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Determinants of Coronary Artery Disease in the Male Master Endurance Athlete

Thesis Submitted for the degree of Doctor of Philosophy
June 2022

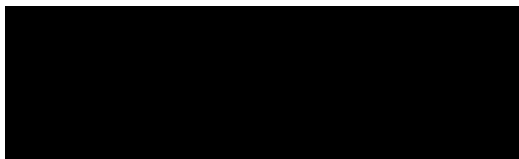
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Declaration

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Abstract

Exercise purports irrefutable cardiovascular morbidity and mortality benefits. Some male master endurance athletes demonstrate high coronary artery calcium scores, and increased prevalence of atherosclerotic plaques and myocardial fibrosis, which translate to increased risk of adverse events in the general population. This PhD explores the role of exercise dose, sporting discipline, blood pressure and diet in the development of coronary artery disease and myocardial fibrosis in this cohort.

220 male master endurance athletes aged 40-65 years, free of known cardiovascular risk factors, symptoms or coronary disease, who exercise for at least 6 hours/week, underwent clinical evaluation including CT calcium scoring and coronary angiography, cardiovascular MRI, 24-hour ambulatory BP monitoring and cardiopulmonary exercise testing.

38% demonstrated ambulatory hypertension and 35% a hypertensive response to exercise (≥ 220 mmHg).

The data demonstrates a greater number of years participating in endurance exercise predicts more coronary calcium (OR 1.04, CI 1.01-1.08) and non-ischaemic myocardial fibrosis (OR 1.04 CI 1.01-1.08). A higher ambulatory systolic BP predicts stenosis >50% in a main vessel (OR_{adjusted} 1.79, CI 1.20-2.66) partially calcified and non-calcified plaque (RRR_{adjusted} 1.5, CI 1.16-1.97) and plaque vulnerability markers (OR_{adjusted} 1.34 (1.06-1.71) and cyclists were more likely to have more stenoses >50% ($p = 0.008$) and partially calcified and non-calcified ($p = 0.02$) than multi-endurance athletes and more plaque vulnerability

markers than runners and multi-endurance athletes ($p = 0.03$). Systolic ambulatory BP and maximal systolic exercise BP predict for ischemic myocardial fibrosis ($OR_{unadjusted}=1.07$ CI 1.006-1.128 and $OR_{adjusted}=1.05$ CI 1.006-1.109 respectively).

This thesis advances the understanding of the impact of chronic endurance exercise on the cardiovascular system of male master athletes. It demonstrates that hypertension is prevalent in master male athletes and highlights the importance of its evaluation for identifying athletes who may harbour more prone to vulnerable coronary disease.

Dedication

I dedicate this thesis to my partner and best friend Aled for his unwavering faith in my ability to achieve this mammoth task, for holding me accountable, for his patience in my moments of despair, struggle and procrastination and for supplying with me with a laptop and giant screen that made the writing of this thesis possible.

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Publications, Presentations and Abstracts

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1. Hughes R, Ojrzynska-Witek N, Augusto J, Bhuva A, **Parry-Williams G**, Papatheodorou S, D'Silva A, Torlasco C, Manisty C, Hughes A, Sharma S, Moon J. 145 Masters athletes demonstrate sex differences in aortic stiffness. *Imaging* 2022:A111–A111.
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1. Low-grade hypertension and coronary atherosclerosis in male master endurance athletes. *BCS Best of the best abstracts oral presentation*. June 2021.
2. Case Presentation: 'The Collapsed Master Athlete'. *Cardiac Risk in the Young Annual Conference*. October 2018.
3. Coronary CT in Athletes; Clinically useful or complicating the conundrum? *European Association of Preventative Cardiology, Sports Cardiology Course*. Aug 2019.
4. Case Presentation: 'Making it big'. *Cardiac Risk in the Young Annual Conference*. October 2019.

Book Chapters/Contributions

Parry-Williams, G, Sharma S. ECG Masters' Collection Favorite ECGs from Master Teachers

Around the World, Vol 2. Section 15. Edited by Shenansa M *et al*. Cardiotext.

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Abbreviations

ABPM	Ambulatory Blood Pressure Monitoring
ACS	Acute Coronary Syndrome
ACC	American College of Cardiology
AF	Atrial Fibrillation

ANS	Autonomic Nervous System
ARVC	Arrhythmogenic Right Ventricular Cardiomyopathy
ASCVD	Atherosclerotic Cardiovascular Disease
AU	Agatston Units
AV	Atrioventricular
BP	Blood Pressure
BPM	Beats Per Minute
BNP	Brain Natriuretic Peptide
CAD	Coronary Artery Disease
CAC	Coronary Artery Calcium
CCS	Chronic Coronary Syndrome
CCTA	Computed Coronary Tomography Angiography
CI	95% Confidence Interval
CMR	Cardiovascular Magnetic Resonance Imaging
CPET	Cardio-pulmonary Exercise Testing
CRF	Cardiorespiratory Fitness
CT	Computed Tomography
CV	Cardiovascular
CVD	Cardiovascular Disease
DII	Dietary Inflammatory Index
EAPC	European Association of Preventative Cardiology
ECG	Electrocardiographic
ECV	Extra-Cellular Volume
EF	Ejection Fraction

EICF	Exercise Induced Cardiac Fatigue
ESC	European Society of Cardiology
ESH	European Society of Hypertension
FRS	Framingham Risk Score
HRE	Hypertensive Response to Exercise
Hs-CRP	Highly Sensitive C-Reactive Protein
HU	Hounsfield Units
IQR	Interquartile range
LA	Left Atrial
LAD	Left Anterior Descending
LAP	Low Attenuation Plaque
LBBB	Left Bundle Branch Block
LGE	Late Gadolinium Enhancement
LMS	Left Main Stem
LV	Left Ventricular
LVH	Left Ventricular Hypertrophy
MACE	Major Adverse Cardiovascular Events
MARC	Measuring Athlete's Risk of Cardiovascular events
MF	Myocardial Fibrosis
MI	Myocardial Infarction
MWT	Maximum Wall Thickness
NC/Fi	Necrotic Core/Fibrous Plaque Ratio
NO	Nitric Oxide
PCAT	Peri-Coronary Adipose Tissue Attenuation

PED	Performance Enhancing Drugs
RBBB	Right Bundle Branch Block
RRR	Relative Risk Ratio
RCA	Right Coronary Artery
RV	Right Ventricular
SCD	Sudden Cardiac Death
SD	Standard Deviation
SV	Stroke Volume
TCFA	Thin Capped Fibroatheroma
VA	Ventricular Arrhythmia
VE	Ventricular Ectopic
VO ₂ Max	Maximal Oxygen Consumption
VPB	Ventricular Premature Beat
VT	Ventricular Tachycardia
WHO	World Health Organisation

‘All parts of the body which have a function, if used in moderation and exercised in labors in which each is accustomed, become thereby healthy, well developed and age more slowly.’ — Hippocrates

1 Introduction

Historical evidence indicates that the Palaeolithic *homo* was reliant on exceptional long-distance running abilities for hunting and survival. Thus, one could argue that as a consequence of evolutionary genetics, *homosapien* are physiologically and anatomically evolved for endurance exercise and must engage with it to maintain a healthy, harmonious state. This may also explain why pursuing a lifestyle of regular aerobic physical exercise protects against atherosclerotic cardiovascular disease (ASCVD) and certain malignancies, slows the ageing process, minimizes disability in later life and increases lifespan by 3–7 years.^{1–3}

