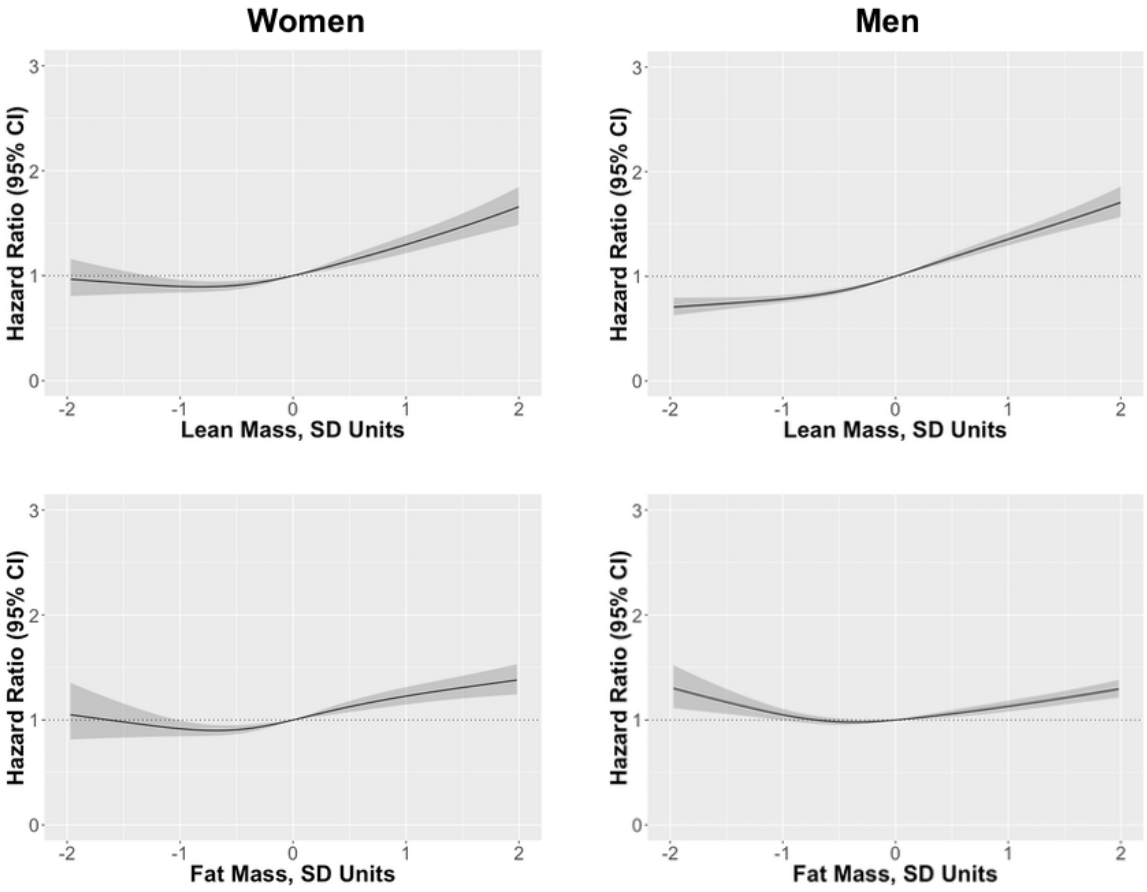

FIGURE 3. Association of lean and fat mass with AF risk in women and men

Outcome	Exposure variable	Sex	Z Score				
			-2	-1	0	1	2
Atrial Fibrillation	**Lean Mass** *(adjusted for fat mass)*	Men	0.70 (0.62-0.80)	0.78 (0.75-0.82)	1.0 (Ref)	1.35 (1.29-1.42)	1.71 (1.57-1.86)
		Women	0.97 (0.80-1.17)	0.90 (0.84-0.96)	1.0 (Ref)	1.30 (1.21-1.38)	1.66 (1.49-1.85)
	Fat Mass *(adjusted for lean mass)*	Men	1.31 (1.11-1.54)	1.05 (1.0-1.11)	1.0 (Ref)	1.13 (1.08-1.18)	1.30 (1.21-1.39)
		Women	1.05 (0.81-1.37)	0.92 (0.84-1.00)	1.0 (Ref)	1.23 (1.15-1.31)	1.38 (1.24-1.54)
Ventricular Arrhythmias	**Lean Mass** *(adjusted for fat mass)*	All	1.58 (1.24-2.01)	1.12 (1.01-1.24)	1.0 (Ref)	1.12 (1.00-1.25)	1.27 (1.02-1.60)
	Fat Mass *(adjusted for lean mass)*	All	0.92 (0.62-1.35)	0.94 (0.83-1.07)	1.0 (Ref)	1.11 (0.99-1.24)	1.23 (1.03-1.47)
Brady-arrhythmias	**Lean Mass** *(adjusted for fat mass)*	Men	0.93 (0.79-1.09)	0.92 (0.86-0.98)	1.0 (Ref)	1.22 (1.15-1.30)	1.55 (1.36-1.76)
		Women	1.12 (0.87-1.46)	1.02 (0.93-1.12)	1.0 (Ref)	1.08 (0.98-1.19)	1.19 (0.99-1.43)
	Fat Mass *(adjusted for lean mass)*	Men	1.12 (0.89-1.41)	1.01 (0.94-1.09)	1.0 (Ref)	1.03 (0.96-1.10)	1.02 (0.93-1.13)
		Women	0.98 (0.67-1.42)	0.84 (0.75-0.94)	1.0 (Ref)	1.29 (1.16-1.42)	1.33 (1.13-1.58)

TABLE 2. Hazard ratios for AF, ventricular and bradyarrhythmias across specified Z scores of lean and fat mass.

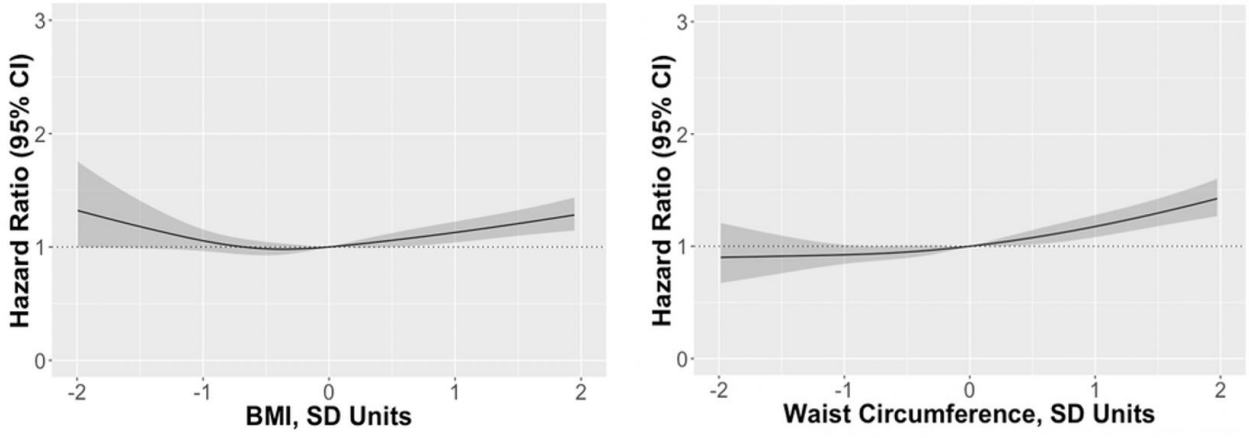

FIGURE 5. Association of BMI and waist circumference with VA risk

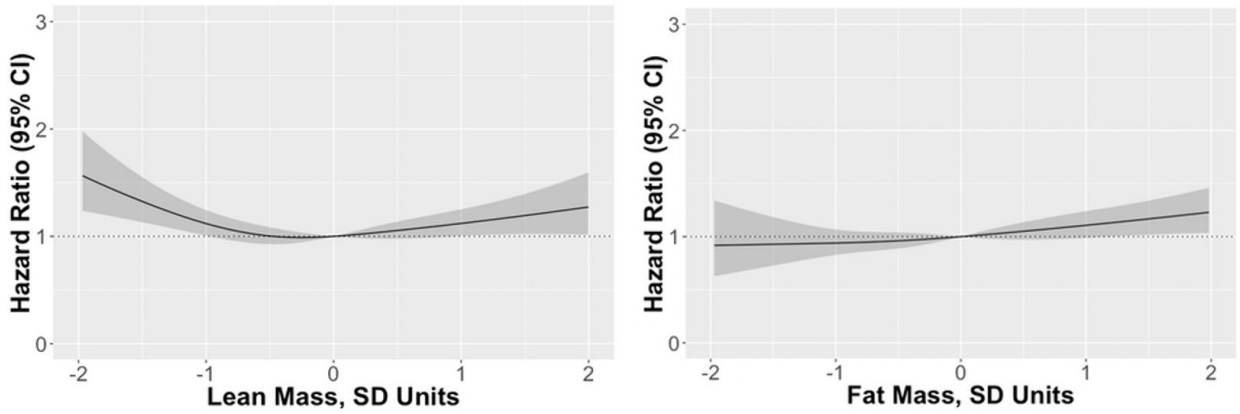

FIGURE 6. Association of BMI and waist circumference with ventricular arrhythmia risk

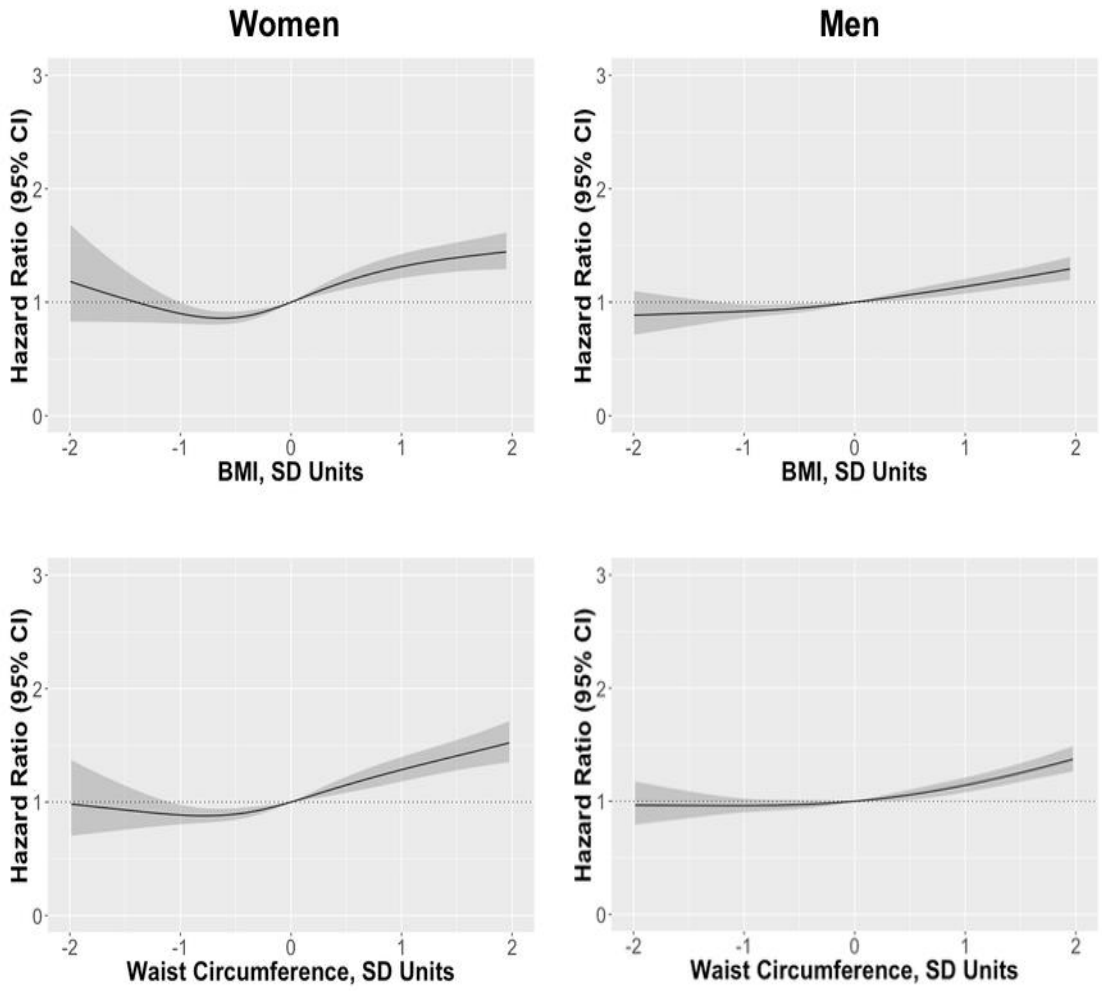

FIGURE 7. Association of BMI and waist circumference with bradyarrhythmia risk

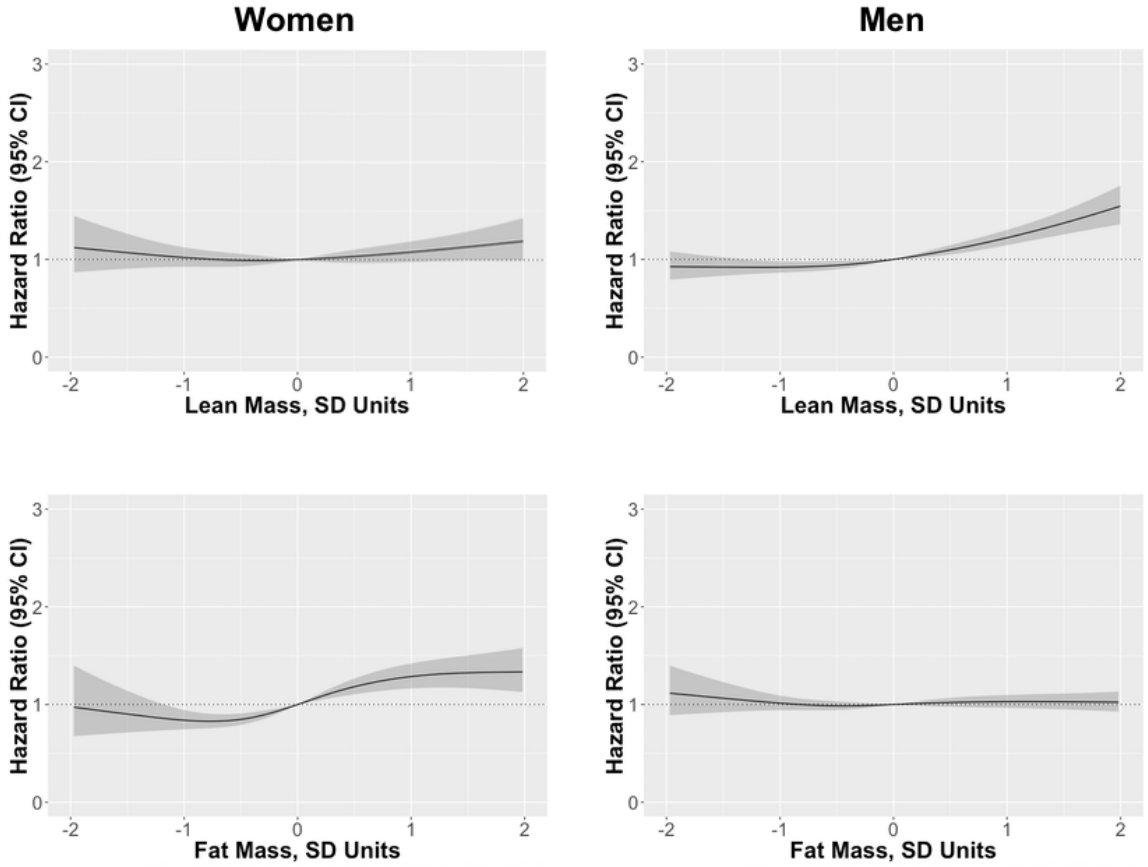

FIGURE 8. Association of lean and fat mass with bradyarrhythmia risk.

Chapter 4: Higher Physical Activity is Associated with Reduced All-cause and Cardiovascular Mortality in Adults with Atrial Fibrillation

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4.1 - INTRODUCTION

The prevalence and incidence of AF has risen significantly over the last decades[38,366]. The healthcare burden of AF is highlighted by the significant rise in AF hospitalizations worldwide[367,368], surpassing other cardiovascular causes such as myocardial infarction and heart failure[369]. The growing prevalence of AF is partly due to the widespread increase in cardiovascular risk factors such as obesity. In this context, the management of modifiable risk factors, including obesity, hypertension and sleep apnea, contributes to improved AF-related outcomes[163].

PA is recommended to improve health outcomes in most patient populations, with current guidelines recommending 150 to 300 minutes per week of moderate intensity PA or 75 to 150 minutes per week of vigorous intensity PA[35]. This level of PA is associated with a lower AF incidence[370]. Among patients with established AF, several studies suggest that regular PA is with lower risk of cardiovascular death and stroke[230] and PA at guideline recommended doses is associated with lower all-cause mortality[233]. Given the increased mortality risk amongst patients with AF[42], larger prospective studies are required to quantify the association between physical activity and mortality amongst AF patients. While vigorous PA in particular is associated with a lower all-cause mortality in the general population[36], the specific role of moderate and vigorous intensity PA on all-cause mortality in AF patients is unclear.

The aim of this study was therefore to leverage the large, prospective UK Biobank study to evaluate the association between total and vigorous PA with mortality in participants with AF.

4.2 – MATERIALS AND METHODS

4.2.1 - Study design

The UK Biobank is a large-scale population-based study which included over 500 000 participants from England, Scotland and Wales between 40 and 69 years old recruited between 2006 and 2010 and has been described in detail elsewhere[371]. The initial assessment visit consisted of anthropometric measurements as well as extensive touch-screen questionnaires about lifestyle habits and prevalent comorbidities[329]. Patients reporting prevalent AF were included in this analysis. The UK Biobank was approved by the UK Biobank Research Ethics Committee (reference number 11/NW/0382)

4.2.3 - Exposure variable

Leisure-time PA was measured at baseline using the International Physical Activity Questionnaire Short Form (IPAQ-SF). This questionnaire consists of seven questions from which total leisure time PA, moderate and vigorous PA in MET-minutes/week can be estimated. Walking is considered to demand 4 METs, activities such as carrying light loads, bicycling at a regular pace or doubles tennis are considered to demand 4 METs thus categorized as 'moderate' whereas heavy lifting, digging, aerobics or fast bicycling are considered to require 8 METs in energy expenditure thus categorized as 'vigorous'[372]. Total PA is the sum of the walking, moderate and vigorous MET-minutes/week.

In adults older than 60 years old, the IPAQ-SF has demonstrated moderate to acceptable validity[373].

4.2.4 - Outcome variables

Date and cause of death were extracted from death certificates held by the NHS Central Register Scotland for participants in Scotland and the National Health Service Information Centre for participants from England and Wales. Person-time for each participant was

obtained from the date of first assessment and censored at date of death or last known follow-up, whichever occurred first.

4.2.5 - Statistical analysis

Baseline variables were reported as mean and standard deviation for normally distributed variables, median, and interquartile range (IQR) for skewed data and proportions for categorical variables. We constructed Kaplan-Meier curves and compared all-cause and cardiovascular mortality across moderate and vigorous PA levels according to international guidelines[35], namely "none" (0 MET-minutes/week), "below" (450 MET-minutes/per week for both moderate and vigorous intensity PA), "within" (450 to 1800 MET-minutes/week of total PA or 450 to 1200 MET-minutes/week of vigorous intensity PA) and "above" (>1800 MET-minutes/week of total PA or >1200 MET-minutes/week of vigorous intensity PA) using the log-rank test. We calculated the risk of death associated with total and vigorous intensity PA as continuous exposure variables adjusted for age, sex, BMI and comorbidities with restricted cubic splines with knots placed at the 5^{th}, 35^{th}, 65^{th} and 95^{th} percentiles to assess the potential non-linear relationship between PA and both all-cause and cardiovascular mortality. We calculated the adjusted risk of all-cause and cardiovascular death associated every 500 MET-minutes/week increments of total and vigorous PA. For each model, we included an interaction term to evaluate possible differences in risk between males and females.