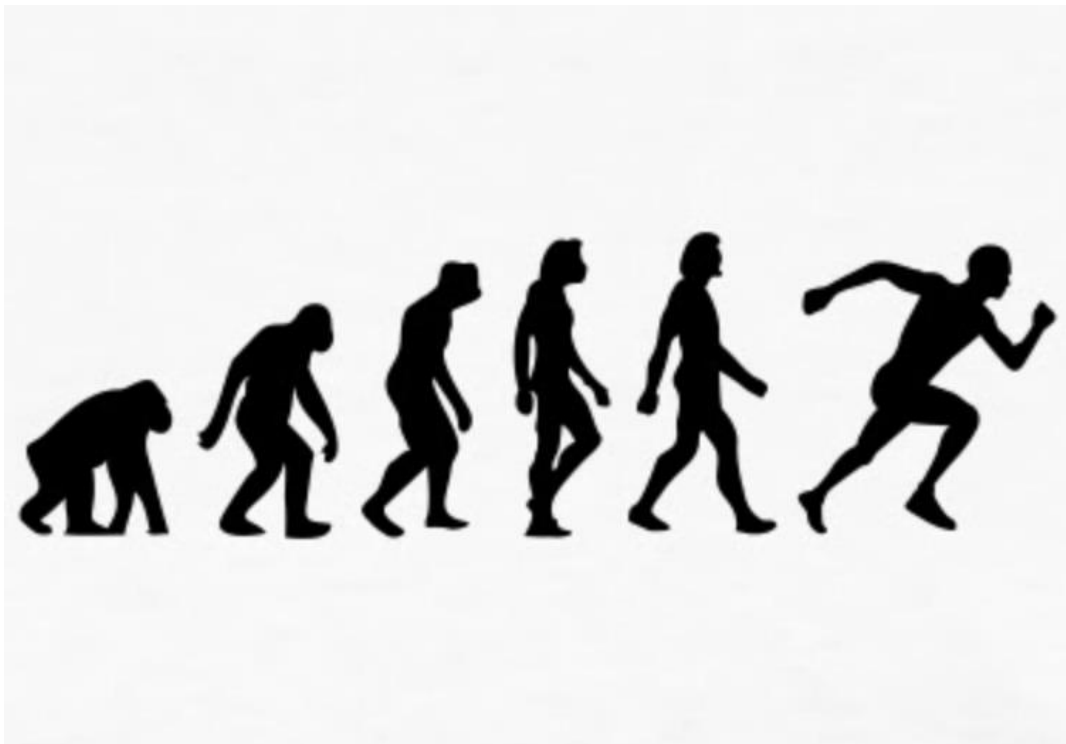


Figure 1.1 Diagrammatic representation of the evolution of *homosapiens*.

The archetype of the modern developed world *homo sapiens* makes for a stark comparison to ancient man. The ever more sedentary population has instant access to an abundance of resources which has led to an end to the necessity for hunting and gathering, poor nutritional practices and high levels of psychological stress. As such physical exercise has become an active and voluntary choice rather than a survival necessity. This way of life is resulting in the accumulation of risk factors that simply did not exist in ancient times, as illustrated by the exceptionally low incidence of coronary artery disease (CAD) in the few remaining primitive tribes.⁴ This genetics-lifestyle disconnect appears to be responsible for the current global 'lifestyle-disease' pandemic.

Conversely, there is a fast-growing population of male master endurance athletes undertaking evermore extreme, gruelling and physiologically demanding challenges. An endurance athlete is an individual who undertakes planned, structured and repetitive movement over a prolonged period, for the purpose of increasing endurance with the intention to compete. These athletes are considered amongst the healthiest humans with the lowest CVD risk on the planet however, a small number of these athletes succumb to sudden cardiac death (SCD) during endurance events, most commonly secondary to complications of CAD.⁵ Although overall, cases of sudden death are rare and endurance athletes live longer, the controversy of SCD during endurance events is attracting evermore media coverage as it grows in popularity. This has disproportionately raised public concern over the risks of exercise and has incentivised some to live by the belief that too much exercise or even any exercise, is deleterious.

Research to date has suggested that male master endurance athletes have a greater prevalence of high coronary artery calcium (CAC) scores, more atherosclerotic plaques and myocardial fibrosis (MF),⁶⁻⁹ leading some to conclude that chronic endurance exercise could be harmful. However, the explanation for these findings and the relationship of such findings to myocardial infarction (MI), arrhythmia and SCD risk in the master endurance athlete, are unknown, with large longitudinal datasets currently lacking. This thesis will outline the baseline cardiac findings from an extensive set of investigations, of a cohort of seemingly healthy male master endurance athletes. It will highlight any potential structural, electrical or functional cardiac abnormalities and proceed to explore a number of potential contributory factors that may explain them. The thesis will pay particular attention to CAD i.e., CAC score, coronary artery plaques, peri-coronary adipose tissue attenuation (PCAT) and markers of plaque vulnerability - as detected by computed tomography coronary angiography (CCTA), and left ventricular MF including late gadolinium enhancement (LGE) and extra-cellular volume (ECV) - as detected by cardiovascular magnetic resonance imaging (CMR). It will describe the blood pressure (BP) profile of the male master athlete, both at rest and during exercise, and describe its relationship to CAD and MF. It will investigate the relationship between 'exercise dose' - taking into consideration volume, intensity and frequency, and CAD and MF, as well as their relationship to the athlete's endurance sport discipline. Finally, the potential role of a pro-inflammatory diet in the development of cardiac abnormalities in a cohort of seemingly healthy middle-aged male endurance athletes will be explored.

Exercise can trigger acute cardiac events including acute MI, ventricular arrhythmia (VA) and SCD,¹⁰⁻¹² particularly in those middle-aged male endurance athletes who are regularly

imposing huge stresses and demands on the cardiovascular system whilst harbouring underlying CVD. This thesis will expand on the current evidence and understanding of the impact of chronic endurance exercise on the heart of the middle-aged man, empowering sports physicians to advise such athletes more confidently about the risks, preventative strategies and where necessary, exercise limitations.

1.1 Benefits of Exercise

Exercise has a beneficial impact on a broad spectrum of the human physiology, largely through its anti-inflammatory, anti-oxidative, autonomic regulatory and atherosclerotic risk factor modifying effects. Pursuing a lifestyle of regular aerobic physical exercise, irrefutably protects against chronic diseases including ASCVD, some malignancies and Alzheimer's disease. Regular exercise also slows the ageing process, minimises disability in later life-in part through reducing the risk of osteoporosis, is a form of anti-depressant and anti-anxiolytic therapy in some individuals and improves fitness, which has been proven to have a beneficial impact on all-cause and cardiovascular mortality.¹³⁻¹⁵ These benefits are the driver for the World Health Organisation (WHO) and European Society of Cardiology (ESC) exercise recommendations which advocate a minimum of 150 minutes of moderate intensity or 75 minutes of vigorous intensity^{15,16} aerobic exercise per week.

1.2 Indirect Cardiovascular Benefits of Exercise

1.2.1 Exercise and Ageing

Ageing is a complex process that in combination with lifestyle factors, results in a gradual loss of the individual's physiological integrity. The progressive accumulation of damage to

the cell and its components eventually culminates in death. López-Otín *et al.* proposed nine cellular and molecular hallmarks contributing to the ageing process, including gene instability, epigenetic alterations, telomere ageing, loss of cellular protein regulation, de-regulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and impaired intercellular communication. Such changes are largely driven by chronic low grade inflammation and oxidative stress from free radicals, all of which are attenuated by regular physical exercise.¹⁷

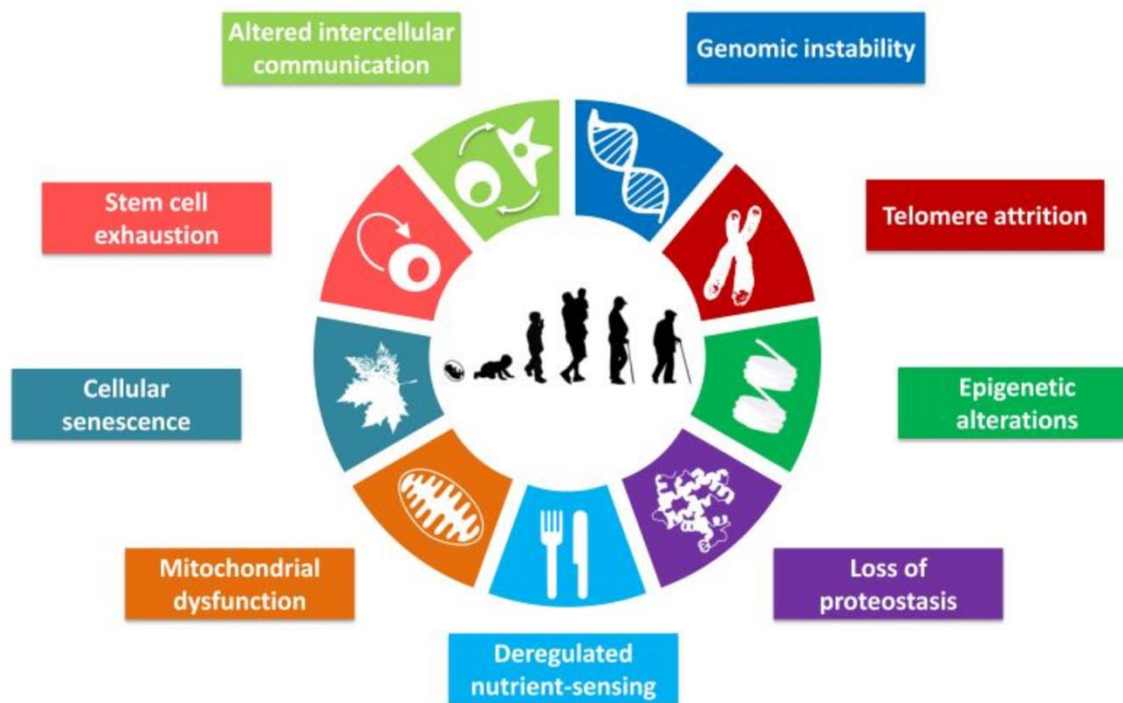


Figure 1.2 The 9 hallmarks of ageing as described by López-Otín *et al.*¹⁸

1.2.2 Exercise and Sarcopenia

Sarcopenia, the loss of muscle mass is one such example of ageing, resulting from impaired regenerative capacity and protein synthesis, despite adequate nutrition and exercise.¹⁹