4.3 - RESULTS

4.3.1 - Baseline characteristics

A total of 402,406 individuals completed a baseline IPAQ-SF questionnaire, from which 2999 had AF at the time of enrolment. This cohort had a mean age of 62±6 years old and 2142 (71%) were female. Mean BMI was 29±5kg/m^2. Median total PA and vigorous PA was 1404 MET-minutes/week (IQR: 622-3114) and 0 MET-minutes/week (IQR: 0–480) for females,

and 1602 MET-minutes/week (IQR: 735-3210) and 160 MET-minutes/week (IQR: 0 - 800) for males, respectively (**Supplement Figure 2**). The baseline characteristics are presented in **Table 1**. The median follow-up time was 7.0 years (IQR: 6.3–7.7).

4.3.2 – Physical Activity and All-Cause Mortality

Kaplan-Meier curves for all-cause mortality categorized by PA guidelines are presented in **Figure 1A** and **Figure 1B**. All-cause mortality was lower amongst those below, within and above total PA recommendations, and those below and within vigorous physical activity guidelines, compared to those with no PA (**Supplementary Table 3**). Dose-response analysis showed non-linear associations between all-cause mortality and both total and vigorous PA with evidence of interaction between total PA and sex ($\chi^2 = 4.4$, $p = 0.04$). There was a significant association between total PA and all-cause mortality among females ($\chi^2 = 15.3$, $p = 0.002$), but not in males ($\chi^2 = 2.7$, $p = 0.4$). In females, total PA doses between 1500 MET-minutes/week (HR 0.35 0.15 – 0.86) and 10000 MET-minutes/week (HR 0.15, 95% CI 0.02 – 0.98) were associated with significant risk reductions (**Table 2, Figure 2**). In the entire cohort, vigorous PA was significantly associated with all-cause mortality ($\chi^2 = 8.9$, $p = 0.01$), with levels from 500 MET-minutes/week (HR 0.75, 95% CI 0.62 – 0.92) up to 2500 MET-minutes/week (HR 0.68, 95% CI 0.48 – 0.97) associated with significantly lower risk (**Table 2, Figure 3**).

In sensitivity analysis excluding the first year of follow up to account for potential reverse causality, there was a significant interaction between gender and total PA ($\chi^2 = 4.4$, $p = 0.04$) with no significant interaction for vigorous PA. In women, total PA between 1500 (HR 0.34, 95% CI 0.14 – 0.84) and 9500 MET-minutes/week (HR 0.15, 95% CI 0.03 – 0.87) were associated with lower all-cause mortality with no significant associations among men (**Supplement Table 4, Supplement Figure 3**). Significant association between vigorous PA and all-cause mortality persisted ($\chi^2 = 9.6$, $p = 0.008$), with significantly lower risk associated

with doses from 500 (HR 0.75, 95% CI 0.61 – 0.92) to 2000 MET-minutes/week (HR 0.64, 95% CI 0.44 – 0.94). (**Supplement Table 5, Supplement Figure 4**).

4.3.3 – Physical Activity and Cardiovascular Mortality

Kaplan-Meier curves for cardiovascular mortality categorized by PA guidelines are presented in **Figure 1C** and **Figure 1D**. In categorical analysis, cardiovascular mortality was reduced only amongst participants exceeding total physical activity guidelines and those meeting vigorous physical activity guidelines (**Supplementary Table 3**). In dose-response analysis, there was no significant interaction between sex and total or vigorous PA. The association between Total PA and cardiovascular mortality did not reach statistical significance ($\chi^2 = 7.1$, $p = 0.07$). However, inspection of regression coefficients showed a marginally lower risk at total PA between 3000 (HR 0.53, 95% CI 0.29 – 0.97) and 4500 MET-minutes/week (HR 0.52, 95% CI 0.28 – 0.99) (**Table 2, Figure 5A**). Conversely, there was a significant association with vigorous PA ($\chi^2 = 10.4$, $p = 0.005$). Doses between 500 (HR 0.66, 95% CI 0.47 – 0.92) and 2000 MET-minutes/week (HR 0.53, 95% CI 0.28 – 0.99) were associated with a lower cardiovascular mortality (**Table 2, Figure 5B**). At extreme levels of vigorous PA >8500 MET-minutes/week of vigorous PA, the lower CI increased above 1.0 (HR 1.66, 95% CI 1.02 – 6.71), indicating potentially higher risk of CV mortality in this range of vigorous PA.

In sensitivity analysis excluding the first year of follow up, total PA was no longer associated with lower cardiovascular mortality at any dose while vigorous PA up to 2000 MET-minutes per week was still associated with lower risk (HR 0.50, 95% CI 0.25 – 0.99) (**Supplemental Table 6, Supplemental Figure 5**). There was a significantly increased risk above 7500 MET-minutes/week (HR 2.33, 95% CI 1.03 – 5.25).

4.4 - DISCUSSION

This study explores the association between self-reported physical activity habits and mortality amongst a large cohort of UK Biobank participants with AF at study enrolment. The main findings of this study are that (i) higher levels of total PA are associated with reduced all-cause mortality amongst women, but not men, (ii) amongst all participants, higher levels of vigorous PA are associated with a reduction in all-cause mortality, and (iii) higher levels of vigorous, but not total, PA up to approximately 2000 MET-minutes/week are associated with a reduction in cardiovascular mortality.

While the IPAQ-SF has demonstrated acceptable validity among UK older adults[373], a systematic review and meta-analysis by Lee et al[34] showed that IPAQ-SF overestimated PA by 84% with respect objective measurements. In a Swedish population with a mean age of 42 years old, Ekelund et al[374] reported similar total PA mean dose for men (1477 MET-minutes/week) and women (1596 MET-minutes/week) although with higher vigorous PA (392 and 201 MET-minutes/week, for men and women, respectively). However, other studies have reported much higher total and vigorous PA levels[375,376].

For all-cause mortality, we observed a significant interaction between total PA and sex. Specifically, we did not find any association between total PA and all-cause mortality in men, whereas lower risk was associated with total PA doses between 1500 and 9500-10000 MET-minutes/week in women. Lower all-cause survival rates among less active AF patients has been reported previously. Data from the EURObservational Research Programme on AF (EORP-AF) Pilot Survey which included 2442 patients showed that survival was significantly lower amongst inactive patients[230]. Notably, we demonstrate the stronger association between PA and all-cause mortality amongst women with AF, which mirrors the findings showing a stronger association between physical activity and the development of AF amongst

women[329]. Previous reports have highlighted sex-based differences in the pathophysiology, presentation and outcomes of AF[377]. Indeed, a large meta-analysis demonstrated a 12% increase in risk of all-cause mortality amongst women compared to men with AF[46]. Although sex-based differences in outcomes may be due to differences in presence of risk factors or comorbidities, our analysis provided statistical adjustment for baseline comorbidities. Nonetheless, these findings highlight a need to understand the interaction between sex and lifestyle behaviours with regards to AF outcomes.

A key finding from this analysis is that vigorous physical activity is associated with lower all-cause mortality. Specifically, we found significant risk reductions up to 2000-2500 MET-minutes/week of vigorous PA with less certainty beyond that level. This data provides support for a benefit of vigorous PA amongst patients with AF, despite the concerns regarding an association between endurance exercise and AF. The risk reduction for all-cause mortality associated with vigorous PA is consistent with observational data from wider populations[36,378,379] as well as those from smaller cohorts of patients with AF[233].

Interestingly, we found no significant association between total PA and cardiovascular mortality. This finding is in contrast with larger cohort studies of participants without AF, in which lower cardiovascular mortality is associated with total and vigorous PA at any dose[378,380]. Furthermore, in patients with AF, Garnvik et al[233] demonstrated a reduction in cardiovascular mortality amongst those participating in >150 minutes of moderate PA per week. However, we did identify a significant association between vigorous PA and cardiovascular mortality, with significantly lower risk up to 2000 MET-minutes/week. Importantly, this data potentially implies that more vigorous forms of exercise may be required to lower the risk of cardiovascular-specific mortality amongst individuals with AF. Prospective, randomized controlled trials are required to confirm whether this is the case.

Although we are unable to determine cause and effect from the results of this observational study, both preclinical and clinical studies have proposed potential mechanisms which may be involved in the relationship between PA and mortality. Regular exercise is associated with improved ventricular compliance and distensibility[248,381], stabilization and regression of coronary atherosclerosis[382], preserved endothelial function[383], reduced visceral and pericardial fat[279], improved insulin sensitivity[384], a dampening of systemic inflammation[385] and a reduction in non-cardiovascular disease incidence and mortality, such as cancer[386]. Importantly, while exercise interventions in AF patients have demonstrated significant improvements in exercise capacity[234,235,237,387,388], quality of life[234,237,387] and AF burden[237], trials conducted so far have not addressed potential mortality benefit. These findings may inform future trials of exercise and other lifestyle interventions amongst patients with AF with regards to major adverse cardiac events and mortality.

This study has several limitations that should be considered upon interpreting these findings. The observational nature of this study prohibits the assessment of causality in the relationship between PA and AF outcomes. The assessment of PA as well as covariates and risk factors are self-reported, which may be subject to bias. Additionally, both moderate and vigorous PA were reported only at baseline and may have changed over the follow-up period. The diagnosis of AF also did not include independent adjudication of 12-lead ECG or rhythm monitoring. Finally, the UK biobank is a relatively healthy cohort which may be subject to 'healthy volunteer' bias[389], potentially limiting the application of these findings to other populations.

4.5 - CONCLUSION

The present study shows significantly higher all-cause and cardiovascular mortality among those not engaged in any PA. Total PA was associated with lower all-cause mortality in women, but not men, although the association between vigorous PA and all-cause mortality persisted across the entire cohort. Importantly, although total PA was no associated with lower cardiovascular mortality, we did find an association that suggests lower cardiovascular mortality amongst participants engaging in up to 2000 MET-minutes/week of vigorous PA. Collectively, these findings lend further weight to the benefits of maintaining physical activity amongst individuals with AF.

4.6 – TABLES AND FIGURES

TABLE 1. Baseline characteristics of participants with AF from the UK Biobank cohort (n=2999).

FIGURE 1. Kaplan-Meier curves for all-cause mortality according to total (A) and vigorous PA guidelines (B) and Kaplan-Meier curves for cardiovascular mortality according to total (C) and vigorous PA guidelines (D).

TABLE 2. Hazard ratios for all-cause and cardiovascular mortality across specific levels of total and vigorous physical activity.

FIGURE 3. Dose-response all-cause mortality risk according to total (A) and vigorous PA dose (B).

FIGURE 4. Dose-response all-cause mortality risk according to total and vigorous PA dose for males and females.

FIGURE 5. Dose-response cardiovascular mortality risk according to moderate (A) and vigorous PA dose (B).

Characteristic	Cohort (*n*=2999)
Age (Years)	62 ± 6
Male / Female	857 / 2142
Body Mass Index (Kg/m^2)	28.7 ± 5.2
Hypertension (n, %)	1352 (45.1)
Type 2 Diabetes (n, %)	269 (9.0)
Coronary Artery Disease (n, %)	372 (12.4)
Heart Failure (n, %)	75 (2.5)
Prior Stroke (n, %)	200 (6.7)
Smoker (n, %)	182 (6.1)
Total Physical Activity (MET-minutes/week)	1546 (697-3186)
Vigorous Physical Activity (MET-minutes/week)	80 (0-720)

TABLE 1. Baseline characteristics

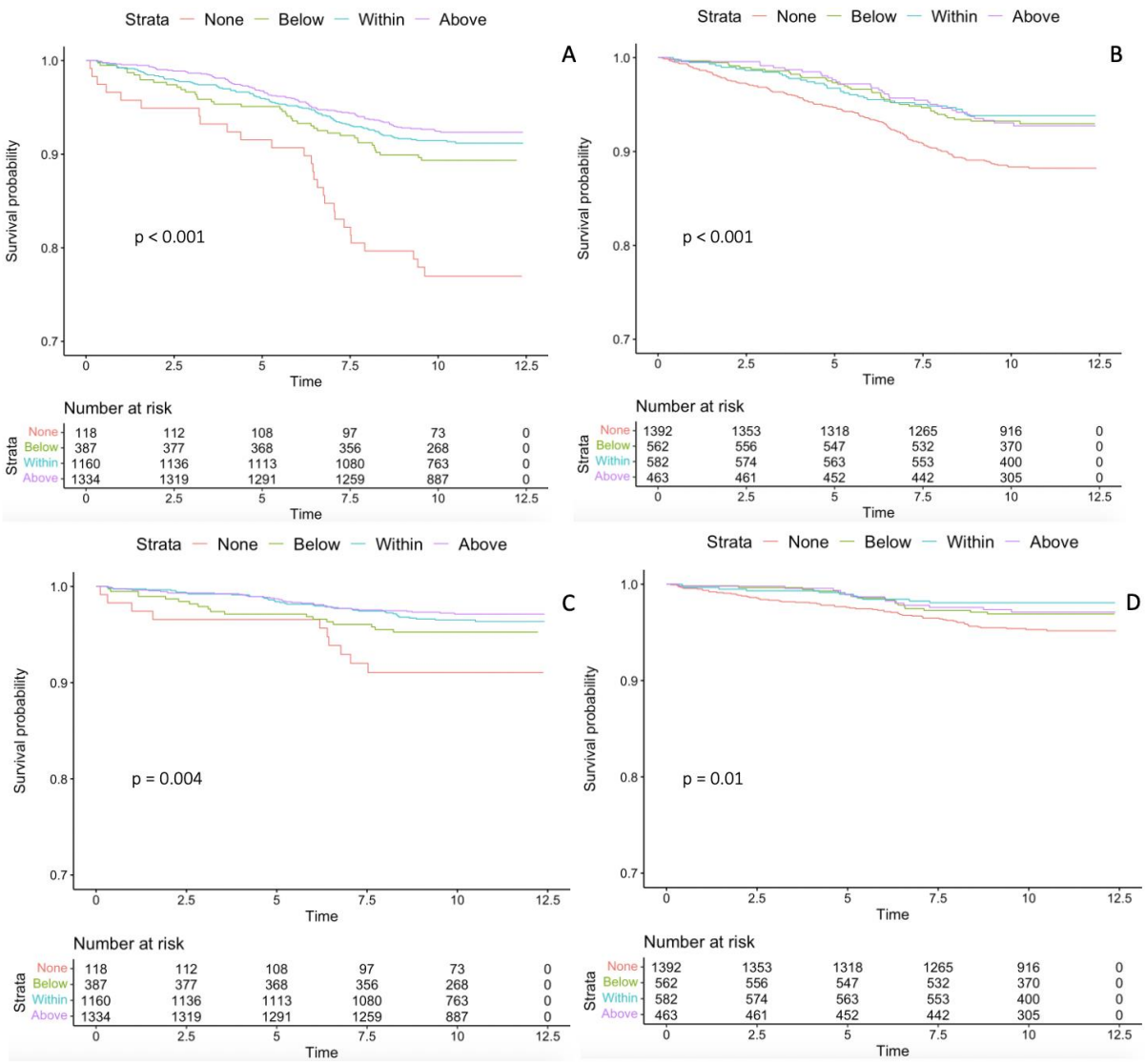

FIGURE 1. Kaplan-Meier curves for all-cause mortality according to total (A) and vigorous PA guidelines (B) and Kaplan-Meier curves for cardiovascular mortality according to total (C) and vigorous PA guidelines (D).

All-cause Mortality							
		PA dose (MET-minutes/week)					
		500	**1000**	**1500**	**2000**	**2500**	**3000**
Total PA HR (95% CI)	*Males*	0.87 (0.69 – 1.10)	0.78 (0.52 – 1.17)	0.73 (0.46 – 1.17)	0.71 (0.45 – 1.12)	0.71 (0.46 – 1.08)	0.71 (0.47 – 1.08)
	Females	0.67 (0.32 – 1.40)	0.47 (0.19 – 1.20)	0.35 (0.15 – 0.86)	0.28 (0.18 – 0.66)	0.23 (0.09 – 0.56	0.20 (0.08 – 0.49)
Vigorous PA HR (95% CI)		0.75 (0.62 - 0.92)	0.64 (0.47 - 0.88)	0.61 (0.43 - 0.89)	0.64 (0.44 - 0.92)	0.68 (0.48 - 0.97)	0.73 (0.51 - 1.05)
Cardiovascular Mortality*							
Total PA HR (95% CI)		0.85 (0.68 - 1.19)	0.74 (0.41 - 1.32)	0.65 (0.34 - 1.26)	0.60 (0.32 - 1.12)	0.56 (0.31 – 1.02)	0.54 (0.30 – 0.97)
Vigorous PA HR (95% CI)		0.66 (0.47 - 0.92)	0.53 (0.31 - 0.91)	0.50 (0.27 - 0.93)	0.53 (0.28 - 0.99)	0.59 (0.32 - 1.09)	0.67 (0.37 - 1.21)

TABLE 2. All-cause mortality and total PA dose-response analysis adjusted for age, sex*, BMI hypertension, coronary artery disease, heart failure, smoking, stroke and valvular disease

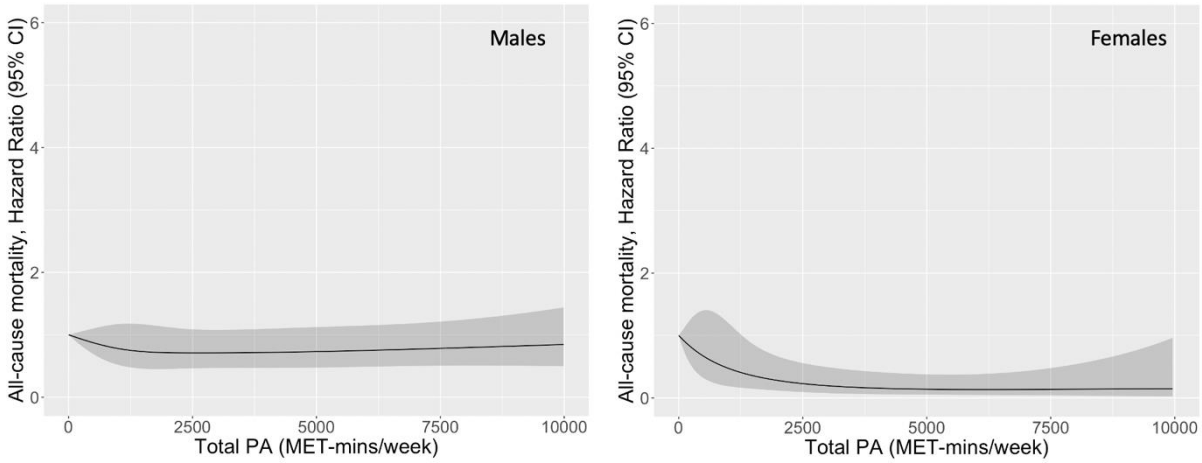

FIGURE 3. Dose-response all-cause mortality risk according to total PA dose for males and females adjusted for age, BMI, hypertension, coronary artery disease, heart failure, smoking, stroke and valvular disease.