Sarcopenia is directly associated with increased CAC in healthy adults and major adverse coronary events in those with CVS risk factors.¹ It results from the replacement of type II 'fast-twitch' muscle fibres and motor units with fat and connective tissue, causing loss of contractile and metabolic myocyte function.^{20,21} This partly explains why athletic performance deteriorates with age, especially with respect to explosive forms of exercise. The onset of sarcopaenia is usually in the 5th decade but only becomes evident in the 7th decade due to the more gradual decline in 'slow-twitch' fibres. Consequently, individuals can continue to be competitive in endurance sports at elite level even in the fifth and sixth decades and participants in such events tend to be older for this reason. A retrospective analysis of 43,551 participants in ultra-marathons worldwide demonstrated the mean age of athletes ranked in the top 10 was 43.4 and 42.1 years in females and males respectively. There was no deterioration in peak running times in athletes until they reached middle age i.e., 49 years of age in females and 54 years of age in males.²²

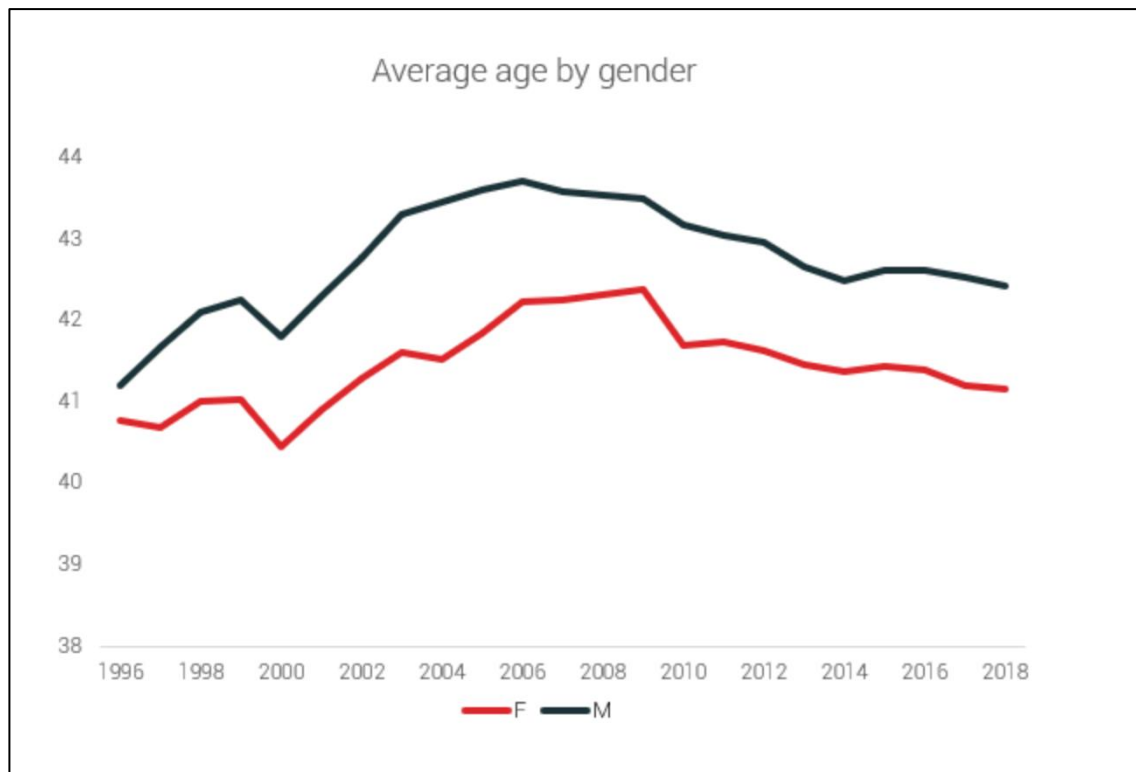


Figure 1.3 Average age of ultra-marathon athletes across the globe between 1996 and 2018

by Ronto *et al.*²³

1.3 Ageing and the Cardiovascular Benefits of Exercise

1.3.1 Cardiovascular Risk Factors

Exercise can be coined a cardiovascular ‘polypill’ due its concomitant benefit on multiple CVS risk factors at once. Age alone is the greatest CVS risk factor; therefore, the ageing human is victim to an incessantly accumulating CVS risk. Up to 59% of the cardiovascular morbidity and mortality reduction associated with exercise results from improvements in the CVS risk factor profile, which in turn reduces cardiovascular ageing.¹³ Reductions in blood pressure, improvement in cholesterol profile and curbing of obesity and secondary insulin resistance are responsible for such improvement.^{24,25} Exercise however does not offset CVS risk entirely.¹ One study of Olympic athletes demonstrated that the common risk factors were prevalent even amongst the most elite with 0.3% exhibiting hyperglycaemia,

3.8% hypertension, 8% smokers, 25% having an increased waist circumference and 32% dyslipidaemia, although endurance athletes had the least risk factors.²⁶

1.3.2 Diet

There is a growing awareness of the importance of dietary intake in determining human health and disease. The UK currently has the highest consumption of processed foods and refined carbohydrates²⁷ with poor nutritional value, and in some cases harmful qualities, in all of Europe, with rising levels of chronic diseases including CAD. There is emerging evidence to suggest the Western lifestyle, in particular diet, exposes individuals to chronic low-grade inflammation, which has been associated with the development of chronic diseases.²⁸ There is uncertainty regarding what constitutes an optimal diet which reflects the often-contradictory nature of scientific nutritional research. The research challenges faced are in measuring and classifying an individual's diet and subsequent long-term outcomes, and limited funding due to a lack of pharmaceutical industry incentive.

As the face of endurance exercise rapidly evolves, with ultra-events and triathlon evermore popular, dietary intake patterns have followed suit. Despite this, overall, there has been little change in the predominant food groups consumed by endurance athletes, with carbohydrates continuing to be the major food group of choice and only very few adopting the emerging keto-adapted high-fat low-carbohydrate diet.²⁹ Concurrently, there is a pervading cultural belief particularly amongst recreational athletes, that exercise negates the impact of poor dietary choices, considering only the calorific aspect of foods as relevant. Finally, due to demand, research examining performance enhancing nutrition amongst athletes is abundant, in contrast there is an absence of data considering the potential

deleterious effects of such diets on long-term health and CVS risk.³⁰ For all the reasons provided above, little attention has been attributed to the potential harmful effects of diet amongst athletes. This thesis aims to begin the exploration of this factor in its contribution to CAD amongst male master endurance athletes with further discussion of the existing literature in the introduction of chapter 7.

1.3.3 Structural and Functional Cardiovascular Changes Associated with Ageing

The cardiovascular system undergoes a plethora of structural and functional changes with age that impact on cardiac reserve. At a cellular level there is a gradual decline in the number of cardiac myocytes, a compensatory increase in myocyte size and replacement fibrosis, resulting in mild left ventricular hypertrophy (LVH).^{31,32}

There is an overall reduction in cardiac energetics with age. Early diastolic filling is reduced because of increased myocardial stiffness, delineated by increased ventricular relaxation time, and changes in early diastolic atrial pressures.^{6,32–35} In addition, vascular and myocardial stiffness increase with ageing and catecholamine sensitivity is lost, resulting in increased afterload.³³ The catecholamine insensitivity, in addition to the intrinsic slowing of the sinoatrial node, also reduces the ability to achieve higher heart rates with age.^{32,36–38}

These changes culminate in a reduced ability to augment stroke volume (SV), reduced EF reserve and explains partly why maximal oxygen consumption (VO₂ max) gradually falls with increasing age.^{32,35,39}

Exercise attenuates the age-related reductions in LV compliance and distensibility and thus the rate of fall in VO₂ max.^{40,41} A study of 102 master athletes revealed that exercise

preserved LV compliance and distensibility and enhanced ventricular-arterial coupling, which reflects LV diastolic pressure and aortic stiffness combined, in a dose-response fashion, with 4-5 sessions per week being the optimal dose for preventing age-related loss. Lower dose, casual exercise was insufficient to prevent this age-related loss of compliance.^{42,43}

1.4 Direct Cardiovascular Benefits of Exercise

The direct cardiovascular benefit of exercise involves a complex interaction of the autonomic nervous system (ANS) and the cellular responses to shear stress. Overall, they are largely determined by its long-term anti-inflammatory and anti-oxidative adaptive effects on the vasculature and myocardium. This in turn protects against myocyte damage, endothelial dysfunction, maintains vascular compliance and prevents thrombogenicity, thus reducing the risk of plaque rupture, coronary occlusion and MI.⁴⁴⁻⁴⁷ High vagal tone also improves myocyte calcium handling through reducing sarcoplasmic leakage, resulting in electrical stability and reduced arrhythmia risk. The release of myokines from skeletal muscle is responsible for the anti-inflammatory milieu created by exercise training. The anti-oxidative mechanisms of exercise are explained by the term 'hormesis'. Hormesis describes the repetitive brief exposure to the damaging effects of moderate oxidative stress, produced by conditions including exercise. This results in a moderate level of reactive oxygen species (ROS) and inflammatory cytokines, to which the cells adapt; such that when exposed to more significant oxidative stress, damage and dysfunction of the mitochondria is reduced, with resistance to apoptotic stimuli and scavenging of free radicals. A relevant example in athletes is the role of ischaemic pre-conditioning in reducing ischaemia and reperfusion injury due to the adaptive consequences of prolonged moderate level oxidative

stress, activation of opioid receptors and release of adenosine and bradykinin.^{1,48} Studies in rats have demonstrated that pre-conditioning is induced with just 1-5 days of exercise training.⁴⁹

1.4.1 Endothelial Protection

Endothelial dysfunction is the primary driver of atherosclerosis. The vascular endothelium is an active and dynamic internal organ responsible for maintaining blood circulation and vascular tone, inflammatory cell adherence and response, cell signalling and homeostasis, and vascular angiogenesis and thrombosis.⁵⁰ The endothelium is injured predominantly by hypercholesterolaemia, hypertension, hyperglycaemia, smoking, haemodynamic factors, immune reactions and bacterial toxins, which reduce nitric oxide (NO) bioavailability, therefore reducing vascular vasodilatation capacity and creating a pro-inflammatory and pro-thrombotic state.⁵⁰

Exercise protects against endothelial damage, even in the absence of improvements in the CVS risk factor profile.⁵¹ The vascular shear wall stress produced because of increased laminar flow during light to moderate intensity exercise, stimulates the release of nitric oxide (NO) through upregulating NO synthase, and reducing NO deactivation, which promotes vasodilatation through smooth muscle relaxation in the vessel wall, and inhibition of platelet aggregation, maintaining vascular homeostasis. The increased levels of prostacyclin and reduced levels of endothelin 1 associated with exercise also contribute to vasodilatation. In addition, NO activates messenger ribonucleic acid (mRNA) and expression of proteins and enzymes involved in scavenging reactive oxygen species, which are the by-product of an imbalance between oxidant and antioxidant stress. This protects the vascular

endothelium from damage thus stabilising and preventing progression of pre-existing atherosclerosis. Studies suggest that this protective effect of exercise on the endothelium is dose dependent.⁵² Animal models have demonstrated that even a single session of resistance training produces NO driven vasodilatation.⁵³ Martinez *et al* exercised rats on a treadmill for 1 hour daily 5 days a week for 8 weeks. Rats who exercised 1 hour per day continuously demonstrated improved aortic vasodilatory capacity consistent with improved vascular function; however, rats exercising in four 15 minute sessions per day showed no improvement, implying a higher threshold at which this response takes effect.⁵⁴ Exercise also stimulates angiogenesis which increases tissue oxygen transport and inhibits cell adhesion molecules that otherwise mediate the inflammatory atherosclerotic process.⁵⁵

There is currently no evidence to suggest that any one exercise type has a preferential benefit on endothelial function over another. A study of 42 hypertensive or pre-hypertensive subjects participating in either resistance, dynamic or combined exercise showed no difference between groups in endothelial function, as measured by brachial artery flow mediated dilatation.⁵⁶

Studies of male endurance athletes demonstrate increased markers of coronary atherosclerosis compared with matched controls. Extreme strenuous and exhaustive exercise increases oxidative stress and can cause a systemic inflammatory response, although this is usually acute and resolves within a few hours.^{55,57} There is speculation that the mechanical coronary stress caused by vigorous exercise disrupts laminar flow and contributes to a net endothelial damage. The oscillatory shear stress associated with the rise in systolic BP in proportion to increasing workload and the loss of vascular homeostasis

resulting in reduced NO availability and increased oxidative stress occurring during endurance exercise, also creates the milieu for endothelial inflammation and proliferation. This acute pro-inflammatory state may even trigger plaque rupture, culminating in MI and subsequent risk of SCD. A small study of 9 athletes compared coronary plaque volume using CCTA before and after participation in the Race across America (a 140-day running race). Four runners had no CAD at the outset or following the event. The other 4 had at least 1 CVS risk factor and evidence of CAD prior to the race. All athletes demonstrated an increase in coronary plaque volume following the race, at the sites of pre-existing plaque, with concomitant increases in CRP supporting a hypothesis that this was an inflammatory related process.⁵⁸ As with many of the beneficial effects of exercise, it appears that optimal endothelial function is best achieved through regular moderate intensity physical exercise⁵⁸.

1.4.2 Arterial Stiffness

There is a close interaction between arterial stiffness and endothelial function. As mentioned above, endothelial shear stress is the predominant determinant of NO release. A study of 130 individuals training for and completing a first marathon at a slow pace demonstrated the benefit of exercise in reducing vascular ageing. Marathon training reduced both central BP and arterial stiffness which translated into a 4-year reduction in vascular age with older and slower marathon runners benefiting most.⁵⁹ This is explained by a reduction in haemodynamic load secondary to the reduced arterial stiffness which consequently protects against endothelial damage.⁶⁰

1.4.3 Cardiovascular Morbidity and Mortality Benefits of Exercise

Ever since Morris *et al* infamously demonstrated in 1953 a higher rate of ASCVD amongst sedentary London bus drivers and administrative post staff, compared to their more active bus conductor and postman colleagues respectively, there has been accumulating evidence of the CVS morbidity and mortality benefit afforded by regular moderate intensity aerobic exercise.^{61,62}

A meta-analysis investigating the relationship between physical activity (measured through either self-reporting or objective assessment) and mortality among 883,372 individuals, demonstrated a 35% risk reduction in CVD death and a 33% risk reduction in all-cause death over 20 years in the physically active groups.²⁴ A further meta-analysis assessing the association between accelerometer-determined physical activity and all-cause mortality showed that, regardless of intensity, a greater exercise volume resulted in reduced mortality.⁶³ The greatest risk reduction occurred between 375 min of light-intensity physical activity and 24 min of moderate-to-vigorous-intensity physical activity per day. Another study showed that even low-intensity leisure-time physical activity conferred a significant reduction in all-cause mortality compared with a sedentary lifestyle.⁶⁴

1.4.3.1 Cardiorespiratory Fitness

An individual's baseline level of cardiorespiratory fitness (CRF) is largely genetically pre-determined,⁶⁵ with exercise training improving CRF by up to 20%.⁶⁶ A high level of CRF is a good predictor of improved metabolic health and reduced morbidity and mortality. Both subjective and objective markers of CRF correlate positively with all-cause and CVS mortality.⁶⁷ In a study of 44,452 male health professionals who were followed up for

475,755 person-years, the ability to exercise intensively was independently associated with a reduced risk of MI and fatal CVS events.⁶⁸ Moderate (4–6 metabolic equivalents (METs)) and high-intensity (6–12 METs) physical activity conferred a significant risk reduction compared with low-intensity (<4 METs) physical activity.⁶⁸ Furthermore, data from several studies have demonstrated that each MET increase in fitness is associated with a 13–20% reduction in CVS and all-cause mortality.^{13,69–71} A greater CRF has also been shown to reduce the risk of hospitalization for heart failure in later life, with each MET increase in fitness reducing this risk by 20%.^{72–74} Similarly, among patients with an established diagnosis of heart failure, exercise training improves VO₂ max and reduces hospitalization for heart failure and mortality by 28% and 35%, respectively.^{75,76}

1.4.3.2 Longevity Amongst Endurance Athletes

Various studies of endurance athletes, including world-class elite athletes, report a profound all-cause and CVS mortality benefit compared with both other sporting disciplines and sedentary controls.⁷⁷ Three seminal studies have shown that endurance athletes have greater longevity compared with the general population. A study of 2,613 Finnish elite athletes revealed that athletes participating in endurance sports lived an average of 5.7 years longer than controls.⁷⁸ Data from 15,000 Olympic medallists showed that athletes lived an average of 2.8 years longer than controls, regardless of sporting discipline or country.⁷⁹ In a 37.4-year follow-up study (range 23.5–49.8 years) of French athletes participating in at least 1 Tour de France event, cyclists demonstrated a 41% lower mortality than the general population.⁸⁰ Similar findings are demonstrated amongst non-elite endurance athletes. In a study of >70,000 participants in the gruelling non-elite Vasaloppet long-distance cross-country ski race, CVS and all-cause mortality were >50% lower than the

predicted standardized mortality ratios for the general population.⁸¹ Therefore, despite the abnormal findings in master endurance athletes, overall, they have improved survival compared with the general population. It is possible that having a genetic predisposition to athletic prowess and longevity occur in common. However, in a study of former elite male athletes and their brothers, followed for a median of 52 years, endurance athletes lived longer and had healthier lifestyles than both their brothers and those practicing non-endurance sports,⁸² suggesting environmental and lifestyle factors, and the direct effects of endurance exercise on the body, also play a role. It is important to acknowledge the data discussed herein, whether from elite or non-elite athletes, does relate to a minority of athletes in the uppermost echelons of their sport often participating on a professional basis. There is a far greater mass majority who lie within a slightly lower performance category whose training regimes although high intensity may not be accompanied by the clean lifestyle of the professional athlete and are instead often accompanied by the additional stresses of a full-time job. Furthermore, the top tier athletes often follow a very different exercise journey to most middle-aged male endurance athletes, tending to relax once they retire from professionalism with their professional years being most commonly the younger years. In contrast the majority of middle-aged athletes, some of whom only begin exercising in middle-age, continue to push themselves hard throughout this period and into the latter years. Therefore, caution must be adopted when applying such data in a cohort who lie below this top tier.