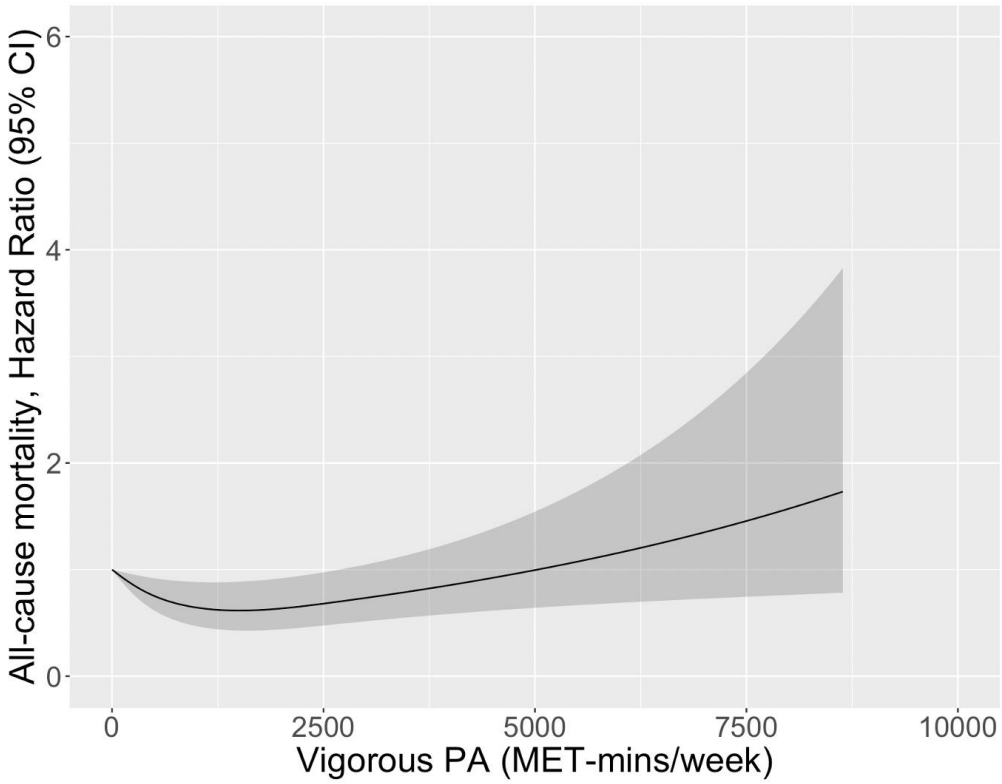

FIGURE 4. Dose-response all-cause mortality risk according to vigorous PA dose adjusted for age, sex, BMI, hypertension, coronary artery disease, heart failure, smoking, stroke and valvular disease.

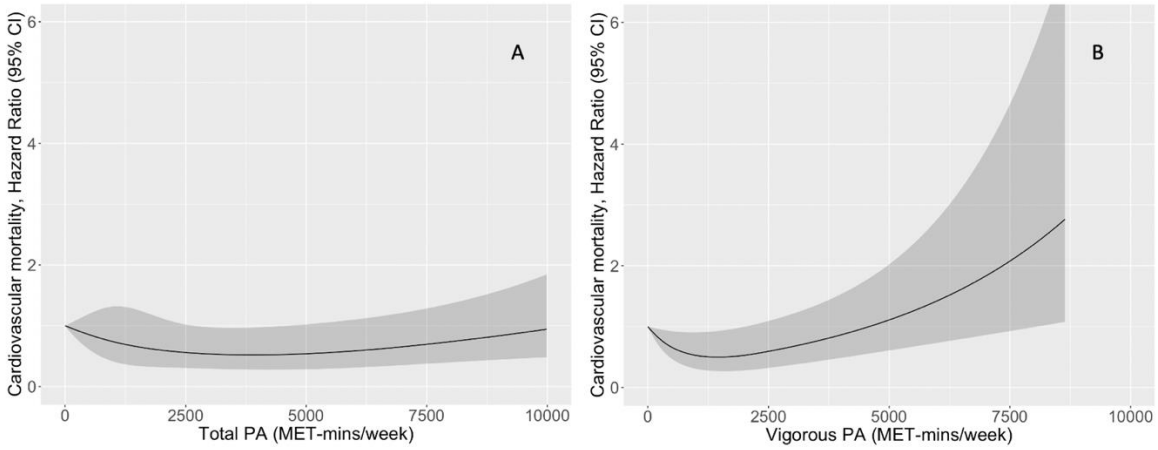

FIGURE 5. Dose-response cardiovascular mortality risk according to total (A) and vigorous PA dose (B) adjusted for age, sex, BMI, hypertension, coronary artery disease, heart failure, smoking, stroke and valvular disease.

Chapter 5: Cardiorespiratory fitness and electroanatomical remodelling in patients with atrial fibrillation

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Presentation from abstract: **Mishima RS**, Elliott AD, Ariyaratnam JP, Jones D, Nguyen O, Noubiap JJ, Malik V, Mahajan R, Lau DH, Sanders P. Cardiorespiratory fitness and electroanatomical remodelling in patients with atrial fibrillation. European Society of Cardiology, Preventive Cardiology 2021 Online Congress.

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ii. permission is granted for the candidate in include the publication in the thesis; and

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5.1 - INTRODUCTION

AF is the most common sustained heart rhythm disorder. The burden of AF has increased substantially over the last decades[38,366,390], and is projected to rise further as a result of a progressively ageing population[391]. The initiation and maintenance of AF is strongly linked to the presence of modifiable cardiovascular risk factors such as hypertension and obesity, inducing electrical and structural remodelling in the atria, ultimately predisposing to AF[138-141].

Greater PA habits and CRF are both associated with reduced incidence of AF, independent of baseline risk factor prevalence. Amongst patients with known AF, higher CRF is associated with improved maintenance of sinus rhythm and lower mortality following AF ablation[392].Similarly, amongst symptomatic, overweight and obese AF patients, higher baseline CRF and an improvement in CRF was associated with reduced AF recurrence over a 5 year follow-up[393]. Despite these observations, how CRF impacts the atrial electroanatomical substrate has not been addressed.

The presence of potentially modifiable, arrhythmogenic risk factors, including obesity, hypertension, OSA and alcohol consumption is associated with electroanatomical changes within the atria, including reduced bipolar voltages and conduction velocities along with higher electrogram fractionation[96,142,143]. Collectively, these studies demonstrate the development of an arrhythmogenic substrate in the presence of these risk factors. We hypothesised that low CRF is independently associated with reduced atrial bipolar voltages, amongst patients undergoing AF ablation. Our aims were to define the electroanatomical substrate amongst patients undergoing AF ablation, following stratification by pre-ablation CRF.

5.2 - METHODS

5.2.1 - Study population

Consecutive patients with symptomatic AF planned for de novo AF radiofrequency ablation at the Centre for Heart Rhythm Disorders were screened for inclusion. Exclusion criteria were a) moderate or severe valvular disease, b) patients unable to perform exercise stress test due to neuromuscular or musculoskeletal problems and c) LVEF below 50%. In addition, following mapping, all maps that could not be completed in sinus rhythm were excluded.

The study protocol was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital.

5.2.2 - Cardiorespiratory Fitness assessment

CRF was evaluated in METs estimated from a symptom-limited maximal treadmill exercise stress test (EST) using the standard Bruce protocol at baseline. Sex and age predicted CRF was calculated using the St James model (METs = 14.7 – [0.13 x age]) for females and the Veterans Affairs referral model (METs = 18 – [0.15 x age]) for males. Consistent with previous studies, patients were categorized as low (<85% of predicted CRF), adequate (85-100% of predicted CRF) and high CRF (>100% of predicted CRF), respectively[392,393].

5.2.3 - Transthoracic echocardiography

Transthoracic echocardiography (TTE) was undertaken in the 30 days preceding the ablation procedure by experienced technicians and reported by board certified cardiologists blinded to patients' CRF. Measurements were obtained as per the American Society of Echocardiography and the European Association of Cardiovascular Imaging guidelines[394,395]. In brief, from the apical 4 chamber and 2 chamber views, LVEF was calculated using the

Simpson's biplane method and LA maximal volume was calculated with the area-length method and indexed to body surface area (BSA). LA diameter was measured in the parasternal long axis and indexed to BSA. Measures of diastolic function (septal e' and E/e' and lateral e' and E/e') were obtained with Doppler imaging in the 4-chamber view. LV mass was calculated using the Devereux formula as follows 0.8{1.04[([LVEDD + IVSd + PWd] 3 − LVEDD 3)]} + 0.6 where LVEDD, IVSd, and PWd represent LV, interventricular septal, and posterior wall thickness in diastole, respectively.

5.2.4 - Electrophysiological study and electroanatomical mapping

All mapping and ablation procedures were performed under general anaesthesia and with uninterrupted oral anticoagulation. Transoesophageal echocardiogram (TOE) was performed to exclude LA thrombus. Vascular access was obtained via the right femoral vein under ultrasound guidance. A decapolar catheter was positioned in the coronary sinus as a reference electrode. Transeptal puncture was performed under fluoroscopic and TOE guidance using an SL0 sheath and a Brockenbrough needle (Abbott Laboratories, Abbott Park, Illinois, United States). Mapping and ablation catheters were subsequently advanced into the LA and heparin was administered to maintain an activated clotting time >350s.

LA electroanatomical mapping was undertaken using a circular Lasso catheter (Biosense-Webster, Diamond Bar, California) or HD grid catheter (Abbott Laboratories, Chicago, IL), using Ensite NavX system (St. Jude Medical, St. Paul, MN, USA). For the purposes of this study, the LA wall was divided into anterior, roof, posterior, inferior, septal and lateral segments as previously described[(96)]. Adequate endocardial contact was ensured by fluoroscopy and projection metrics reported by the mapping system. Points not consistent with surface electrocardiogram P-wave were excluded. Electrogram analysis was performed

by two independent investigators (RSM and JPA) blinded to each patient's CRF and risk factor profile. Electroanatomical maps were analysed offline.

Total and regional peak-to-peak regional voltage was defined as the difference between the peak positive and peak-negative components of the detected activation complex on the roving waveform. Low voltage areas (LVA) were defined as those where the bipolar voltage was ≤0.5 mV as described previously[96,396]. Total and regional voltage heterogeneity was calculated using the coefficient of variation (SD/mean × 100) as previously described[96,138].

Conduction velocity (CV) was obtained from isochronal maps that were created offline. In brief, distance and difference in activation time between 2 points parallel to the activation wavefront were used to calculate CV, and values from 3 to 5 pairs of points were averaged as described previously[96,396]. Total and regional CV heterogeneity was calculated using the coefficient of variation (SD/mean × 100) as previously described[96,138].

Complex fractionated electrograms (CFE) were defined as a) fractionated signals: complex activity of ≥50ms duration with ≥3 deflections crossing the baseline; and b) double potentials: potentials separated by an isoelectric interval when the total electrogram duration was ≥50ms. Electrograms meeting either of these criteria were considered fractionated and combined for analysis. Results are reported as percentage of CFE (%CFE).

5.2.5 - Follow-up

Patients were followed up 24 hours after the procedure, before hospital discharge and at 3, 6, 9 and 12 months with ECG and 4-day Holter monitor. Recurrence was defined as documented

atrial arrhythmia lasting >30 seconds and documented on 12-lead electrocardiogram or Holter monitor, or during interrogation of an implanted cardiac device

5.2.6 - Statistical analysis

Categorical variables are reported as absolute number and proportions and continuous variables are reported as mean ± SD when normally distributed or median (95% confidence interval) when non-normally distributed. Normal distribution was determined by inspection of frequencies histograms. Baseline characteristics and TTE parameters were compared using ANOVA or Kruskall-Wallis tests accordingly. Electroanatomical characteristics were compared using ANCOVA using BMI as a covariate. Student's t or Mann-Whitney tests were used to perform pairwise comparisons. A P value of 0.05 was considered statistically significant. Statistical software utilized was SPSS version 25.0.

5.3 - RESULTS

5.3.1 - Baseline characteristics

A total of 108 patients underwent de novo AF ablation procedures and were screened for inclusion. One had severe valvular disease and in 16 CRF was not assessed so they were excluded. Furthermore, 18 had AF maps, 13 had incomplete maps and 2 had paced maps so they were excluded as well **(Figure 1**).

Baseline characteristics are presented in **table 1**. The sample consisted of 11 women (19%) and 47 males (81%) with a mean age of 59 ± 10 years old. The mean time between EST and ablation was 4.5 ± 2.5 months. The median number of points collected was 300 (IQR 300 – 622). There were no significant differences in clinical characteristics or medication use between low, adequate and high CRF. As expected, there were significant differences in absolute METs between low (5.6 ± 2.5 METs), adequate (8 ± 2.2 METs) and high CRF (10.5

± 2.6 METs) (p<0.001). Similarly, percent of predicted CRF achieved was significantly different across groups (62.6 ± 23, 93 ± 5 and 116.6 ± 9.5, respectively) (p<0.001). There were no significant differences in echocardiographic characteristics except for index LV mass which was lower in the high CRF group (**Table 2**). After a median follow up of 11 months (IQR 3.9 - 17.9), recurrence rate was 38%, 37.5% and 48% in the low, adequate and high CRF groups, respectively (p = 0.9).

5.3.2 - Atrial Voltages

Total and regional voltages within each group are shown in **Figure 2A**. The low CRF group had lower mean global bipolar voltages than both the high CRF (1.85 mV [0.83 – 2.33] vs 3.07 mV [2.53 – 3.70], p = 0.04) and adequate CRF groups (1.85 mV [0.83 – 2.33] vs 2.91 mV [2.50 - 3.50], p = 0.008). Regional bipolar voltages are shown in **Figure 2A**. Compared with the high CRF group, patients with low CRF demonstrated lower bipolar voltages in the roof (1.30 mV [0.73 – 3.33] vs 3.08 mV [2.72 – 3.76], p = 0.004), posterior (1.47 mV [0.99-2.13] vs 3.68 mV [2.83-4.32], p < 0.001) and inferior wall segments (1.47 mV [0.78-2.15] vs 3.10 mV [2.00 - 4.32], p = 0.003). Compared to the adequate CRF group, low CRF group had lower posterior (1.47 mV [0.99 - 2.13] vs 3.65 mV [2.87 – 4.02], p = 0.004), inferior (1.47 mV [0.78 – 2.15] vs 3.58 mV [2.94 – 4.12], p = 0.002) and lateral wall voltages (1.65 mV [0.82 – 3.49] vs 3.88 mV [2.28 – 5.36], p = 0.012). Representative voltages maps from each group are shown in **Figure 3**. Total and regional voltage heterogeneity was not different across groups.

Total and regional low voltage areas are shown in **Figure 2B**. Amongst the low CRF group, % LVA was higher in the roof and posterior walls compared to high CRF group (15.4% [5-59] vs 3.7 % [0.7-7.7], p = 0.009 and 8.6% [4.7-46] vs 3.4 [1-7], p = 0.04, respectively). Compared with the adequate CRF group, low CRF group had greater % LVA globally (17.7%

[14-51] vs 10.4 [3.7-16.7], p = 0.02), and specifically within the posterior (8.6% [4.7-46] vs 2.3% [0-6.15], p = 0.03) and inferior (20% [11.5-50] vs 4.5% (0-9.5], p = 0.001) wall segments.

5.3.3 - Conduction velocity

Global and regional conduction velocities across groups are shown in **Figure 4**. Representative activations maps from each group are shown in **Figure 5**. Global atrial conduction velocity did not differ between low, adequate and high CRF groups. Similarly, we found no evidence of regional differences in conduction velocity. Total and regional conduction heterogeneity was not significantly different across groups.

5.3.4 - Complex Fractionation

The % of complex fractionated signals within each group are shown in **Figure 6**. The proportion of complex signals was significantly higher in the low CRF group, compared to both the adequate (14.6 ± 17.7% vs 33.3 ± 17%, $p<0.05$) and high CRF groups (11.1 ± 12% vs 33.3 ± 17%, $p<0.05$). Patients in the low CRF group exhibited a higher proportion of complex signals in anterior (15 ± 21% vs 35.4 ± 24%, $p<0.05$), roof (14.1 ± 17% vs 37 ± 26%, $p<0.05$), posterior (9.3 ± 18% vs 27.7 ± 24%, $p<0.05$), inferior (6.2 ± 12% vs 36.1 ± 23.6%, $p<0.001$), septal (17.6 ± 24.6% vs 43 ± 26%, $p<0.05$) and lateral (4.8 ± 9.1% vs 20.7 ± 23.8%, $p<0.05$) wall segments, when compared with the high CRF group. Compared to the adequate CRF group, the proportion of complex signals within the anterior (12.5 ± 21.1% vs 35.5 ± 25%, $p<0.05$) and inferior (7.5 ± 17.7% vs 36.1 ± 23.6%, $p<0.001$) wall segments were higher in the CRF group. There were no significant differences in complex signals between adequate and high CRF groups.

5.4 - DISCUSSION

These results highlight three novel and clinically relevant key findings demonstrating the atrial electroanatomical changes observed with low cardiorespiratory fitness amongst symptomatic patients undergoing AF ablation:

1. Patients with low CRF demonstrate lower global atrial voltage, when compared to patients with adequate or high CRF. In addition, there was regional heterogeneity to this observation with lower bipolar voltages in the roof, posterior, inferior and lateral wall segments.
2. The proportion of complex signals was significantly higher amongst patients with low CRF compared to both adequate and high CRF groups.
3. Despite changes in atrial voltage and complex signals, there was no association between CRF group and conduction velocity.

This study demonstrates significant electroanatomical remodelling associated with lower CRF in patients with AF. Importantly, these findings provide some mechanistic insight into the observation that low CRF is associated with increased recurrence of AF. In the CARDIO-FIT Study[393], baseline CRF, below 85% of age and sex predicted CRF, was associated with lower arrhythmia free survival amongst overweight and obese patients with symptomatic AF. Similarly, A recent study demonstrated that low CRF, again below 85% of that predicted by age and sex, is associated with increased AF recurrence, the need for repeat rhythm control procedures, arrhythmia-related hospitalizations and death after an AF ablation[392].

Electroanatomical characteristics such as voltage and fractionation are considered surrogates of LA remodelling and have important prognostic implications. It is likely that progressively lower voltages represent more advanced structural remodelling. Low voltage areas are correlated with areas of late-gadolinium enhancement in magnetic resonance imaging[397,398]

and associated with AF recurrence after ablation[399,400]. In addition, Ammar-Busch et al showed that most AF driver regions are correlated with CFEs and in the vast majority of patients, termination site during ablation show a fractionated electrogram, suggesting that CFEs are a surrogate of AF perpetuation[401].

These findings are consistent with evidence showing that the presence of other modifiable risk factors is associated with left atrial structural and electrical remodelling, thus creating a favourable substrate for AF. Preclinical models have demonstrated that cardiovascular risk factors increase both AF vulnerability and duration via multiple mechanisms including but not limited to left atrial stretching, dilation and fatty infiltration[138,139], fibrosis[140] and autonomic remodelling[141]. In humans, specific electroanatomical alterations have been described in relation to risk factors such as ageing[402] (diffuse areas of low voltage with regional conduction slowing and fractionation across the crista terminalis), hypertension[143] (global and regional reductions in atrial voltage with an increase in the heterogeneity of voltage and significant conduction impairment), congestive heart failure[396] (regional conduction slowing with a greater fractionation and areas of low voltage and electrical silence), obstructive sleep apnoea[142] (lower regional voltages, slower conduction velocities and higher fractionation) and obesity[96] (lower posterior wall voltages along with diffuse conduction velocity reduction and higher fractionation).

Although we demonstrate that low CRF is associated with evidence of adverse electroanatomical remodelling, there is evidence showing that endurance exercise may predispose to AF, particularly at high training volumes. The potential mechanisms leading to the paradoxical development of AF in this setting includes increased vagal tone and abrupt sympatho-vagal shifts[240,241], atrial dilation in response to the repeated and prolonged demand of increased cardiac output[223,403,404] and atrial fibrosis mediated by inflammatory

pathways[243,405]. However, exercise training induced AF is typically found amongst healthy participants with much more extensive exercise training histories, and subsequently higher CRF, than seen in this cohort. The association between higher physical activity and CRF and the management of cardiovascular risk factors is clearly established in the literature[258,406]. The findings presented here, support a direct association between higher CRF and a less advanced atrial substrate that potentially underscores the observation that AF patients with higher CRF, have less recurrent AF and improved outcomes. Whether AF patients with much higher CRF, such as those who participate in endurance training activities, show evidence of electroanatomical remodelling different to those participants observed in this cohort, remains to be established.

This study has a number of important limitations that should be considered; Firstly, this is a single-centre, retrospective study that prevents the establishment of cause and effect. Additionally, this study design is open to potential confounding from risk factors and/or comorbidities that may not have been assessed. Second, the relatively low number of patients may prevent the detection of subtle between-group differences. Certainly, this small cohort does not allow interpretation of the differences in ablation outcomes. Third, variations in either physical activity and/or CRF over time were not assessed. Further studies are required to evaluate the changes in atrial structural and electrical remodelling that occurs in AF patients who participate in exercise training. Fourth, CRF was evaluated using a standard exercise test thus there is a possibility that CRF may be underestimated in some cases although the achieved percent of predicted maximal heart rate was not different between groups. Finally, the number of female participants is low, potentially limiting the broader generalisation of these findings to female patient cohorts.

5.5 - CONCLUSIONS

In conclusion, AF patients with low CRF show evidence of a more advanced atrial arrhythmogenic substrate that includes significant reductions in regional voltages along with higher fractionation with preserved conduction velocities. These findings reinforce the role of low CRF as an independent marker of left atrial electroanatomical remodelling.

This chapter has described the associations between PA and all-cause and cardiovascular mortality among individuals with established AF. Chapters 5 will describe the electroanatomical LA features in patients with AF in relation to their exercise capacity among patients referred for AF ablation.

5.6 - TABLES AND FIGURES

TABLE 1. Patient baseline characteristics

TABLE 2. Trans-thoracic echocardiographic characteristics

FIGURE 1. Consort diagram

FIGURE 2. Mean atrial voltages (2A) and percentage of low voltage areas (2B) according to cardiorespiratory fitness (CRF) category (<85%, 85-100% and >100% of predicted CRF).

FIGURE 3. Sample voltage maps

FIGURE 4. Conduction velocities according to cardiorespiratory fitness (CRF) category (<85%, 85-100% and >100% of predicted CRF).

FIGURE 5. Sample activation maps

FIGURE 6. Percentage of complex fractionated electrograms according to cardiorespiratory fitness (CRF) category (<85%, 85-100% and >100% of predicted CRF).

	<85% Predicted CRF (n=13)	85-100% Predicted CRF (n=16)	>100% Predicted CRF (n=29)	P-value
Age (years)	60.6 ± 10	59 ± 13	58 ± 10	0.6
Gender (female %)	2 (15.4)	4 (25)	5 (17.2)	0.7
Body mass index (kg/m^2)	32 ± 8	29 ± 3	28 ± 4	0.08
Persistent AF (%)	7 (53.8)	12 (75)	15 (51.7)	0.3
Hypertension (%)	10 (77)	9 (53.9)	17 (58.6)	0.4
Type 2 diabetes mellitus (%)	2 (15.4)	2 (12.5)	3 (10.3)	0.9
Coronary artery disease (%)	2 (15.4)	1 (6.3)	4 (13.8)	0.7
Stroke or TIA (%)	3 (23.1)	1 (6.3)	2 (6.9)	0.2
Obstructive sleep apnoea (%)	3 (23.1)	3 (19)	6 (20.7)	0.9
Chronic obstructive pulmonary disease (%)	2 (15.4)	0	1 (3.4)	0.15
Cardiorespiratory fitness (METs)	5.6 ± 2.5	8 ± 2.2	10.5 ± 2.6	<0.001
Mean percentage of predicted CRF (%)	62.6 ± 23	93 ± 5	116.6 ± 9.5	<0.001
Mean percentage of predicted max HR (%)	82.4 ± 18.2	78.7 ± 13.9	83.9 ± 15.2	0.6
Beta blockers (%)	8 (61.5)	12 (75)	22 (75.8)	0.6
Amiodarone (%)	3 (23)	5 (31)	4 (14)	0.3
Flecainide (%)	4 (30.7)	5 (31)	13 (44.8)	0.6
Calcium channel blockers (%)	4 (30.7)	3 (18.7)	2 (7)	0.1

TABLE 1. Patients' baseline characteristics

	<85% Predicted CRF (n=13)	85-100% Predicted CRF (n=16)	>100% Predicted CRF (n=29)	P-value
LV Ejection fraction (%)	54 ± 14	61 ± 8	60 ± 8	0.08
LA volume index (mL/m^2)	40 ± 11	41 ± 17	36 ± 8	0.2
Indexed LA diameter (cm/m^2)	1.9 ± 0.4	2.4 ± 1.4	2.0 ± 0.3	0.15
Septal e' (cm/sec)	7.7 ± 3.1	7.5 ± 2.2	7.5 ± 2.3	0.8
Septal E/e'	15.8 ± 15	11.7 ± 4.7	12.7 ± 10.5	0.8
Lateral e' (cm/sec)	10.3 ± 3.8	10.7 ± 2.2	10.5 ± 3.4	0.9
Lateral E/e'	9.9 ± 6.7	8.1 ± 3.2	8.6 ± 5	0.8
Indexed LV mass (g/m^2)	89.2 ± 25.7	88.3 ± 30	72.3 ± 19.3	0.04
Indexed LVEDD (cm/m^2)	2.4 ± 0.3	2.6 ± 0.3	2.5 ± 0.3	0.6

TABLE 2. Trans-thoracic echocardiographic characteristics

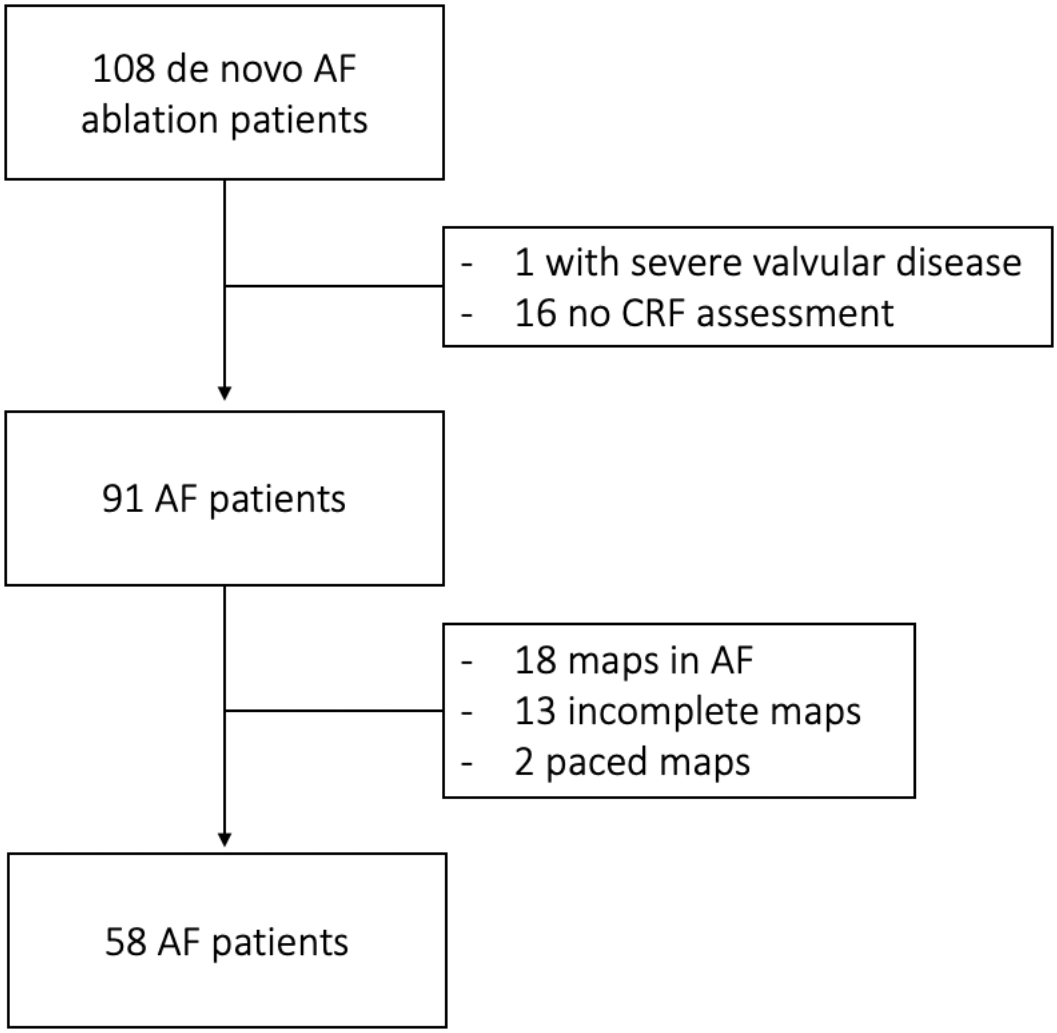

Figure 1. Consort diagram. AF = Atrial fibrillation. CRF = Cardiorespiratory fitness.

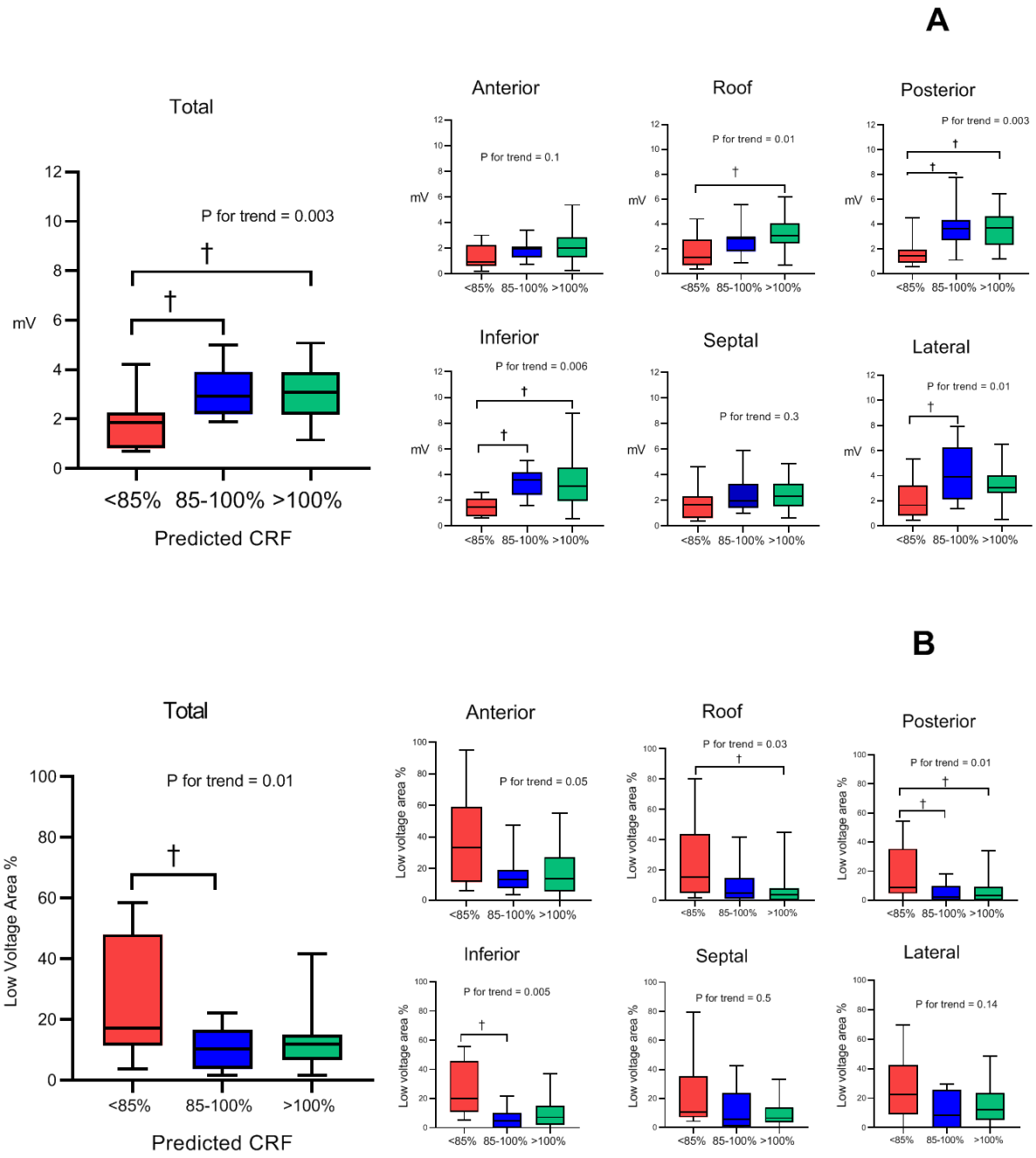

FIGURE 2. Mean atrial voltages (2A) and percentage of low voltage areas (%LVA) (2B) according to cardiorespiratory fitness (CRF) category (<85%, 85-100% and >100% of predicted CRF). (†) $p < 0.05$.

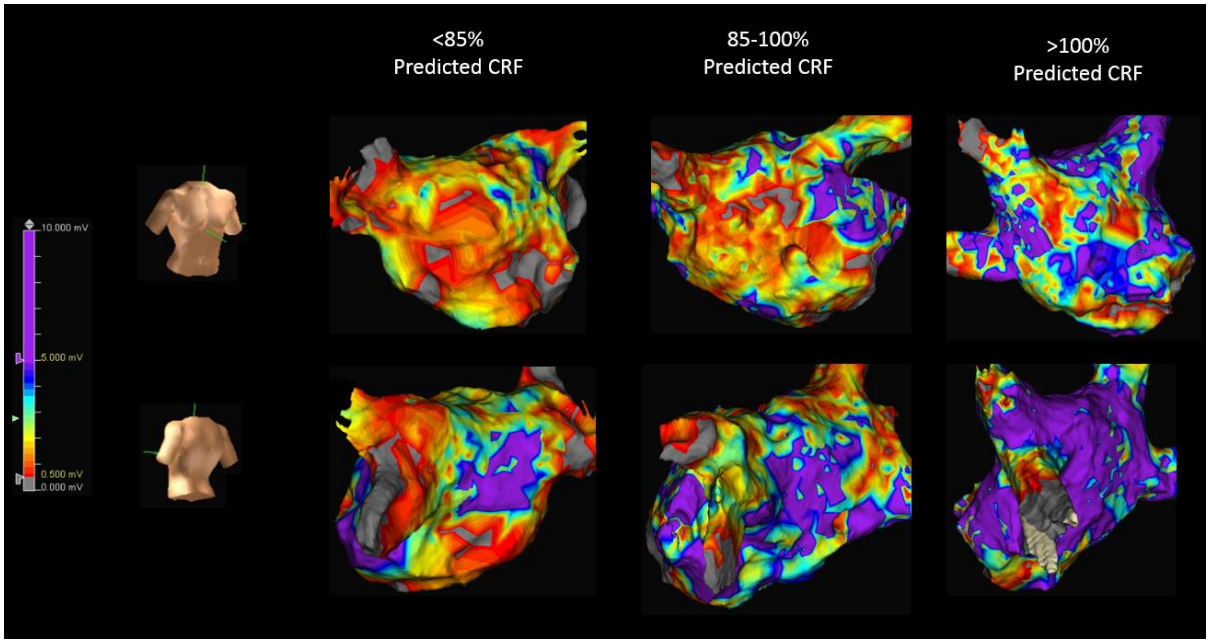

FIGURE 3. Sample voltage maps per predicted cardiorespiratory fitness (CRF) category

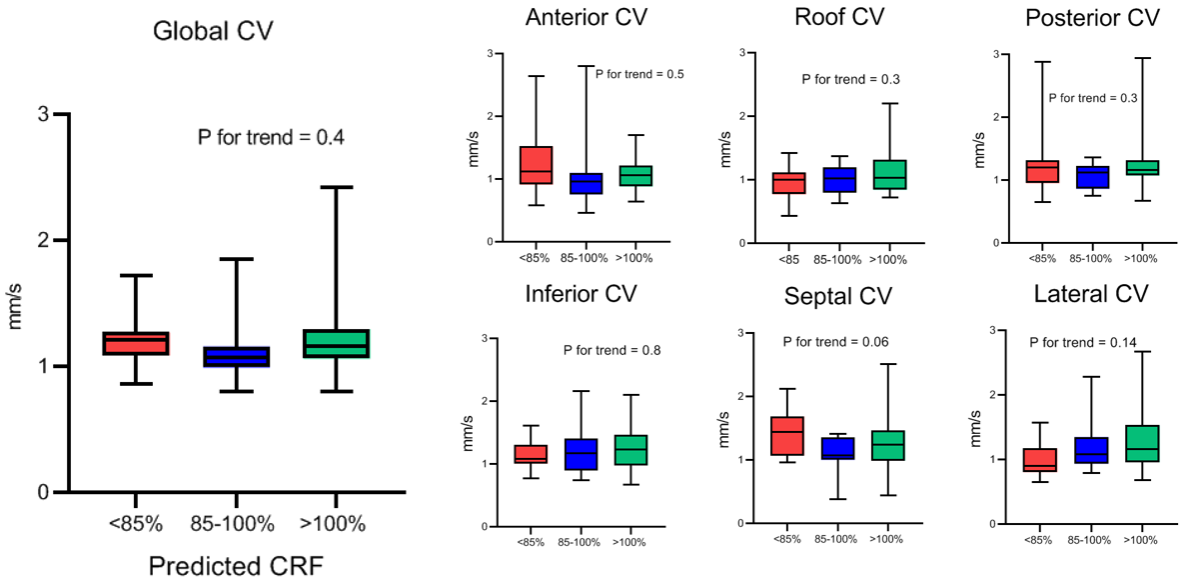

FIGURE 4. Total and regional conduction velocity according to cardiorespiratory fitness (CRF) category (<85%, 85-100% and >100% of predicted CRF).