1.5 Physiological Effects of Endurance Exercise on the Heart – The ‘Athlete’s Heart’

For the purposes of this thesis, an endurance athlete is defined as *an individual who trains for and/or participates in endurance events including marathon, ultramarathon, triathlon,*

cyclosporives or similar. These individuals often exercise at 15–20 times the level of the current exercise recommendations¹⁶ The number of such individuals has grown exponentially as evidenced by the burgeoning increase in mass endurance events (see figure 1.4). Increased event uptake is driven by a multitude of factors including the growing awareness of the importance of activity for health amongst the population and an escalation of the endurance events market. Corporate companies fund events for employees and there is an evolving interest in sports training holiday camps and the tourist industry organising events in holiday areas at off-peak times that would otherwise be low in business. Additional factors include drivers more specific to the UK, including gyms and brands such as Adidas creating ‘start running’ clubs and movements such as parkrun and couch to 5K - providing an entry point for otherwise exercise naïve individuals into endurance sport. Inspiration and motivation to participate in endurance events was also gained from the latest Olympic successes in triathlon, open-water swimming and cycling.⁸³ Not only has participation increased but athletes are pushing themselves to do more events in less time with challenges being ever-more extreme. Participation in ultra-marathon events, defined as an event lasting more than 4-6 hours, has increased globally by 1676% in the last 23 years.²³

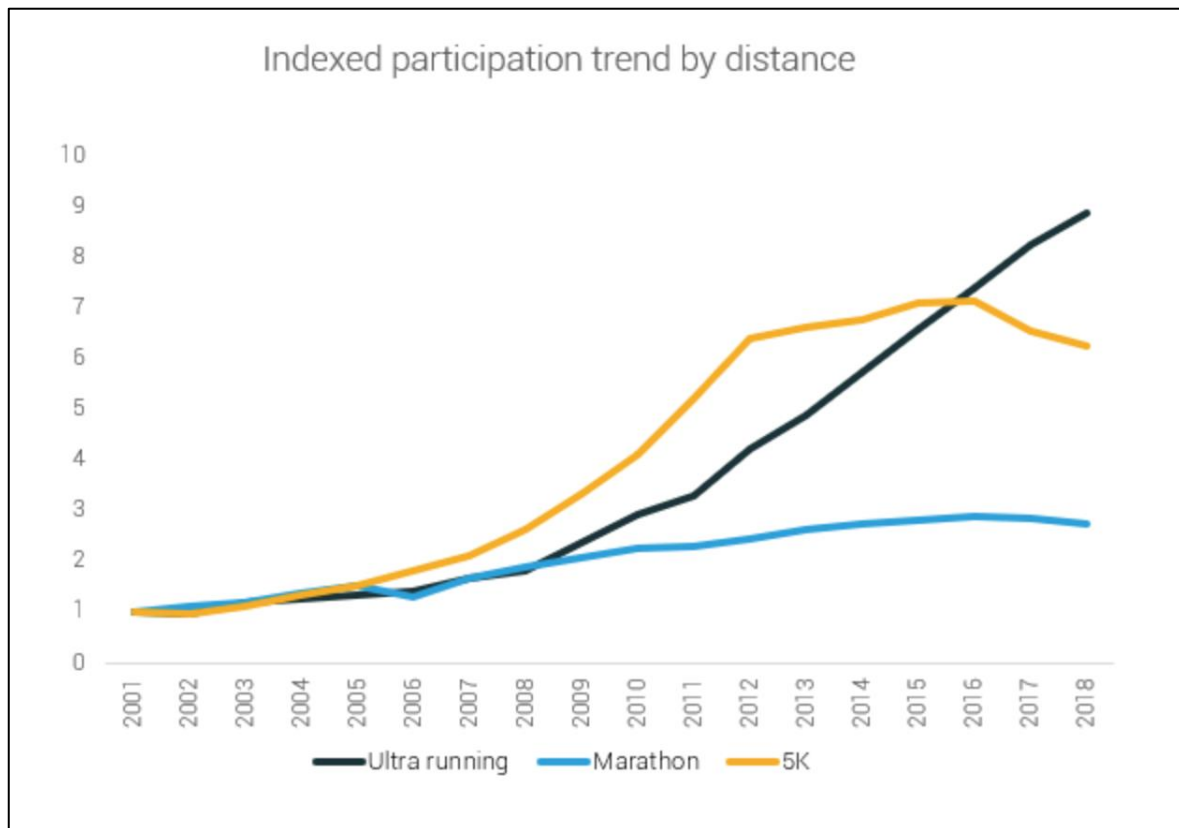


Figure 1.4 Graph of trends in participation in endurance events (ultra-running, marathons and 5k) between 2001 and 2018.²³

The CVS system of these endurance athletes mounts a five to seven-fold increase in cardiac output⁸⁴ to sustain sufficient oxygen delivery to exercising muscles, which is achieved through an array of well-defined physiological, structural and functional cardiac adaptations that develop over time, collectively known as the ‘athlete’s heart’. Precisely delineating these adaptations and their physiological boundaries is of paramount importance given the potential overlap of adaptation with cardiac diseases that can predispose individuals to SCD during sport. Given the CVS demands of endurance sports, it is of little surprise that endurance athletes develop some of the most profound adaptations to exercise. These cardiovascular adaptations include sinus bradycardia and increased QRS voltages, increased cardiac chamber size, enhanced diastolic ventricular filling and higher peak oxygen

consumption (VO₂ max) during exercise stress testing.⁸⁵ These adaptations are explored in greater detail below.

1.5.1 Determinants of the Athlete's Heart

The presence and degree of physiological CVS adaptation to exercise varies according to age, sex, ethnicity and duration, volume, intensity, and pattern of, exposure to, and type of exercise.^{86–88}

1.5.2 Electrical

The electrocardiographic (ECG) adaptations of endurance exercise are largely secondary to increased vagal tone, down regulation of *if* channels and a relative increase in cardiac size. These changes include sinus bradycardia, first-degree atrioventricular block, Mobitz type I atrioventricular block, increased QRS voltages, incomplete right bundle branch block (RBBB) and the early repolarization pattern.⁸⁵ Figure 1.5 shows an example of the ECG features that are commonly found in the hearts of endurance athletes.