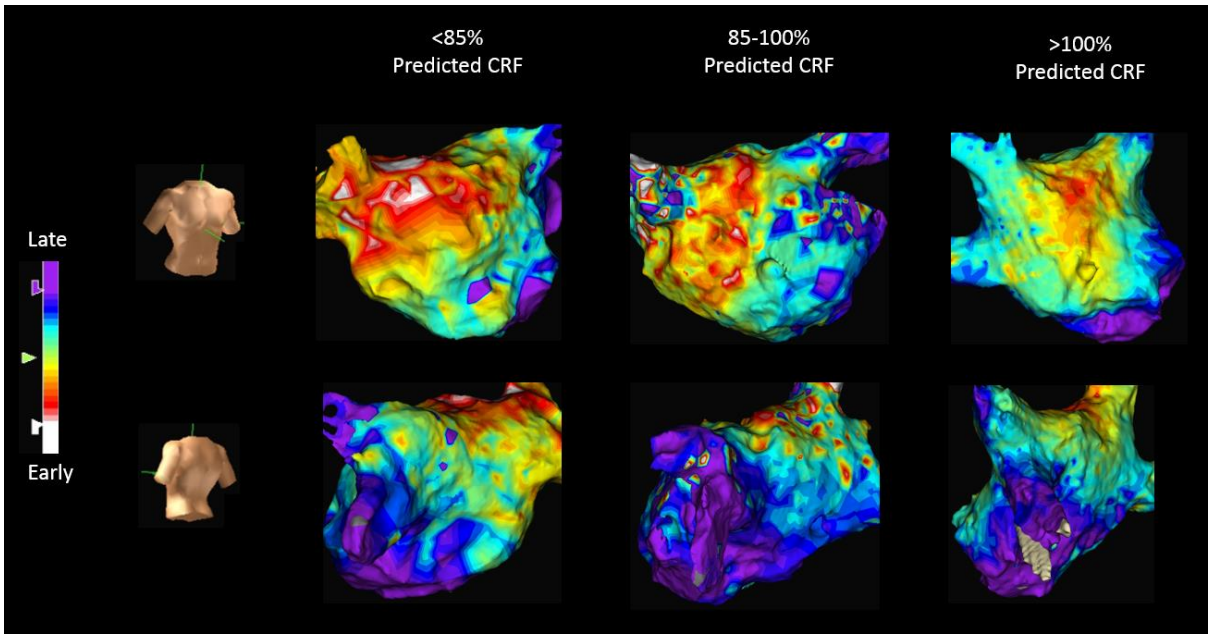

FIGURE 5. Sample activation maps per predicted cardiorespiratory fitness (CRF) category (<85%, 85-100% and >100% of predicted CRF).

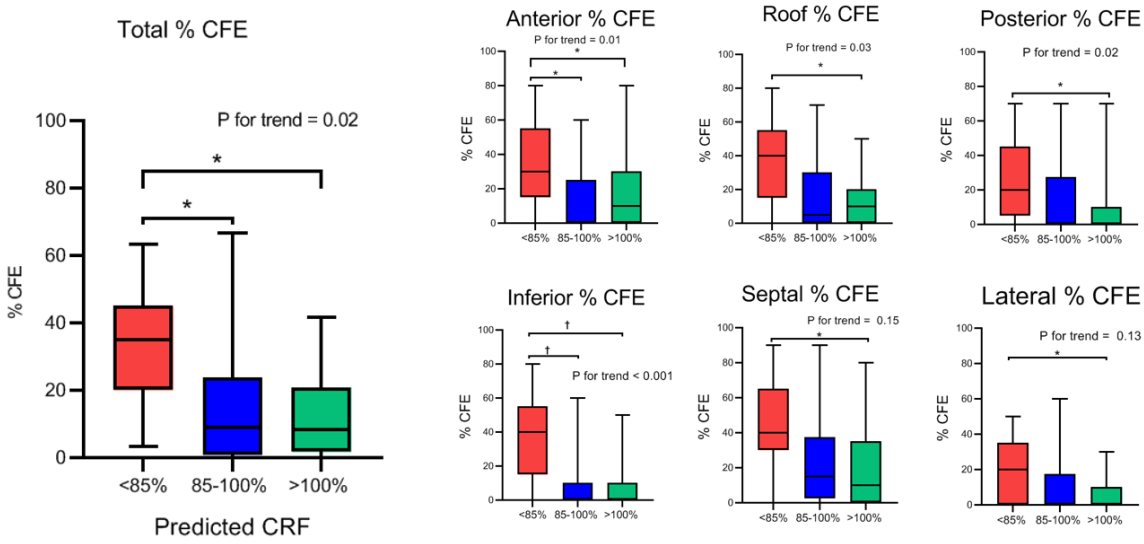

FIGURE 6. Percentage of complex fractionated electrograms according to cardiorespiratory fitness (CRF) category (<85%, 85-100% and >100% of predicted CRF). CFE = Complex fractionated electrograms, CRF = Cardiorespiratory fitness.

Chapter 6: Cardiorespiratory fitness, obesity and left atrial function in patients with atrial fibrillation

i. **Presentation from abstract:** **Mishima RS**, Ariyaratnam JP, Malik V, Pitman BM, Elliott AD, Sanders P. Cardiorespiratory fitness and electroanatomical remodelling in patients with atrial fibrillation. European Society of Cardiology, Preventive Cardiology 2021 Online Congress.

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Overall percentage (%)	50%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date 15/06/2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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6.1 - INTRODUCTION

AF is the most common supraventricular arrhythmia and ranks among the leading causes of mortality and morbidity worldwide[38,407]. The development and progression of AF is associated with a complex process of atrial remodelling that includes LA dilation, fibrosis and inflammation leading to atrial myopathy, promoted in large part by the presence of modifiable cardiovascular risk factors[134].

Structural LA abnormalities observed in AF patients are associated with electrical remodelling as well as mechanical dysfunction. Mechanical dysfunction appears to precede AF onset[408] and may be accentuated amongst those with comorbid conditions[409]. LA strain (LAS) has emerged as a novel and reliable tool to assess LA structural remodelling and mechanical function[410-413]. Amongst patients with AF, LA strain independently predicts outcomes including maintenance of sinus rhythm after cardioversion[414], catheter ablation success[415,416], and stroke[417].

Modifiable risk factors, such as obesity and hypertension, have been shown to promote structural and electrical remodelling resulting in the development of AF. In both animal models and in humans, sustained obesity is associated with LA fatty infiltration, LA enlargement, conduction abnormalities and electrogram fractionation[138]. Furthermore, observational evidence highlights a strong association between higher CRF and the maintenance of sinus rhythm amongst patients with AF[232,393]. However, the mechanism by which preserving CRF is associated with improved AF outcomes, remains unclear.

Exercise training leads to notable physiologic adaptations, including atrial and ventricular dilatation in association with improved diastolic function and reduced LV stiffness[250,418]. In this study, we sought to investigate whether atrial function and stiffness, assessed using transthoracic echocardiography, was associated with CRF amongst patients with AF. In addition, we examined whether obesity influenced these parameters in the same population. We hypothesised that preserved CRF and normal body mass would be associated with enhanced function and reduced stiffness of the LA.

6.2 - METHODS

This study has been approved by the Human Research Ethics Committee at the University of Adelaide (Ethics approval number H-2021-076).

6.2.1 - Study population

Consecutive patients with AF referred for clinical assessment including both TTE and treadmill EST at the Centre for Heart Rhythm Disorders from March 2020 until January 2021 were screened for inclusion. Exclusion criteria were a) active malignancy, b) AF at presentation, c) moderate to severe valvular disease, LVEF <50% or low-quality images impeding LAS analysis, d) EST stopped due to musculoskeletal problems or arrhythmia. Anthropometric measurements were obtained by trained technicians and BMI was calculated. Clinical characteristics were obtained from patient review. Body mass and height were recorded, and body mass index computed immediately prior to EST. Patients were classified as obese, overweight and normal body mass according to their BMI (≥ 30, 25 to <30 and <25 kg/m^2, respectively).

6.2.2 - Cardiorespiratory Fitness

A symptom-limited EST using the standard Bruce protocol was performed. Final speed and grade were used to calculate METs as a surrogate of CRF. Patients were continuously monitored with a 12-lead ECG and blood pressure was measured manually at every stage of the Bruce protocol.

6.2.3 - Transthoracic Echocardiography

Comprehensive TTE was performed by experienced sonographers, blinded to EST performance, using commercially available ultrasound machines (General Electrics Vivid 9 and Vivid 7 Dimension). Two dimensional (2D) and Doppler images were acquired with the patients in left-lateral decubitus from parasternal and apical views, and subcostal views in supine position, and measurements were performed in accordance with the American Society of Echocardiography and the European Association of Cardiovascular Imaging guidelines[394] using dedicated software (EchoPAC version 113). LA volumes were calculated as previously described[419]. LA volume index (LAVI) was calculated with LA maximal volume (LAmax) obtained at the end of ventricular systole by modified Simpson's biplane method of discs from the apical four- and two-chamber views and divided by body surface area (BSA). LA minimum volume (LAmin) was calculated at ventricular end-diastole. LA emptying fraction (LAEF) was calculated as (LAmax–LAmin/LAmax) x 100. LVEF was calculated using the Simpson's biplane method. LA to left ventricular (LV) ratio was calculated with the formula LAmax/LV end diastolic volume as previously described[419] in order to assess disproportionate LA remodelling compared to LV remodelling.

Doppler measurements were obtained as per international recommendations[395]. Briefly, peak E velocity and peak A velocity were obtained with pulsed wave doppler from apical four

chamber view, and mitral valve E/A ratio was calculated with the formula peak E velocity/peak A velocity. Tissue doppler imaging was used to acquire septal e' and lateral e' and these were divided by peak E velocity to obtain septal E/e' and lateral E/e', respectively.

LA strain (LAS) measurements were performed as previously described[419]. Briefly, LA endocardial borders were manually traced in four and two chamber views and region of interest was adjusted for the LA wall. After that, the dedicated LA strain software automatically divided the atrium into six segments **(Figure 1)**; the tracking quality for each segment was automatically assessed, and tracing was repeated when the software rejected more than 1 segment. Peak LAS reservoir (LASr) and booster (LASb) were obtained using R-R wave gating. LASr was used to calculate LA stiffness index using the formula (mean E/e')/LASr[419].

6.2.4 - Statistical analysis

Continuous variables are summarized using mean ± SD. Categorical variables are presented as count and percentages. Clinical and echocardiographic variables were compared across BMI categories using ANOVA test for continuous variables and Chi^2 test for categorical variables. Linear regression models were used to examine the relationship between a) exercise capacity in METs or BMI as the predictor variables and b) LA max, LA min, LA to LV ratio, LASr, LASb, LASc, LA stiffness index and LAEF as dependent variables. Models were adjusted for age, sex and BMI or METs, respectively. Analysis was conducted using RStudio version 1.3.1093 (R Foundation for Statistical Computing, Vienna, Austria) and p-values < 0.05 were considered significant.

6.3 - RESULTS

Between March 2020 and January 2021, a total of 203 patients with a history of AF were referred for treadmill EST and transthoracic echocardiography at the Centre for Heart Rhythm Disorders. After exclusion of 49 who met pre-defined exclusion criteria, 154 were included in the final analysis **(Figure 2)**.

6.3.1 - Baseline characteristics

Baseline clinical characteristics for the whole sample are presented in **Table 1**. For the whole sample, the average age was 62 ± 10 years, and the percentage of females was 26%. The mean BMI was 27.3 ± 4 kg/m^{2}and the METs achieved was 10.3 ± 3. The obese group had a greater proportion of patients with persistent AF, previous ablation, and obstructive sleep apnoea with no differences in METs achieved. Echocardiographic parameters, stratified by BMI group, are presented in table 2. The mean left ventricular ejection fraction was 65 ± 5% and the mean LA maximal volume indexed for BSA was 32 ± 10 mL/m^2.

6.3.2 - Cardiorespiratory Fitness and Left Atrial Volume

In unadjusted models, CRF was not significantly associated with LAmax (β = -0.5, 95% CI -1.1 – 0.1, p<0.09) but it was inversely associated with LAmin (β = -0.7, 95% CI -1.2 – (-0.2), p<0.009) and LA to LV ratio (β = -0.03, 95% CI -0.04 - (– 0.01), p<0.001) (Table 2). In age, sex and BMI adjusted models, the association between CRF and LAmax (β = -0.8, 95% CI -1.6 – (-0.02), p<0.04), LAmin (β = -1.5, 95% CI -2.1 – (-0.8), p<0.001) and LA to LV ratio (β = --0.03, 95% CI -0.04 – (-0.01), p<0.004) was statistically significant **(Table 2)**.

6.3.3 - Obesity and Left Atrial Volume

The obese group had significantly higher indexed LAmax (38.88 ± 14.61 ml/m^2) and LAmin (23.34 ± 11.94 ml/m^2) compared to overweight (30.34 ± 7.21 and 17.03 ± 7.11 mL/m^2) and normal BMI groups (31.61 ± 9.02 and 18.27 ± 8.23 mL/m^2) ($p < 0.001$ and $p = 0.004$, respectively). LA to LV ratio was higher in the obese (0.71 ± 0.31) compared to overweight (0.57 ± 0.19) ($p = 0.02$) with no significant difference compared to normal BMI (0.61 ± 0.23, $p = 0.3$) (Table 3). In both unadjusted and adjusted linear regression models, BMI was not associated with LAmax, LA min or LA to LV ratio **(Supplemental table 7)**.

6.3.4 - Cardiorespiratory fitness and Left Atrial function parameters

CRF showed a significant association with LA functional parameters (Table 2, Figure 3). In unadjusted models, CRF was positively associated with LA strain in the reservoir (β = 1.5, 95% CI 0.9 – 2.1, p<0.001), conduit (β = 0.7, 95% CI 0.3 – 1.1, p=0.001), and booster phases (β = 0.8, 95% CI 0.4 – 1.2, p<0.001). Likewise, there was a positive association between CRF and LAEF (β = 1.3, 95% CI 0.1 – 2.3, p=0.02). LA stiffness index was inversely associated with CRF (β = -0.02, 95% CI (-0.03) – (-0.01), p<0.001). When adjusted for age, sex and BMI, associations between CRF and LA function parameters remained significant **(Table 2, Figure 3)**.

6.3.5 - Obesity and Left Atrial function parameters

LA strain measurements (LASr, LASc and LASb) were not significantly different among the obese (25.79 ± 9.49%, 12.77 ± 6.51% and 13.23 ± 5.42%, respectively) compared to the overweight (30.6 ± 11.12%, 13.83 ± 6.59% and 16.64 ± 7.02%) and normal BMI (30.18 ± 8.53, 14.17 ± 5.87 and 16.01 ± 6.03) groups (P for trend = 0.1, 0.7 and 0.07, respectively) (Table 3, Figure 4A, 4B and 4C). LA stiffness index (0.35 ± 0.18, 0.32 ± 0.17 and 0.32 ±

0.14, respectively) and LAEF (40.11 ± 18.75%, 44.45 ± 16.47% and 42.59 ± 18.15%, respectively) did not differ between normal, overweight and obese BMI groups (P for trend = 0.6 and 0.5, respectively) (Table 3, Figure 4D and 4E). In both unadjusted and adjusted linear regression models, only LASc showed a significant inverse relationship with BMI in unadjusted model (β = -0.2, 95% CI [-0.4] – [-0.006], p=0.04) which was not significant after adjustment for age, sex and METs (β = -0.2, 95% CI [-0.4] – 0.09, p=0.2) **(Supplemental table 7, supplemental figure 6)**.

6.4 - DISCUSSION

This study of patients with a history of AF in sinus rhythm, demonstrates three important findings; (1) Higher CRF is independently associated with improved LA mechanical function and reduced stiffness after adjustment for age, sex and BMI, (2) higher CRF is associated with reduced LA remodelling and (3) obesity is associated with LA dilatation but preserved LA mechanical function.

Higher CRF is associated with a lower AF incidence, particularly in the obese[210]. Baseline CRF is also associated with a lower arrhythmia recurrence and lower mortality after AF ablation[232]. However, there is limited understanding as to the biological mechanisms supporting the association between higher CRF and improved outcomes. This study provides novel insights into the benefits associated with higher CRF in patients with AF; namely, preserved LA systolic function, and lower LA stiffness, both of which may contribute to lower risk of AF recurrence[420].

Although there is a lack of data amongst patients with AF, the association between LA function and CRF is supported by data from other patient groups. In a cohort of 669 patients

with suspected heart failure with preserved ejection fraction (HFpEF), Ye et al[413] reported a linear association between LASr and exercise capacity. Similarly, in a population of 65 patients with heart failure with preserved and mid-range EF, lower LASr, LASb and LASc were associated with impaired peak oxygen consumption[421]. The association of abnormal LAS with reduced exercise capacity has also been demonstrated with cardiac magnetic resonance (CMR) in patients with HFpEF[422]. In our cohort, we demonstrate a moderate association between exercise capacity and LA function through each of the atrial phases, which may have important clinical implications.

That higher CRF is associated with greater LA function may have important implications beyond rhythm control in patients with AF. Lower LA function is associated with risk of cardioembolic stroke, independent of AF episodes[423]. Additionally, LA remodelling is central to the development of HFpEF[409,424]. Therefore, patients with higher CRF may represent a cohort with comparatively lower risk of both AF recurrence and significant comorbidities, including stroke and heart failure. Prospective studies of well phenotyped AF patients will be key in determining whether this is the case.

The assessment of LA stiffness may represent a key measure of the extent of pathophysiological remodelling within the LA. Measures of LA stiffness, derived from simultaneous invasive LA pressure and cardiac MRI measurements, are independently associated with AF recurrence after ablation[420]. In addition, amongst patients undergoing AF ablation, LA stiffness is associated with elevated natriuretic peptides, pro-fibrotic markers, diastolic dysfunction and AF recurrence[425]. More recently, Kishima et al[426] showed that higher LA stiffness was independently associated with LA low voltage areas using electroanatomical mapping. Our study reveals the novel finding that higher CRF is

independently associated with non-invasive estimates of lower LA stiffness and higher LASr, thus suggesting a more compliant LA in this subset of patients.

Although we are unable to establish cause and effect based on these observational findings, our data is consistent with earlier findings that exercise training amongst previously sedentary individuals, contributes to improved LAEF and left ventricular stiffness[250,427]. Additionally, higher measures of LA function can be seen in masters endurance athletes[418]. The observational nature of our study does not permit the analysis of whether exercise interventions can further increase LA function in this cohort, although previous studies demonstrate a preservation of atrial function amongst AF patients randomised to exercise training, compared with non-exercise controls[237].

In contrast, we found no evidence of an association between LA mechanical dysfunction and BMI status. This finding is in line with the results of Gulel et al[428] who found no significant differences in LA mechanical function assessed by LAS. More recently, Cichón et al[429], reported no significant differences in LASr in the 4-chamber view with a significant yet clinically minimal difference in the 2-chamber view. In contrast, Chirinos et al[430] showed a reduced LASr and LASc with a higher LASb function among overweight and obese middle-age adults. The link between obesity and AF is well established. In both animal models and humans, obesity promotes the development of conduction slowing and heterogeneity, alongside atrial fibrosis and lowering of bipolar voltages within the atria[96,138]. Despite relatively preserved LA function in the context of high BMI, we found significantly higher LA volumes, even when scaled to LV size(431)[36], indicating disproportionate LA remodelling in this group. Of future interest will be whether long-term changes in body mass, modifies LA mechanical function given the dynamic relationship between BMI and AF[165].

This study is not without its limitations. First, this is a cross-sectional single-centre study that is not geared to determine causality. Some patients had to be excluded due to unsatisfactory speckle-tracking with echocardiography. Cardiac magnetic resonance may offer improved capabilities to detect subtle differences in LA function. Importantly, this study relies on indirect measurements of haemodynamic parameters, thus confirmation with invasive measurements is warranted. However, the pragmatic approach of combining non-invasive imaging with exercise test data provides enhanced clinical translation. We also did not include imaging during exercise, which may reveal different patterns of LA function and its association with CRF. Finally, we excluded patients in AF at the time of the test which may introduce bias towards a relatively healthy AF patient cohort.

6.5 - CONCLUSIONS

Among patients with AF, CRF was independently associated with a lower LA stiffness as well as a higher LA systolic function while obesity was associated with increased LA volumes with relatively preserved LA mechanical function. These findings highlight potential mechanisms through which higher CRF is associated with improved AF outcomes. Further prospective, randomised studies are warranted to evaluate the effects of lifestyle-based interventions that may concomitantly promote the maintenance of sinus rhythm and improve LA structure and function.

This chapter has described the electroanatomical LA features in patients with AF in relation to their exercise capacity in patients referred for AF ablation. In this study, significant electroanatomical LA remodelling in relation to low CRF has been demonstrated. The following chapter (chapter 6) will look at LA mechanical function in relation to exercise capacity in patients with AF.

6.6 - TABLES AND FIGURES

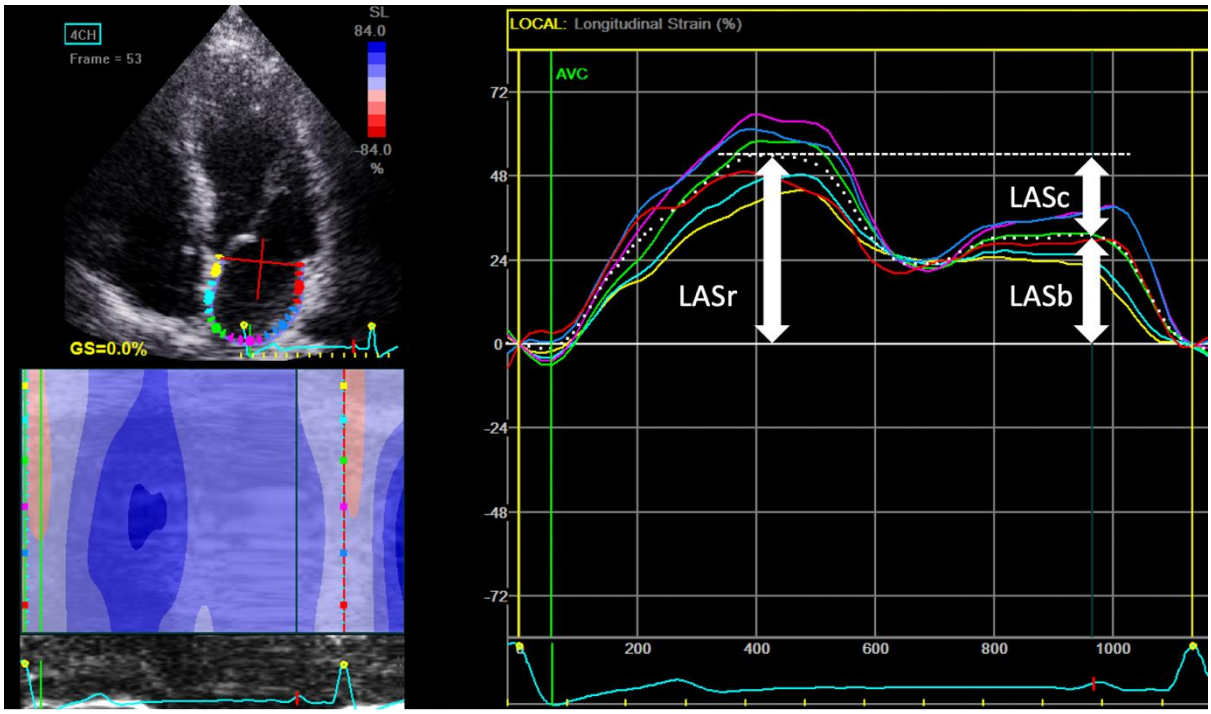


FIGURE 1. Left atrial strain curve

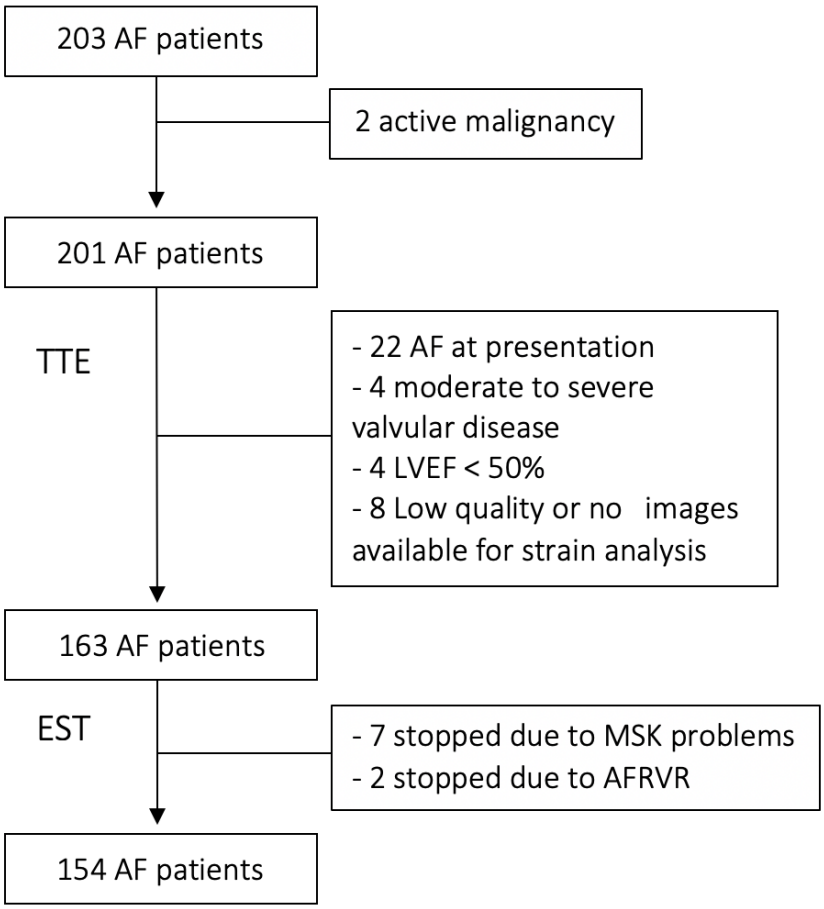


FIGURE 2. Consort diagram. AF = Atrial fibrillation, TTE = Transthoracic echocardiogram, LVEF = Left ventricular ejection fraction, EST = Exercise stress test, MSK = musculoskeletal, AFRVR = AF with rapid ventricular response

Variable	Total Cohort (n=154)	Normal (n=41)	Overweight (n=88)	Obese (n=25)	
Age (years)	62 ± 10	63 ± 11	63 ± 10	60 ± 9	0.5
Gender (female, %)	40 (26)	13 (32)	18 (20)	9 (36)	0.2
Body mass index (kg/m2)	27.3 ± 4	23.1 ± 1	27.2 ± 1	34.2 ± 6	<0.01
Persistent AF (%)	41 (27)	4 (10)	28 (32)	9 (36)	0.01
Previous AF ablation (%)	91 (59)	17 (41)	59 (67)	15 (60)	0.02
Hypertension (%)	107 (69)	20 (48)	64 (73)	23 (92)	<0.01
Type 2 diabetes (%)	11 (7)	0	8 (9)	3 (12)	0.1
Hyperlipidaemia (%)	68 (44)	13 (32)	42 (48)	13 (52)	0.2
Coronary artery disease (%)	10 (6)	2 (5)	8 (9)	0	0.2
Stroke / TIA (%)	12 (8)	3 (7)	9 (10)	0	0.2
Obstructive sleep apnoea (%)	38 (25)	6 (15)	21 (24)	11 (44)	0.02
Beta-blockers (%)	55 (36)	3 (7)	6 (7)	2 (8)	0.1
Sotalol (%)	11 (7)	3 (7)	6 (7)	2 (8)	0.9
Flecainide (%)	44 (29)	19 (46)	18 (20)	7 (28)	0.01
METs	10.3 ± 3	10.5 ± 3	10.5 ± 2	9.3 ± 3	0.08
Peak systolic blood pressure (mmHg)	172 ± 24	169 ± 23	173 ± 25	169 ± 24	0.6
Peak heart rate (bpm)	142 ± 22	140 ± 24	142 ± 21	147 ± 21	0.4

TABLE 1. Baseline clinical characteristics (n = 154).

Dependent variable	Model 1 (unadjusted)		
	β (95% CI)	**R^2**	**P Value**
LA max	-0.5 (-1.1 to 0.1)	0.01	0.09
LA min	-0.7 (-1.2 to -0.2)	0.04	0.009
LA to LV ratio	-0.03 (-0.04 to -0.01) (<0.001)	0.08	<0.001
Reservoir LA strain	1.5 (0.9 to 2.1)	0.13	<0.001
Booster LA strain	0.8 (0.4 to 1.2)	0.09	<0.001
Conduit LA strain	0.7 (0.3 to 1.1)	0.06	0.01
LA stiffness index	-0.02 (-0.03 to -0.01)	0.09	<0.001
LA ejection fraction	1.3 (0.1 to 2.3)	0.01	0.02
	Model 2 (adjusted for age, gender and BMI)		
	β (95% CI)	**R^2**	**P Value**
LA max	-0.8 (-1.6 to -0.02)	0.02	0.04
LA min	-1.5 (-2.1 to -0.8)	0.10	<0.001
LA to LV ratio	-0.03 (-0.04 to -0.01)	0.07	0.004
Reservoir LA strain	1.9 (1.1 to 2.7)	0.16	<0.001
Booster LA strain	1.2 (0.7 to 1.7)	0.14	<0.001
Conduit LA strain	0.7 (0.1 to 1.2)	0.06	0.002
LA stiffness index	0.03 (-0.04 to -0.02)	0.11	<0.001
LA ejection fraction	3.2 (1.8 to 4.5)	0.12	<0.001

TABLE 2. Association of CRF with LA echocardiographic variables.

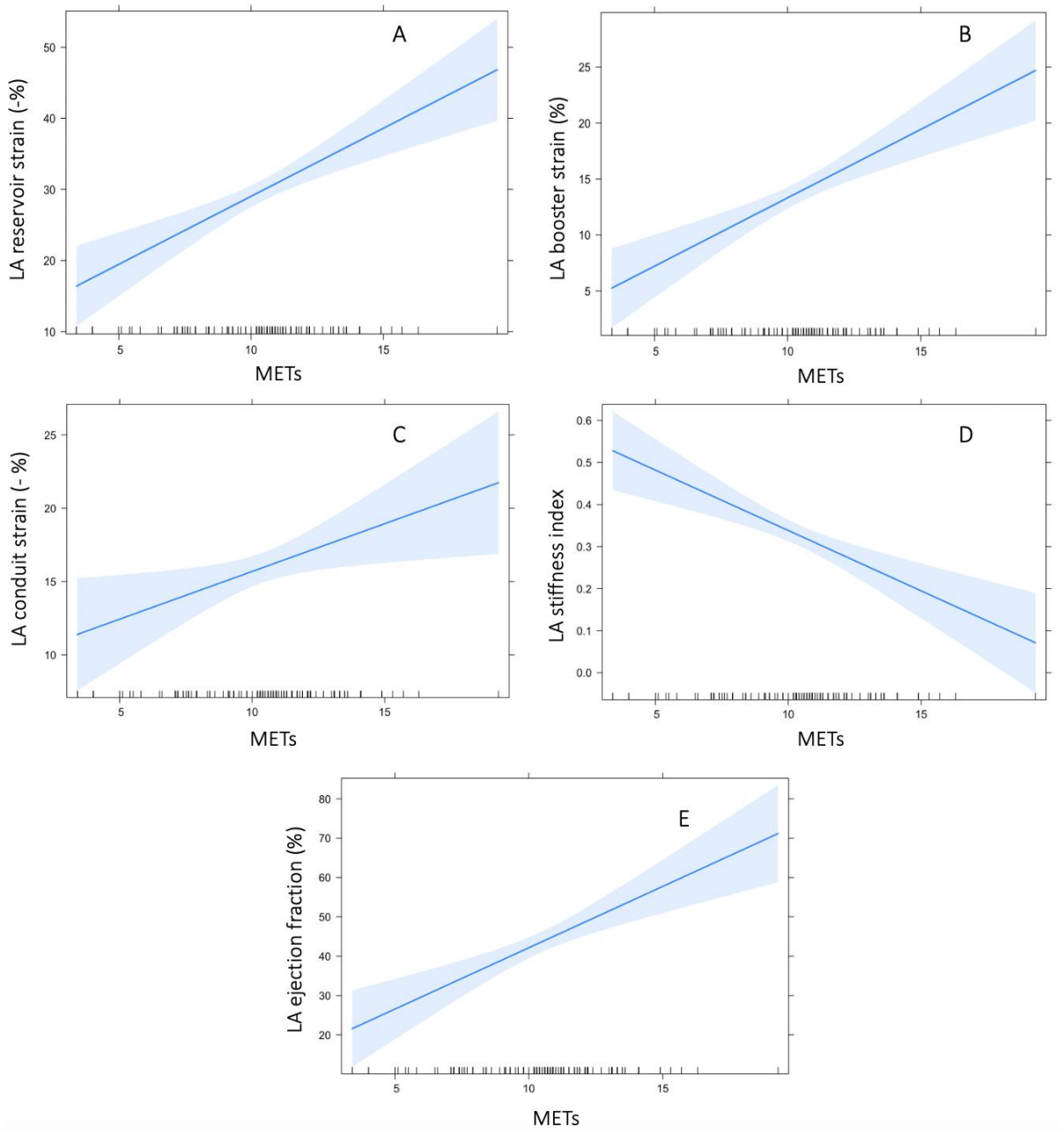


FIGURE 3. Linear models of LA function according to CRF (METs).

	Total (n=154)	Normal (BMI < 25, *n* = 41)	Overweight (BMI 25-29.9, *n* = 88)	Obese (BMI ≥ 30, *n* = 25)	*P* value
Left ventricular ejection fraction (%)	65 ± 5	64 ± 5	65 ± 4	63 ± 6	0.09
LA max volume index (mL/m^2)	32.07 ± 9.68	31.61 ± 9.02	30.34 ± 7.21	38.88 ± 14.61	< 0.001
LA min volume index (mL/m^2)	18.39 ± 8.59	18.27 ± 8.23	17.03 ± 7.11	23.34 ± 11.94	0.004
LA to LV ratio	0.60 ± 0.23	0.61 ± 0.23	0.57 ± 0.19	0.71 ± 0.31	0.02
LA ejection fraction (%)	43.25 ± 17.26	42.59 ± 18.15	44.45 ± 16.47	40.11 ± 18.75	0.5
Mitral valve E/A ratio	1.74 ± 0.81	1.69 ± 0.53	1.79 ± 0.93	1.62 ± 0.74	0.6
Septal E/e'	9.89 ± 3.13	10.50 ± 3.48	9.59 ± 2.79	9.89 ± 3.56	0.3
Lateral E/e'	7.52 ± 2.39	7.64 ± 2.65	7.47 ± 2.34	7.49 ± 2.23	0.9
LA reservoir strain (%)	29.71 ± 10.32	30.18 ± 8.53	30.60 ± 11.12	25.79 ± 9.49	0.1
LA booster strain (%)	13.75 ± 6.37	14.17 ± 6.87	13.83 ± 6.59	12.77 ± 6.51	0.7
LA conduit strain (%)	15.92 ± 6.60	16.01 ± 6.03	16.64 ± 7.02	13.23 ± 5.42	0.07
LA stiffness index	0.33 ± 0.17	0.32 ± 0.14	0.32 ± 0.17	0.35 ± 0.18	0.6

TABLE 3. Echocardiographic characteristics stratified by BMI status

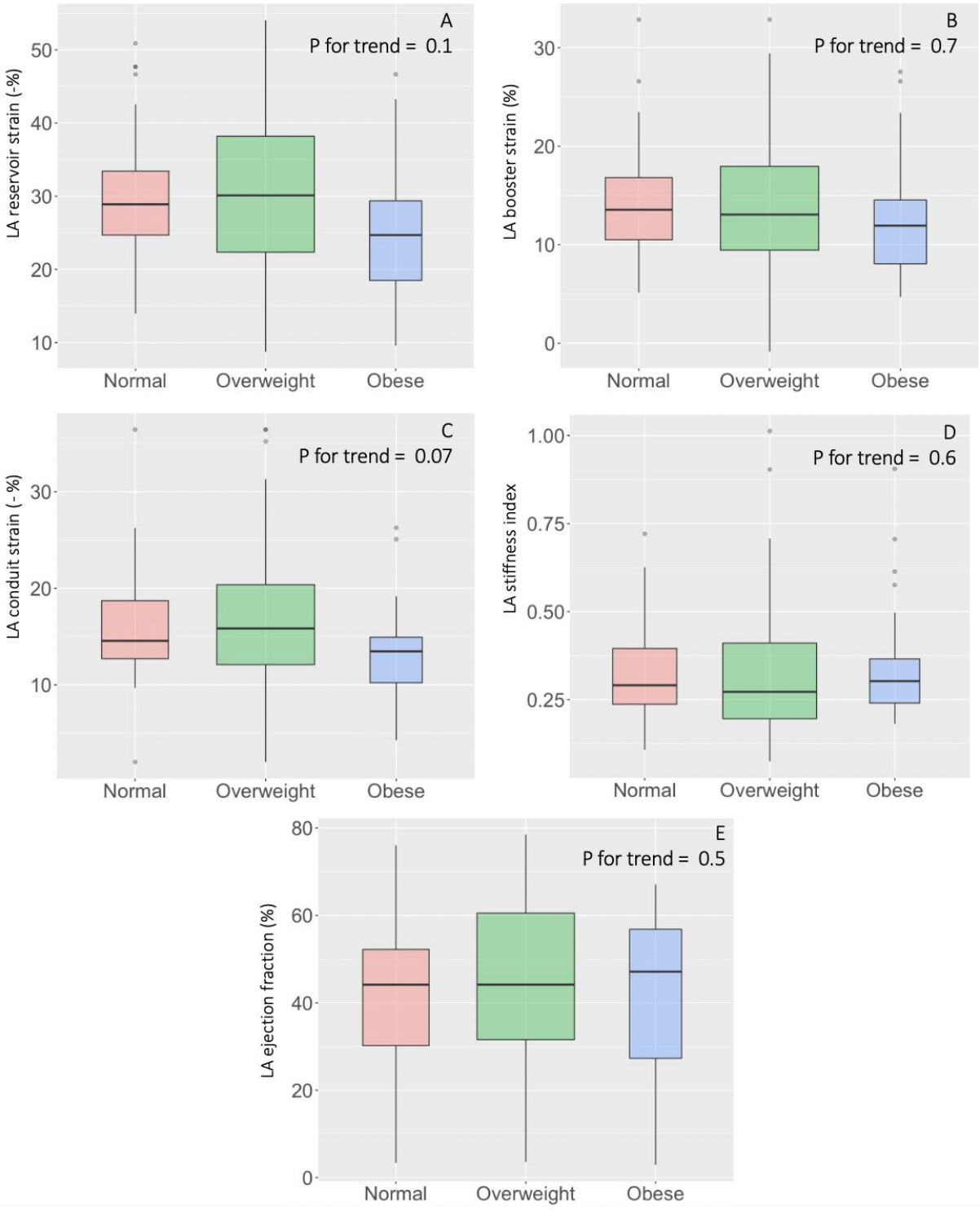


FIGURE 4. LA function parameters in normal, overweight and obese categories

Chapter 7: Conclusions

This thesis unravels the fundamental role of PA in the incidence and prognosis of AF, as well as differential electrical and mechanical LA features in relation to CRF in AF patients. By combining epidemiological and physiological data, this thesis shows: a) that there is a non-linear dose-response association between weekly PA and AF incidence, with PA doses well above current PA guidelines being associated with a significantly lower risk of AF and, importantly, no evidence of an increased risk at very high levels, b) that there is a significant association of both lean and fat mass with the incidence of AF with no interaction with PA, c) that total PA is associated with a lower all-cause mortality only in females with no association with cardiovascular mortality, while vigorous PA up to 2000 to 2500 MET-minutes/week is associated with lower all-cause and cardiovascular mortality, d) that lower cardiorespiratory fitness is associated with a more severe level of LA electrical and mechanical remodelling even in sinus rhythm. These findings could be useful in the prescription of PA for those at high risk or established AF and to further the understanding of the role of CRF in the LA substrate modification.