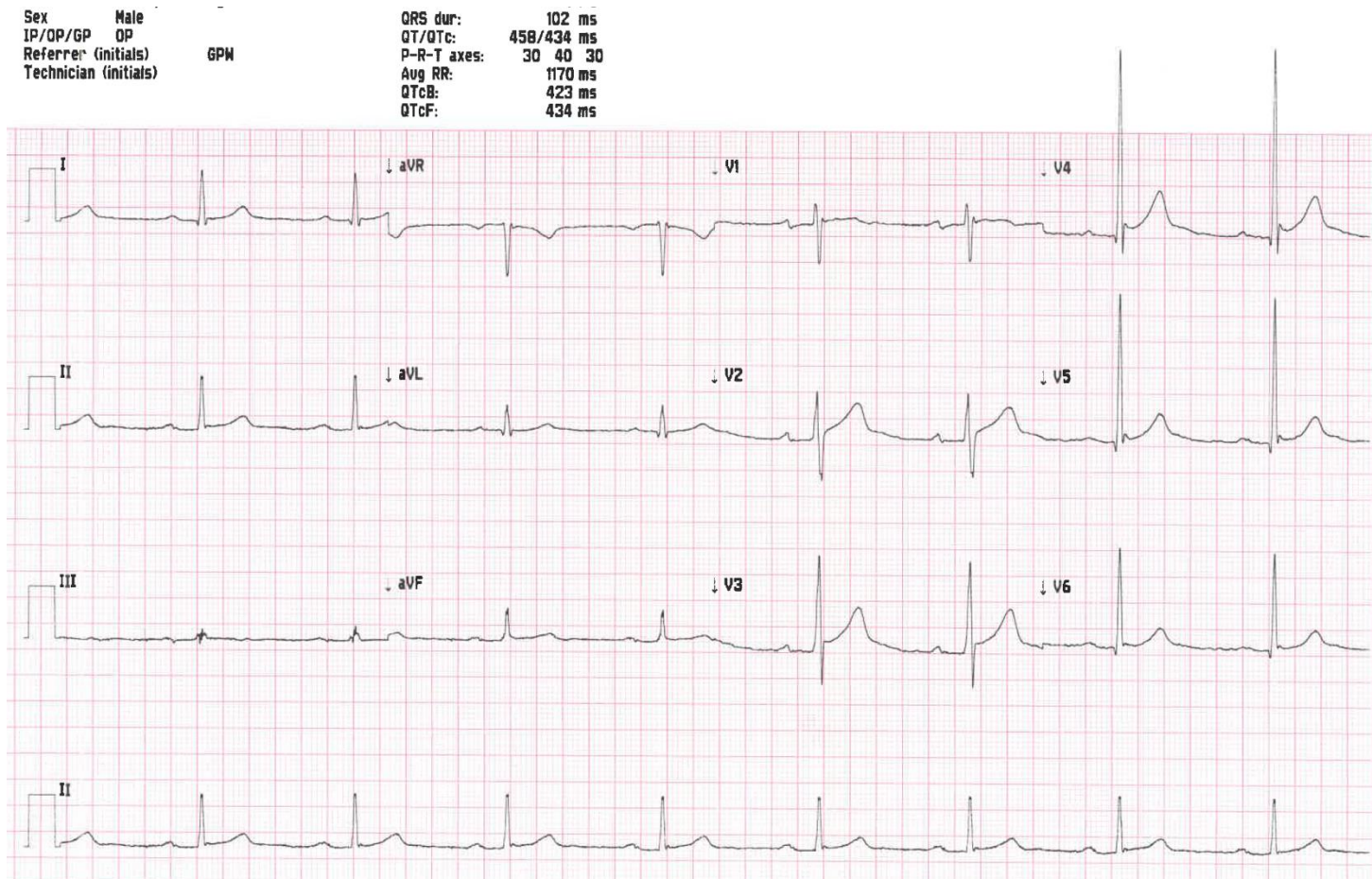


Figure 1.5 Twelve Lead ECG recording of 47-year-old ultra-marathon runner participating in the study. Typical ECG features of the endurance athlete's heart including sinus bradycardia, 1st degree AV block (PR interval 230 ms), LVH by Sokolow's criteria and an early repolarisation pattern with J-point elevation in leads V3-V6.

1.5.3 Structural

Athletes have a 15–20% increase in LV wall thickness, a 10% increase in LV cavity size and a 24% increase in right ventricular (RV) cavity size.⁸⁶ In general, adult male endurance athletes with a body surface area $\geq 2\text{m}^2$ have the largest cardiac dimensions⁸⁹ and up to 50% have cavity dimensions that exceed the upper limits of normal for the general population.⁹⁰ In an Italian study of >1,000 Olympians, the LV end-diastolic dimension measured up to 70 mm in some male athletes,⁹⁰ compared to the accepted upper limit cut-off of 59mm. The same group reported that 1.7% of Olympians (mostly endurance athletes) had an LV wall thickness above the normal range (≥ 12 mm), some as much as 16 mm.⁹⁰

The RV in athletes undergoes quantitative changes that are similar to those of the LV, with balanced cavity enlargement and preserved systolic function.^{91,92} More than 50% of athletes have RV outflow tract and basal RV diameters exceeding the upper limits of normal for the general population.⁹² In some endurance athletes, the RV is slightly larger than the LV.⁹²

Morganroth *et al* used ventricular geometry to describe the combination of LV chamber size and wall thickness adaptation in athletes. He claimed that endurance athletes developed eccentric hypertrophy i.e., increased LV mass and end diastolic volumes, and resistance athletes developed concentric hypertrophy i.e., increased wall thickness and LV mass with no relative increase in cavity size.⁹³ More recent data suggests a less dichotomous classification with most athletes exhibiting normal LV geometry (70-90%).^{94,95} Amongst endurance athletes, eccentric hypertrophy is the predominant adaptation phenotype, however Finocchiaro *et al* also demonstrated concentric hypertrophy (4%) and concentric remodelling (6%) in a small number of athletes participating in dynamic exercise. Exercise

dose and pattern in addition to demographics were the determinant factors in these variations.^{94–96}

1.5.4 Functional

Caso *et al* studied tissue doppler parameters of diastolic function in water polo players showing increased deceleration times, increased ratio of early peak (E') to late (A') diastolic filling velocity and increased early peak diastolic function (E'), all consistent with enhanced diastolic function³⁹ Weiner *et al* studied 12 rowers who underwent an augmentation in the training intensity at 90 days (acute augmentation phase) and 39 months (chronic phase). They observed an augmentation of diastolic indices at both stages demonstrated in the early phase by an increase in LV E' and later by an increase in both E' and A'.⁸⁸

The ability of the trained endurance athlete to augment SV and VO₂ max up to high workloads is largely mediated by enhanced diastolic filling. Older athletes achieve this largely by increasing the LV end-diastolic volume which eventually becomes limited by the reduction in early diastolic filling and resultant reduction in ventricular preload.⁹⁷ None the less, Molmen *et al* showed that older (72 ± 1 years) trained participants still achieve a greater maximum exercise ejection fraction (EF) compared to age-matched sedentary controls, despite there being no difference at rest.⁹⁸ In a study of young, trained endurance athletes versus controls, athletes were able to continue increasing SV in line with increasing workloads, whereas non-athletes reached a plateau.³⁵ Prolongation of diastolic filling time was the primary mechanism by which SV continued to augment.

1.5.5 Cardiovascular Adaptation Specific to Master Endurance Athletes

Studies defining the athlete's heart to date focus predominantly on younger athletes, in whom SCD would result in the greatest life-years lost. However, in endurance sports it is the master athlete who is at greatest risk of SCD whilst exercising.

For the purposes of this thesis, a master endurance athlete is defined as *an individual over the age of 35 who either trains for and/or participates in endurance events including marathon, ultramarathon, triathlon, cyclosporives or similar.*

Although adaptation in master endurance athletes is largely similar to young athletes, differences arise due to the interaction between the physiological adaptations to exercise and the cardiac effects of ageing. Few studies have examined cardiovascular adaptation specifically in master athletes. Our own experience demonstrated an up to 15% greater end diastolic volume and 9.9% greater LV maximal wall thickness (MWT) in master endurance athletes compared to non-athletic controls.⁶ From a functional perspective LV ejection fraction (LVEF) was unchanged, however, SV was increased as were indices of diastolic function.⁶ Compared to young athletes, master endurance athletes generally show a greater increase in LV MWT and left atrial (LA) cavity size and a smaller increase in ventricular cavity size.⁶ Baldi *et al* reported wall thicknesses of 20-22% greater amongst master athletes (mean age 65 years) compared with age-matched controls, but only 5% greater in young athletes⁹⁹ and Grimsmo *et al* showed LA size exceeding 80% of the normal range in some master endurance athletes.¹⁰⁰ The lesser magnitude of LV cavity dilatation demonstrated in master athletes is likely to be determined by the inability to exercise as intensively with increasing age, reduction in left ventricular preload, and the age-related decline in

myocytes; whereas the increased LV afterload, due to reduced compliance in the aorta, explains the greater LV wall thickness and LA cavity size, compared to young athletes. The LV geometry of the male master endurance athletes has been examined in one study by Dores *et al* who identified a prevalence of eccentric hypertrophy of 28%, concentric remodelling of 15% and concentric hypertrophy of 8.1% with a higher intensity and volume of exercise associated with an increased likelihood of remodelling.¹⁰¹ Comparing this to the younger cohort (21.8 ± 5.7 years) study by Finocchiaro *et al*,⁹⁵ the prevalence of concentric remodelling (15 vs 6%) and concentric hypertrophy (8.1 vs 4%) were at least twice as high in the master athlete population consistent with findings of increased LV MWT in the master athlete.

1.5.6 De-training Effects

Studies of detraining in lifelong endurance athletes show a degree of regression of cardiac cavity dimensions, and LVH, although some athletes reveal a persistently increased LV mass, cavity size and LA diameter. Pelliccia *et al* examined endurance athletes (mean age 35 ± 15 -49 years) between 1 and 13 years after detraining and reported that LV cavity dimensions failed to normalise in 50% of athletes, more than 20% of whom had substantial persistent LV dilatation of ≥ 60 mm. Increased body weight and on-going exercise practices were thought to play a part; however, there is still some suggestion that in some genetically pre-disposed athletes, this adaptation process is irreversible; the consequences of which are unknown.¹⁰² Two studies of ex-professional cyclists (age >40 years) have demonstrated persistence of LV hypertrophy even amongst those who were retired from cycling entirely.^{103,104} Retired cyclists also revealed impaired left ventricular myocardial relaxation.¹⁰⁴

1.6 Potential Deleterious Effects of Endurance Exercise

In 490 BC, Pheidippides, an Athenian courier, is said to have run to Sparta to seek help as the Persians landed at Marathon in Greece, and subsequently from Marathon to Athens to deliver the news of the victory of the battle of Marathon. On his arrival he exclaimed 'hail, we are winners' after which he immediately collapsed and died. This was the first ever report of sudden death in a long-distance runner and marked the beginning of such events being noted and recognised in scientific circles. In 2012 Trivax and McCullough suggested prolonged strenuous exercise resulted in arrhythmogenic remodelling predisposing an athlete to a risk of SCD. They coined the effects of endurance exercise on the heart 'Pheidippides cardiomyopathy'.¹⁰⁵

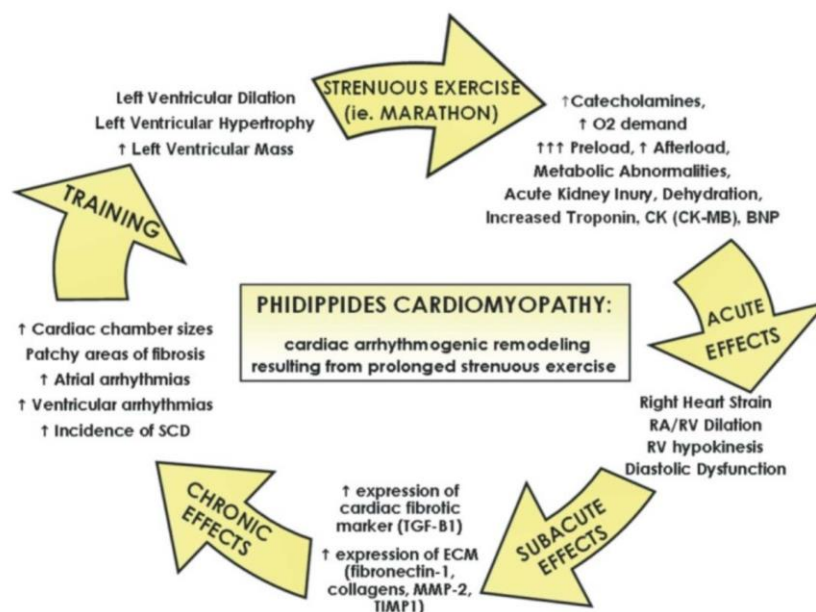


Figure 1.6 Flow diagram demonstrating the chronological features of 'Pheidippides cardiomyopathy'.¹⁰⁵

1.6.1 Exercise Dose

Despite the evidence demonstrating that overall exercise, and specifically endurance exercise, confers improved cardiovascular morbidity and mortality, there are reports to suggest a gradual decline in mortality benefit with increasing exercise dose suggesting that there may be dose beyond which exercise may have a detrimental effect on the CV system in some individuals.

The term 'exercise dose' can encompass volume (both per session and over a lifetime), intensity and frequency of exercise. As previously discussed the WHO and more recently the ESC recommend a minimum of 150 min of moderate-intensity or 75 min of vigorous-intensity or equivalent combinations of aerobic physical activity per week to accrue the cardiovascular and other health benefits of exercise.^{15,16} Individuals engaging in endurance sports exercise at levels far beyond these recommendations.

The Copenhagen City Heart Study suggested a reverse J-shaped curvilinear dose-response relationship between lifetime exercise exposure and CVS mortality, with a gradual plateau among individuals who exercise most intensively; (figure 1.7) by studying healthy joggers (n=1098) and non-joggers (n=3,950)¹⁰⁶ Joggers were grouped into light, moderate and strenuous categories of exercise; the joggers in the strenuous category performed 4–6 times the current recommendations for exercise. The greatest reduction in mortality was observed in light joggers (HR 0.22, 95% CI 0.10–0.47), followed by moderate joggers (HR 0.66, 95% CI 0.32–1.38). Strenuous joggers (HR 1.97, 95% CI 0.48–8.14) had an increased mortality compared with these groups. However, the study was criticized for the small

number of individuals included, the low number of deaths and the large confidence intervals for the hazard ratios in the strenuous-jogger category.

The Aerobics Centre Longitudinal Study¹⁰⁷ of 55,137 individuals with a mean age of 44 years revealed that just 5–10 min of running per day at <6 mph was sufficient to reduce all-cause mortality by 38%. However, maximal benefit was gained by those running 6–12 miles per week divided over three sessions at a pace of 6–7 mph.¹⁰⁷ Running more than six times per week at a pace of >8 mph and accumulating >20 miles per week conferred no incremental reduction in mortality compared with running one to three times per week at 6–7 mph and accumulating 6–12 miles per week. Further analysis of runners in the highest tertiles of exercise (31–49 MET hours per week) suggested a decline in the trend for a reduction in cardiovascular and all-cause mortality when compared with non-runners, although no upper limit at which exercise became detrimental was demonstrated.¹⁰⁸

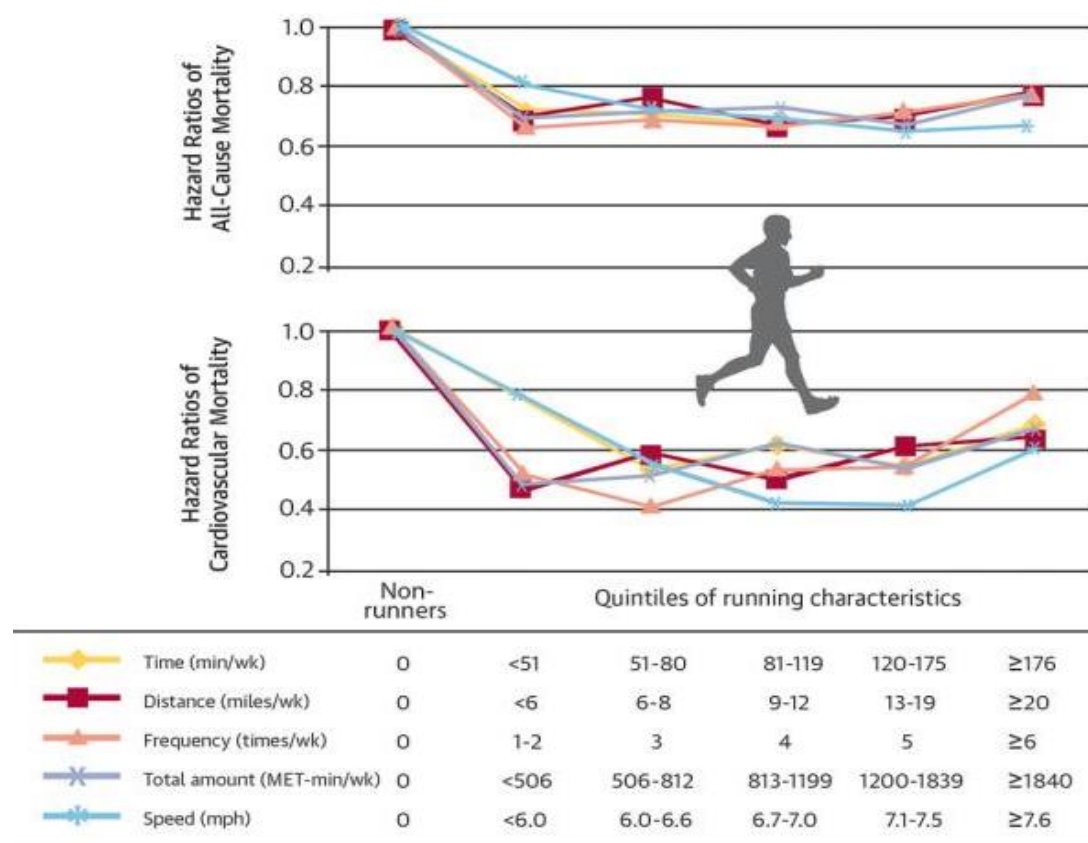


Figure 1.7 Reverse J-shaped Curve of Exercise Dose and All-cause and Cardiovascular Mortality Risk.¹⁰⁷

Several studies have attempted to define a threshold ‘dose’ of exercise at which the cardiovascular morbidity and mortality benefits are optimized. A meta-analysis by Kyu *et al* consisting of a follow-up of 149-million-person years, revealed that the ideal dose of exercise was 3000 MET mins per week i.e., 4 times the current recommendations¹⁰⁹. Other smaller studies concur that the threshold lies around 3–5 times the current minimum recommendation,^{64,110} however, much larger studies with higher mortality rates are required to substantiate this concept.