Physical activity (PA) is an essential component in the management of cardiovascular risk with current guidelines recommending a minimum of 450 metabolic equivalent of task (MET)-minutes/week of PA for significant health benefits. Nonetheless, the association between PA and AF risk is less clear and often contradicting. This thesis systematically reviewed and summarized the evidence from prospective cohort studies. Fifteen studies reporting data from 1,464,539 individuals (median age 55.3 years; 51.7% female) were included. Risk of AF is significantly reduced among those achieving up to 1900 MET-minutes/week of PA, with no significant risk modifications at 2000 MET-minutes/week and

beyond. Moreover, we found important sex differences, with men showing no AF risk benefit associated with high PA doses as opposed to women, where evidence showed AF risk reductions among those within and beyond PA guidelines. Importantly, this is the most comprehensive review conducted to date. The dose-response analysis provides evidence to guide exercise prescription in order to maximize its benefits while avoiding potential harms.

Obesity is a well-known cardiovascular risk factor and its importance in AF incidence and maintenance is well-established. In addition, both obesity and CRF play a significant role in AF prognosis. In recent years, epidemiological evidence suggests that lean body mass may also contribute to AF incidence even after adjustment for body fat measurements. Importantly, body composition modification is an important mechanism that could explain the associations observed between PA and AF risk. This thesis presents data from 491,297 participants, aged 40-69 years, with completed body composition assessment, who were recruited as part of the UK Biobank cohort. The association between body mass index, lean and fat mass with incident arrhythmias, including AF, ventricular arrhythmias and bradyarrhythmias identified through electronic medical records was assessed, After adjustment for fat mass, higher lean mass was associated with a 35 and 30% increased AF risk in men and women, respectively, a 12% increased risk of ventricular arrhythmias with higher lean mass and a 22% increased risk of bradyarrhythmia in men only. Lower lean mass was associated with lower risk of AF in both males and females and bradyarrhythmias in men only. Low lean mass was not associated with risk of ventricular arrhythmias. There was no evidence of interaction between body composition and PA on the association with incident arrhythmia. These results add to those demonstrated previously linking AF incidence with greater lean mass and suggest that the arrhythmogenic effect of obesity may be induced by lean and fat mass. There were non-linear associations observed across all analysis and evidence of differential effects for males and females. This chapter provides important data on

the potential role of body composition in the incidence of not only AF but also other clinically relevant arrhythmias.

Large epidemiological studies have demonstrated the association between greater physical activity and lower mortality. In patients with AF, several studies suggest that regular PA is associated with improved outcomes although the evidence regarding all-cause and cardiovascular mortality is limited. This thesis reports the association between self-reported total and vigorous PA habits and mortality amongst a large cohort of UK Biobank participants with AF at enrolment. The main findings of this study are that higher levels of total PA are associated with reduced all-cause mortality amongst females, but not males. In addition, higher doses of vigorous physical activity are associated with a reduction in all-cause mortality in the whole cohort while higher levels of vigorous, but not total, PA up to around 2000 MET-minutes/week are associated with significant cardiovascular mortality reductions. This study represents the largest cohort looking at PA and mortality in an AF population, demonstrating a lower survival among those not engaging in any PA. In addition, while vigorous forms of PA were associated with improved mortality even at low doses, a large proportion of the patients reported no engagement in such activities. This finding highlights the need to increase PA volumes, paticularly the vigorous forms of PA.

Current evidence has linked traditional cardiovascular risk factors such as obesity, hypertension and obstructive sleep apnea to the initiation and maintenance of AF. The presence of these potentially modifiable risk factors is associated with LA electroanatomical abnormalities, including reduced bipolar voltages and conduction velocities along with higher electrogram fractionation with no significant differences across CRF groups in terms of cardiovascular risk factors. Collectively, this data suggests that the above-mentioned link is mediated by the development of an arrhythmogenic substrate. This thesis provides novel data

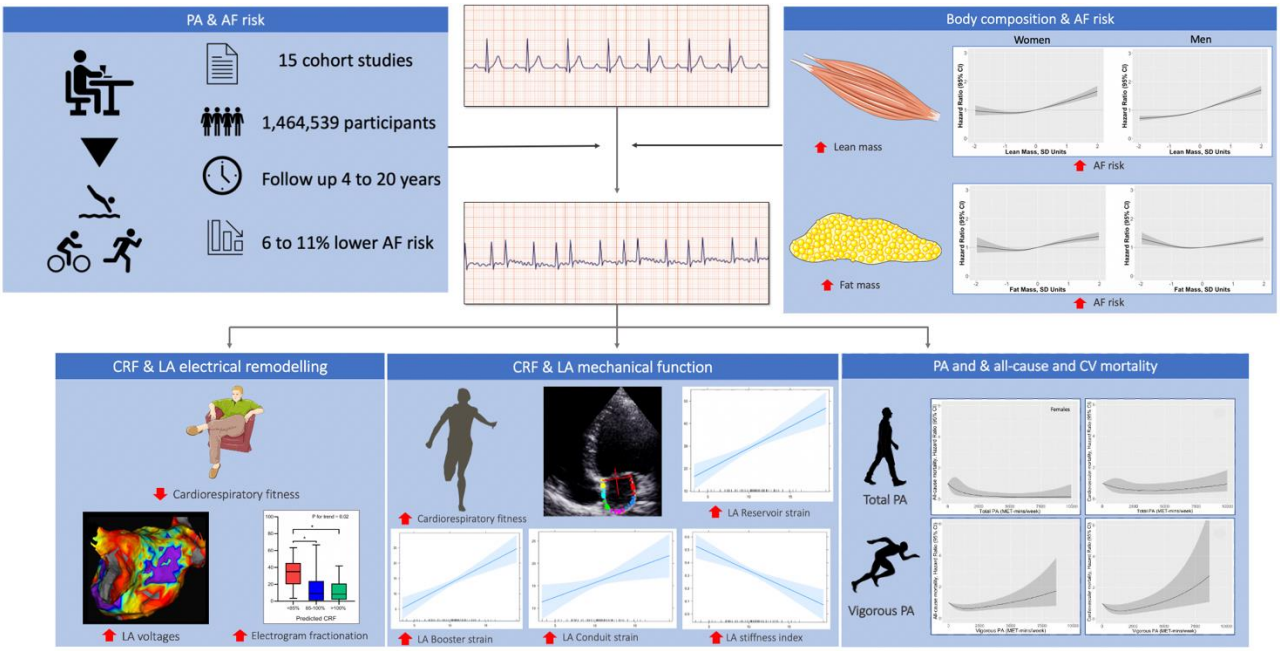
compares electroanatomical characteristics of patients undergoing an AF ablation, categorised by their exercise capacity in three levels according to the achieved percentage of the predicted CRF for age and gender (low, adequate and high) measured by an exercise stress test using the Bruce protocol. The results of this study show that AF patients with low CRF display a more advanced atrial arrhythmogenic substrate that includes significant reductions in regional voltages along with higher fractionation with preserved conduction velocities. These novel findings demonstrate an independent association of low CRF with a more severe LA electroanatomical remodelling which may not be mediated by the presence of other risk factors.

Finally, in addition to electrical remodelling, structural LA abnormalities and mechanical are observed in AF patients and seem to precede AF initiation as well as increase the risk of stroke. Moreover, similar to what happens with electrical abnormalities, structural/mechanical dysfunction appears to be worse among those with comorbid conditions. LAS is a reproducible and non-invasive echocardiographic tool which allows the quantification of cardiac chambers mechanical function. The sixth chapter of this thesis looks at the association between LA mechanical function at rest and exercise capacity among 154 paroxysmal and persistent AF patients who were referred for exercise testing. CRF was positively associated with LAEF and LAS. An inverse association between CRF and both LA stiffness index and LA to LV ratio was also observed. Obese patients had significantly higher indexed LA volumes compared to overweight and normal BMI patients. The association between obesity and measures of LA function and stiffness did not reach statistical significance.

This thesis has a number of limitations as well as strengths. First, the majority of the epidemiological work used only one dataset which may limit the generalizability of the results to other populations. Second, self-reported PA measures using questionnaires in chapters 1, 2

and 3 may be subject to recollection bias. In addition, PA was measured at baseline. Third, in these three first chapters AF history cannot be ascertained. Fourth, in chapters 4 and 5, CRF was estimated from a treadmill exercise stress test without gas exchange measurements thus we cannot ascertain that maximum exercise capacity was achieved. On the other hand, this thesis has several strengths. Firstly, chapter 1 summarizes the available epidemiological evidence in light of recent studies looking at the relationship between PA and AF risk which has been conflicting. Second, chapters 2 and 3 include a very large number of participants. Third, chapters 4 and 5 utilize novel electroanatomical mapping and echocardiographic imaging techniques to assess the LA remodelling with respect exercise capacity.

In conclusion, this thesis provides important novel insights into the association of PA and CRF in the incidence, prognosis and arrhythmogenic substrate of AF **(Summary figure)**. While guideline recommended doses of PA are associated with a significant risk reduction of AF, risk reduction is still present at higher doses. Furthermore, both lean and fat mass are associated with increased AF risk with no interaction with PA. Among patients with established AF, PA is associated with reduced all-cause mortality while only vigorous forms of physical activity were associated with reduced cardiovascular mortality. Finally, reduced CRF in patients with AF was associated with electrical as well as mechanical abnormalities within the left atria.



SUMMARY FIGURE. PA = Physical activity, AF = Atrial Fibrillation, CRF = Cardiorespiratory Fitness, LA = Left atrium, CV = Cardiovascular.

Chapter 8: Future directions

While the present thesis has made a significant contribution to the understanding of PA, CRF and AF, there are still questions that warrant further investigation.

This thesis shows significantly lower AF risk with increasing doses of PA up to around 4 times the minimum guideline recommendation, with no significant association with more PA. PA habits can vary over time thus it is possible that the patients' PA habits changed over the follow up period. Would these variations affect the outcome? And if this is the case, in which direction would these changes occur? This thesis has also shown the independent relationship of body composition with arrhythmia incidence. Given that lifestyle-based interventions such as diet and exercise can potentially modify body composition, would these modifications affect arrhythmia outcomes as well? Previous exercise-based structured interventions ranging from 8 to 16 weeks have demonstrated an AF burden reduction along with exercise capacity increase as well as improved quality of life after the intervention. These studies include a relatively low number of patients which limits their ability to assess other outcomes such as AF risk and mortality. Furthermore, the interventions as well as the follow-up are relatively short thus prevent us from understanding whether these beneficial effects can be sustained over time.

This thesis also shows evidence of a more advanced LA electrical and mechanical remodelling associated with low CRF present in sinus rhythm. Previous studies have investigated mechanistic links between risk factors and LA remodelling which is a complex pathogenic process involving progressive inflammation and fibrosis. Nevertheless, key

questions remain unanswered. Can exercise interventions prevent the development or progression of LA electrical remodelling and mechanical dysfunction? Can exercise revert these abnormalities once established? What are the haemodynamic consequences of these changes? What is the role of more accurate tissue characterization of other imaging techniques such as cardiac magnetic resonance?

While this thesis provides key findings that significantly add to the current knowledge of AF, these questions warrant further research.

APPENDIX

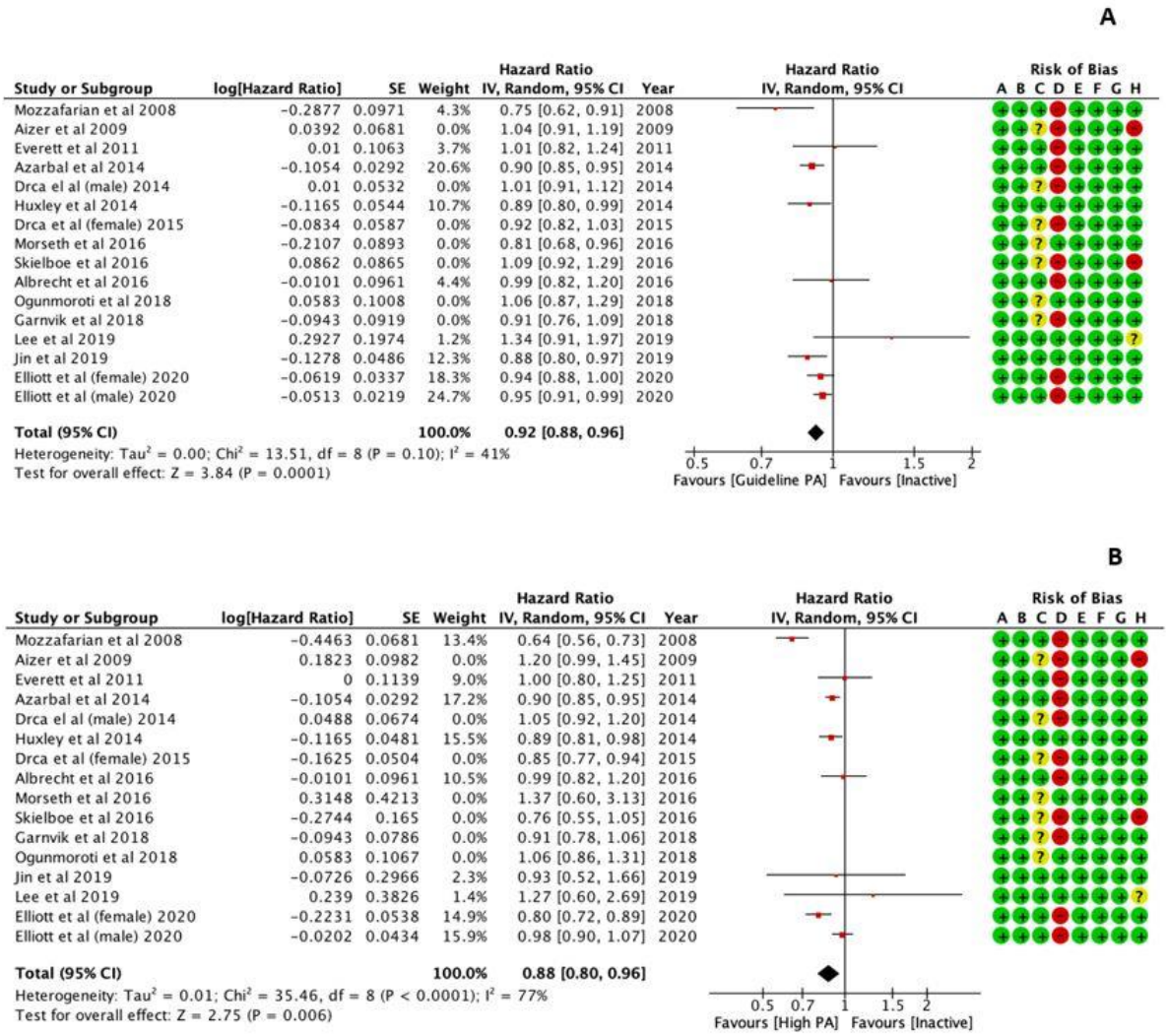
PubMed	Physical activity	Exercise [MH] OR Exercise [tiab] OR Physical activity [MH] OR Physical activity [tiab] OR PA [tiab] OR Physical Exertion [MH] OR Physical Exertion [tiab] OR physical fitness [MH] OR physical fitness [tiab] OR cardiorespiratory fitness [MH] OR cardiorespiratory fitness [tiab] OR CRF [tiab] OR sports [MH] or sport [tiab] OR Physical Education and Training [MH] OR Physical Education and Training [tiab] OR exercise therapy
	Atrial fibrillation	Atrial Fibrillation [MH] OR Atrial Fibrillation [tiab] OR AF [tiab] OR Atrial Arrhythmia [MH] OR Atrial Arrhythmia [tiab]
Embase	Physical activity	'physical activity'/exp OR 'physical activity'/syn OR 'PA' OR 'exercise'/exp OR 'exercise'/syn OR 'fitness'/exp OR 'fitness'/syn OR 'cardiorespiratory fitness'/exp OR 'cardiorespiratory fitness'/syn OR 'sport'/exp OR 'sport'/syn
	Atrial fibrillation	'atrial fibrillation'/exp OR 'atrial fibrillation'/syn OR 'AF' OR 'heart atrium arrhythmia'/exp OR 'heart atrium arrhythmia'/syn

Supplement table 1. Search term grid

Study	BMI	Hypertension	T2DM	CAD	Heart failure	OSA
Mozzafarian et al[20]	26.8	232/5446 (4.2%)	78/5446 (1.4%)	95/5446 (1.7%)	NR	NR
Aizer et al[8]	24.7	4368/16921 (25.8%)	405/16921 (2.4%)	NR	NR	NR
Everett et al[9]	26	9195/34759 (26.5%)	9195/34759 (2.7%)	NR	NR	NR
Huxley et al[19]	27.8	NR	NR	NR	NR	NR
Azarbal et al[12]	NR	34641/81317 (42.6%)	3211/81317 (4%)	2492/81317 (3.1%)	521/81317 (0.6%)	NR
Drca et al (male)[10]	26.2	10700/44410 (24.1%)	4263/44410 (9.6%)	3795/44410 (8.9%)†	3795/44410 (8.9%)†	NR
Drca et al (female)[13]	25	7163/36513 (19.6%)	1394/36513 (3.8%)	1490/36513 (4%)†	1490/36513 (4%)†	NR

Morseth et al[17]	23.9	501/20494 (2.4%)	120/20494 (0.6%)	375/20494 (1.8%)‡	375/20494 (1.8%)‡	NR
Skielboe et al[21]	24.8	750/15818 (4.7%)	342/15818 (2.1%)	323/15818 (2%)	NR	NR
Garnvik et al[15]	27.2	16254/43602 (37.3%)	1706/43602 (3.9%)	1163/43602 (2.7%)	617/43602 (1.4%)	NR
Albrecht et al[11]	27	1680/7018 (24%)	1160/7018 (16.5%)	NR	NR	NR
Ogunmoroti et al[7]	28.3	2113/6506 (32%)	622/6506 (10%)	NR	NR	NR
Jin et al[16]	23.7	107925/501690 (2.2%)	31396/501690 (6.3%)	4555/501690 (0.9%)	NR	NR
Lee et al[18]	23.4	29098/211992 (13.7%)	5724/211992 (2.7%)	6993/211992 (3.3%)§	NR	NR
Elliott et al[14]	27.3	106876/402406 (26.5%)	20385/402406 (5%)	18420/402406 (4.6%)	683/402406 (0.2%)	1440/402406 (0.3%)
NR = Not reported, † history of CAD or heart failure combined; ‡ results reported as "cardiovascular disease" including heart attack, stroke, and/or angina; § history of CAD or stroke combined.						

Supplementary Table 2. Additional participant characteristics from included studies. BMI = Body Mass Index, T2DM = Type 2 Diabetes Mellitus, CAD = Coronary Artery Disease, OSA = Obstructive sleep apnoea.



Supplemental figure 1. Sensitivity analysis excluding assumed PA level between below ('inactive') vs above guideline PA (1A) and inactive vs high PA (1B).

	ALL-CAUSE MORTALITY		CV MORTALITY	
	Total PA	**Vigorous PA**	**Total PA**	**Vigorous PA**
Model 1 (unadjusted)				
None	Reference	Reference	Reference	Reference
Below	0.44 (0.27 – 0.71)	0.58 (0.41 – 0.82)	0.52 (0.24 – 1.12)	0.64 (0.37 – 1.09)
Within	0.35 (0.23 – 0.54)	0.52 (0.36 – 0.74)	0.38 (0.19 – 0.76)	0.40 (0.21 – 0.76)
Above	0.31 (0.20 – 0.47)	0.59 (0.41 – 0.86)	0.30 (0.15 – 0.61)	0.59 (0.33 – 1.08)
Model 2 (adjusted for age and sex)				
None	Reference	Reference	Reference	Reference
Below	0.42 (0.26 – 0.68)	0.58 (0.41 – 0.83)	0.49 (0.27 – 1.07)	0.63 (0.37 – 1.08)
Within	0.33 (0.22 – 0.51)	0.52 (0.36 – 0.75)	0.35 (0.17 – 0.70)	0.39 (0.21 – 0.75)
Above	0.28 (0.18 – 0.43)	0.60 (0.41 – 0.87)	0.27 (0.14 – 0.55)	0.59 (0.32 – 1.06)
Model 3 (adjusted for age, sex, BMI, hypertension, CAD, HF, Stroke, Smoking and Valve Disease				
None	Reference	Reference	Reference	Reference
Below	0.48 (0.29 – 0.78)	0.70 (0.49 – 0.99)	0.61 (0.28 – 1.32)	0.85 (0.49 – 1.47)
Within	0.41 (0.27 – 0.63)	0.59 (0.41 – 0.85)	0.52 (0.26 – 1.05)	0.46 (0.24 – 0.88)
Above	0.34 (0.22 – 0.54)	0.72 (0.49 – 1.05)	0.36 (0.17 – 0.77)	0.78 (0.42 – 1.42)
Total PA: None (n=118), Below (n=387), Within (n=1160), Above (n=1334); **Vigorous PA**: None (n-1392), Below (n=562), Within (n=582), Above (n=463)				

Supplement Table 3: Hazard ratios for all-cause and cardiovascular mortality for each categorical group of physical activity.

		PA dose (MET-minutes/week)					
		500	**1000**	**1500**	**2000**	**2500**	**3000**
Total PA HR (95% CI)	**Males**	0.91 (0.71 – 1.16)	0.84 (0.54 – 1.29)	0.80 (0.49 – 1.31)	0.78 (0.48 – 1.27)	0.78 (0.50 – 1.23)	0.78 (0.50 – 1.22)
	Females	0.64 (0.30 – 1.38)	0.45 (0.17 – 1.17)	0.34 (0.14 – 0.84)	0.27 (0.11 – 0.65)	0.24 (0.10 – 0.55)	0.19 (0.10 – 0.49)

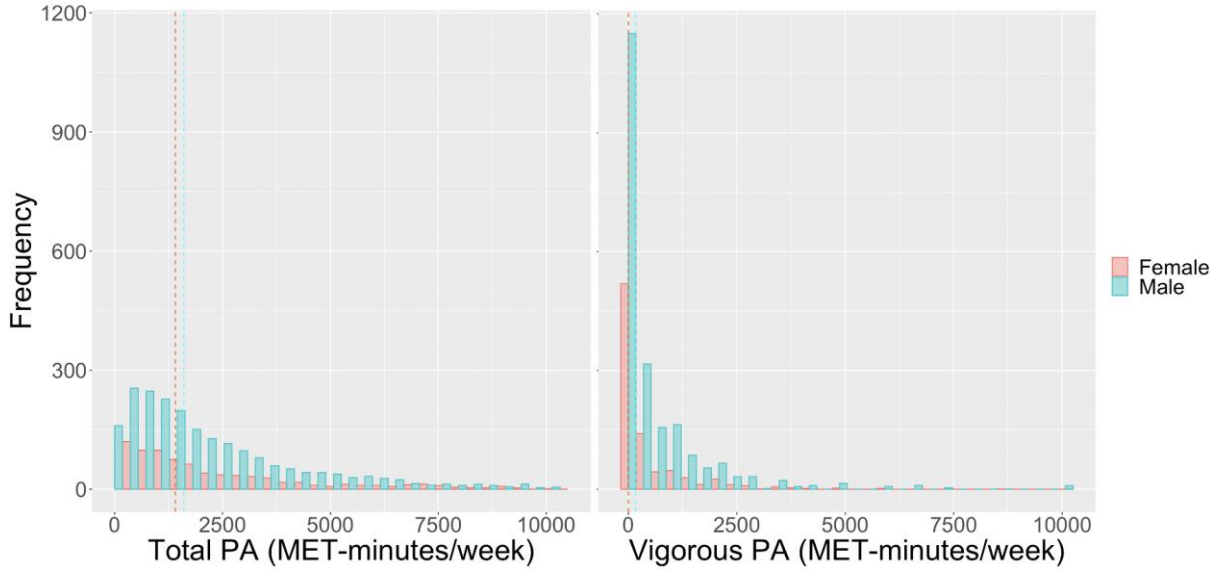
Supplement Table 4. Total PA adjusted hazard ratios (95% Confidence Interval) for all-cause death excluding the first year of follow up.

	PA dose (MET-minutes/week)					
	500	**1000**	**1500**	**2000**	**2500**	**3000**
Vigorous PA HR (95% CI)	0.75 (0.62 - 0.92)	0.64 (0.46 - 0.89)	0.61 (0.42 - 0.89)	0.64 (0.44 - 0.94)	0.70 (0.48 – 1.00)	0.75 (0.52 - 1.09)

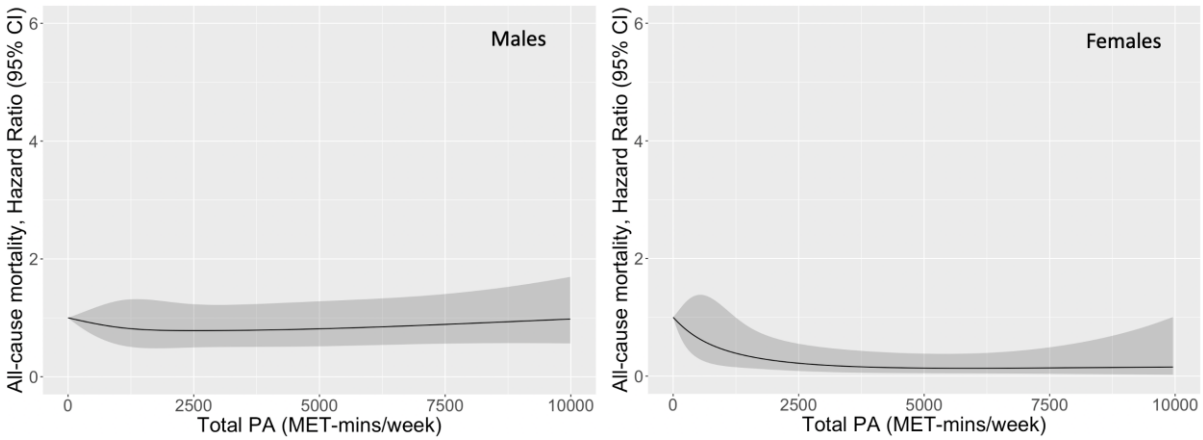
Supplement Table 5. Vigorous PA adjusted hazard ratios (95% Confidence Interval) for all cause death excluding the first year of follow up.

	PA dose (MET-minutes/week)					
	500	**1000**	**1500**	**2000**	**2500**	**3000**
Total PA HR (95% CI)	0.88 (0.62 – 1.26)	0.78 (0.42 – 1.45)	0.70 (0.34 – 1.40)	0.63 (0.32 – 1.23	0.58 (0.31 – 1.10)	0.55 (0.30 – 1.04)
Vigorous PA HR (95% CI)	0.63 (0.44 – 0.91)	0.49 (0.27 – 0.88)	0.47 (0.24 – 0.92)	0.50 (0.25 – 0.98)	0.57 (0.29 – 1.09)	0.66 (0.35 – 1.23)

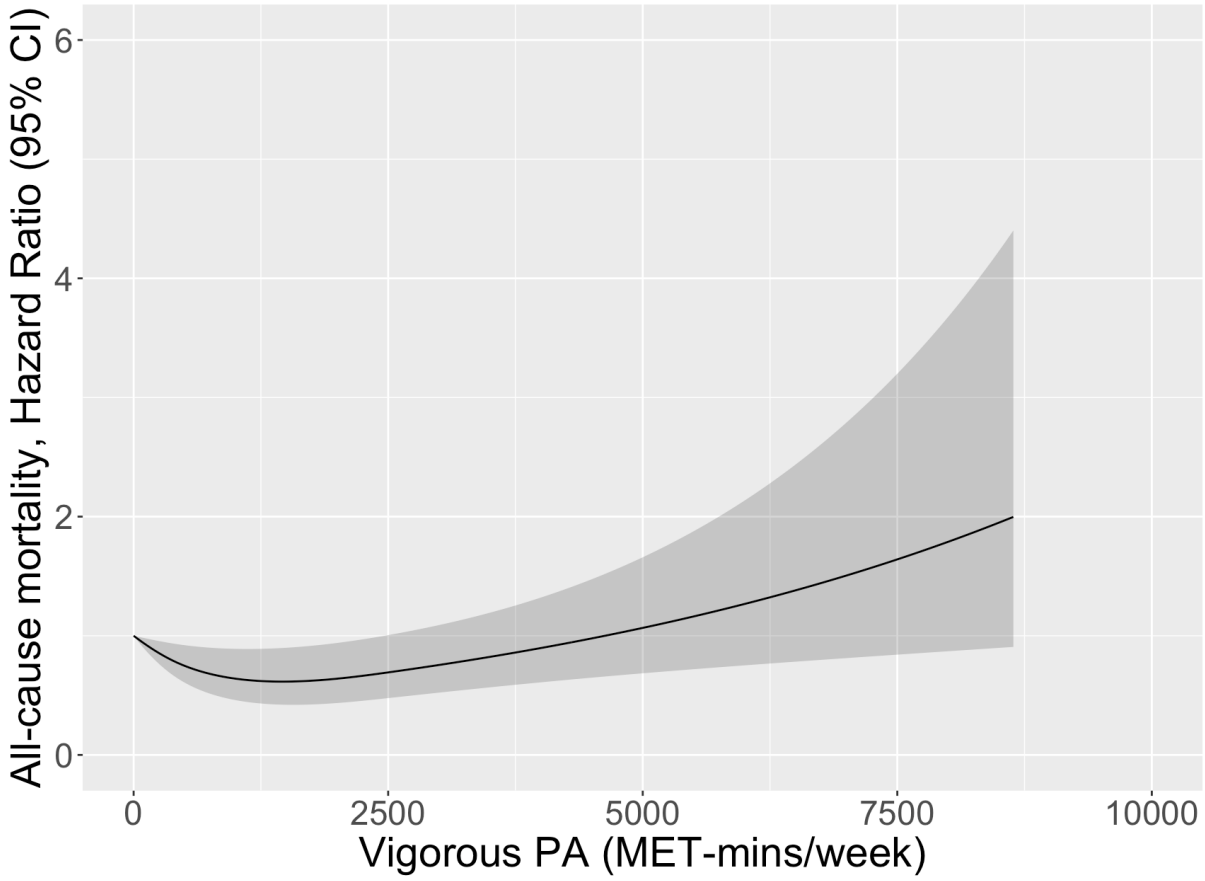
Supplement Table 6. Hazard ratios (95% Confidence Interval) for cardiovascular death excluding the first year of follow up excluding the first year of follow up.



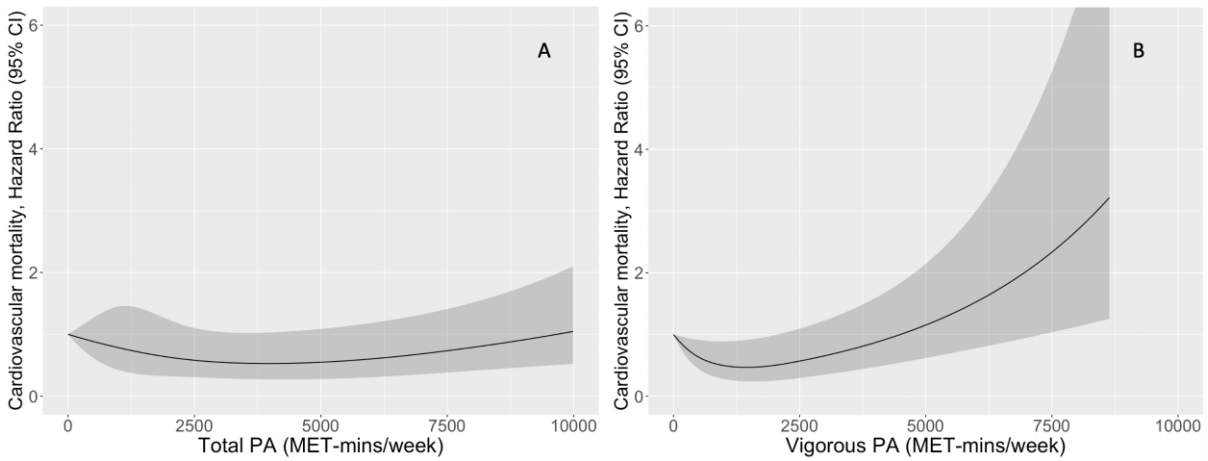
Supplement Figure 2. Total and vigorous PA distribution by sex.



Supplement Figure 3. Dose-response all-cause mortality risk according to total PA in males and females adjusted for age, sex, BMI, hypertension, coronary artery disease, heart failure, smoking, stroke and valvular disease excluding the first year of follow up.



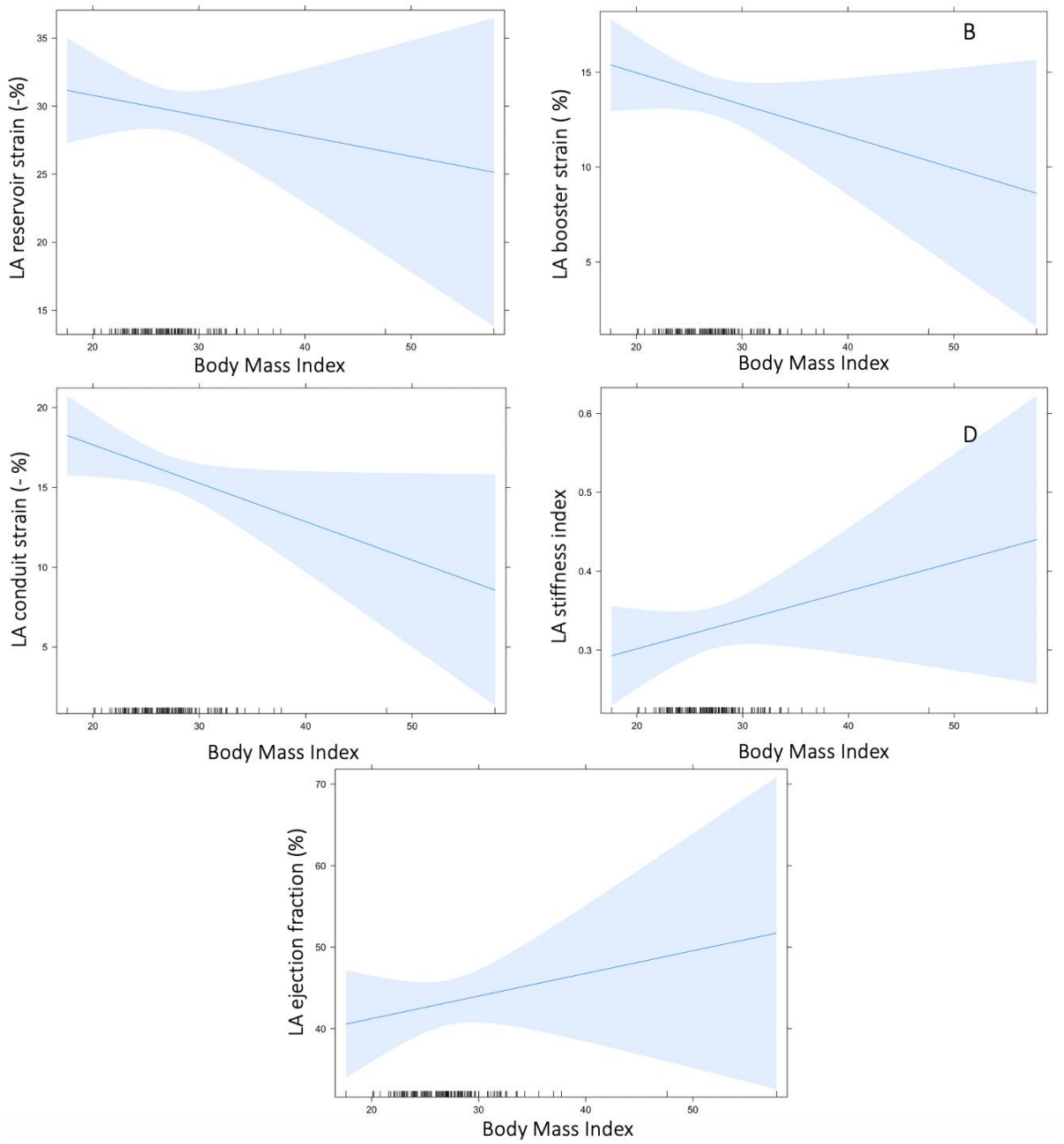
Supplement Figure 4. Dose-response all-cause mortality risk according to vigorous PA dose (B) adjusted for age, sex, hypertension, coronary artery disease, heart failure, smoking, stroke and valvular disease excluding the first year of follow up.



Supplement Figure 5. Dose-response cardiovascular mortality risk according to total (A) and vigorous PA dose (B) adjusted for age, sex, BMI, hypertension, coronary artery disease, heart failure, smoking, stroke and valvular disease excluding the first year of follow up.

Dependent variable	Model 1 (unadjusted)		
	β (95% CI)	**R^2**	**P Value**
LA max	0.3 (-0.06 to 0.6)	0.01	0.1
LA min	0.08 (-0.2 to 0.4)	-0.005	0.6
LA to LV ratio	0.003 (-0.004 to 0.01)	-0.001	0.4
Reservoir LA strain	-0.4 (-0.8 to -0.07)	0.03	0.02
Booster LA strain	-0.2 (-0.4 to 0.06)	0.007	0.1
Conduit LA strain	-0.2 (-0.5 to -0.006)	0.02	0.04
LA stiffness index	0.03(-0.002 to 0.01	0.003	0.2
LA ejection fraction	0.3 (-0.3 to 0.9)	-0.001	0.4
	Model 2 (adjusted for age, gender and METs)		
	β (95% CI)	**R^2**	**P Value**
LA max	0.1 (-0.2 to 0.5)	0.02	0.4
LA min	-0.2 (-0.5 to 0.1)	0.1	0.3
LA to LV ratio	-0.0005 (-0.009 to 0.008)	0.07	0.9
Reservoir LA strain	-0.1 (-0.5 to 0.2)	0.2	0.4
Booster LA strain	0.03 (-0.2 to 0.3)	0.1	0.8
Conduit LA strain	-0.2 (-0.4 to 0.1)	0.06	0.2
LA stiffness index	-0.001 (-0.01 to 0.005)	0.1	0.7
LA ejection fraction	0.1 (-0.2 to 0.5)	0.02	0.4

Supplement table 7. Association of BMI with LA echocardiographic variables.



Supplement figure 6. Linear models of LA function according to BMI

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