1.7 Adverse Cardiovascular Findings in Master Endurance Athletes

Animal studies in rats subjected to an enforced endurance training programme have shown raised levels of biomarkers of fibrosis, increased cavity size, fibrosis of the atria and RV, and inducible ventricular arrhythmias (VA), compared with sedentary rats.^{111,112} Observations in human subjects following mass endurance events include a transient rise in serum biomarkers of myocardial damage, temporary RV, and to a lesser extent LV systolic dysfunction, and impaired myocardial relaxation (figure 1.8). It is speculated by some that such observations represent transient myocardial inflammation and such repetitive insults may result in myocardial scar, adverse cardiac remodelling a propensity to cardiac arrhythmias and SCD.^{113,114}

Several reports also reveal persistent RV dysfunction and an increased prevalence of coronary atherosclerosis, MF and atrial fibrillation (AF) in a small proportion of ostensibly healthy master endurance athletes.¹¹⁵

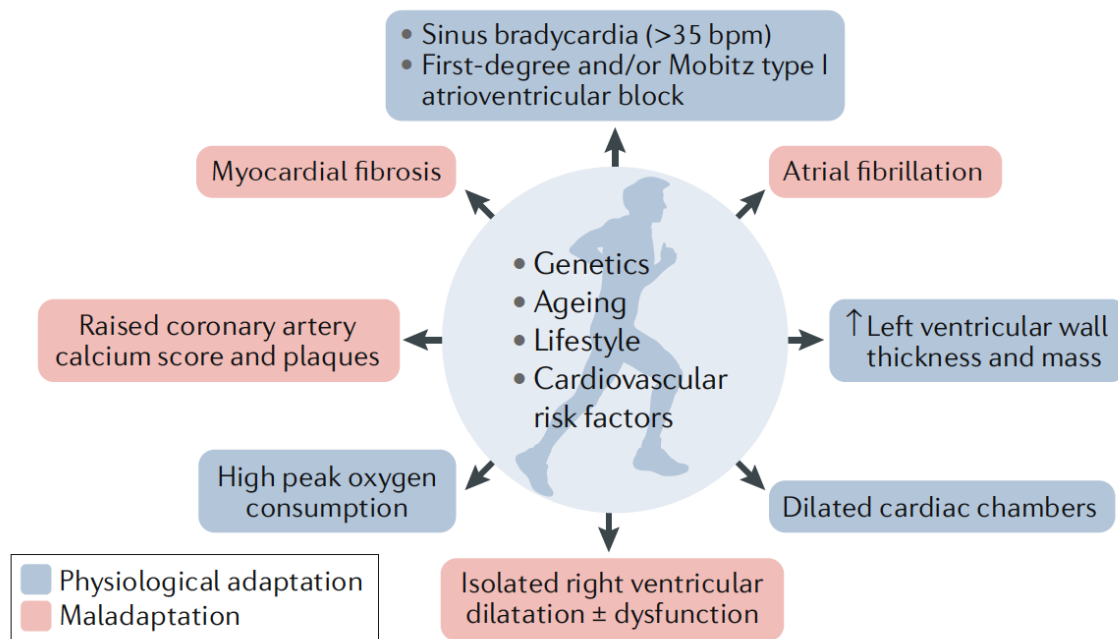


Figure 1.8 Diagram illustrating factors considered key physiological (blue) and potentially pathological adaptations (red), amongst male endurance athletes.¹¹⁵ Key factors

determining these changes include genetics, age, lifestyle and underlying CVS risk factors.

Amongst the abnormalities detected in male master endurance athletes, the greatest body of evidence exists for the association between lone AF and chronic endurance exercise, with an up to 5-fold increased risk in individuals actively participating in these sports.¹¹⁶

The culmination of these adverse findings has called for further research into the potentially deleterious impact of chronic endurance exercise on cardiovascular morbidity and mortality.

1.7.1.1 Acute Cardiac Effects of Endurance exercise

1.7.1.1.1 Biomarkers

Intensive endurance exercise is associated with a transient rise in circulating levels of biomarkers of cardiac damage, including B-type natriuretic peptide (BNP) and troponin.

BNP is raised in up to 77% of exercise participants¹¹⁷ and believed to be a marker of myocardial damage or impaired cardiac function. Sahlen *et al* demonstrated that the best predictor of post-event BNP was pre-event BNP, suggesting their determinants were the same. In addition, they identified that 2.2% of athletes with a raised BNP had serious CVD.¹¹⁸

Troponin is acutely raised in around half of marathon participants and can reach levels consistent with acute MI;¹¹⁹ however, the pattern of rapid rise and fall in serum troponin levels detected is not consistent with the usual pattern observed in the context of MI, suggesting an alternative physiological process (figure 1.9). A study of athletes participating in a 91km cycle race demonstrated that only those athletes found to have obstructive CAD angiographically had a persistent troponin rise 24 hours post-event.¹²⁰ Two further studies have demonstrated that the type of troponin molecule released following exercise is not the same as in acute MI.^{121,122} It has also been demonstrated that troponin levels are higher amongst inexperienced runners. This may be a reflection of higher CAD risk but equally this may be explained by the major determinant of troponin level being cardiac workload, as measured by intensity, and to a lesser extent, exercise duration.^{123–125}

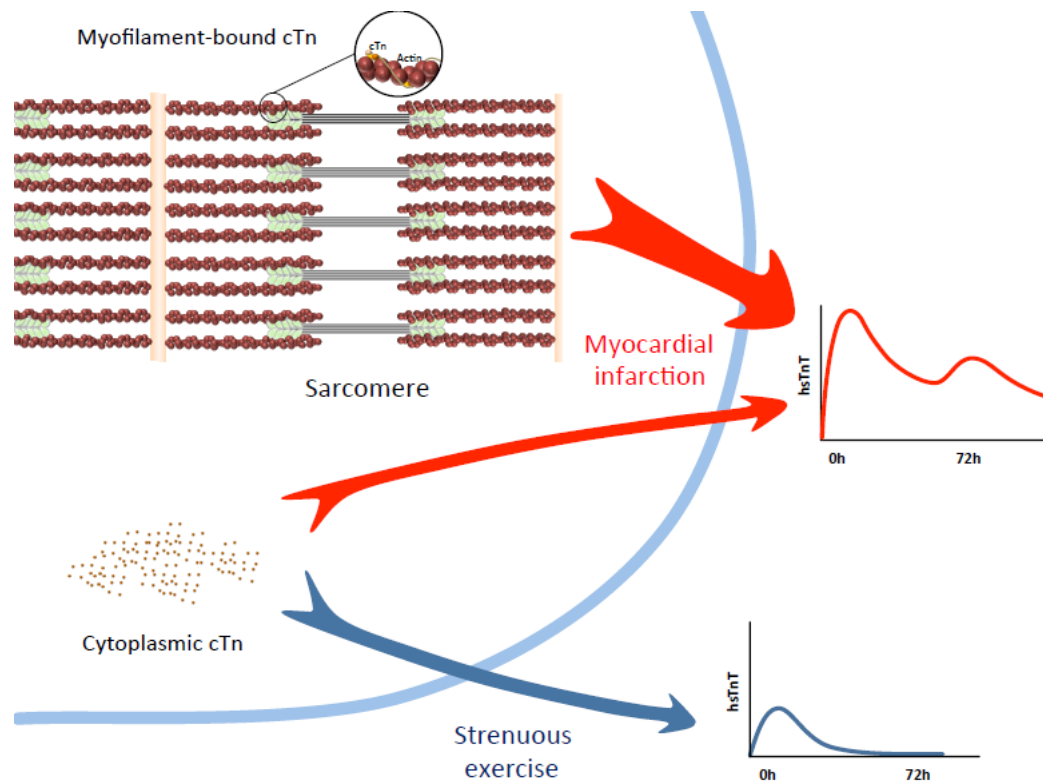


Figure 1.9 Schematic of troponin release after MI versus endurance exercise.¹²⁶ Different mechanisms of troponin release between after MI and endurance exercise and the consequent profile of troponin elevation and clearance.

Studies evaluating the acute effects of raised levels of cardiac biomarkers in association with endurance exercise, have shown inconsistency in the correlation between troponin leak and abnormalities on functional imaging, to suggest a deleterious physiological effect.^{113,127}

Neilan *et al* demonstrated in 60 non-elite Boston marathon runners with post-race raised biomarkers (including troponin and BNP), more diastolic dysfunction, increased pulmonary pressures, and RV dysfunction.¹²⁸ La Gerche *et al* demonstrated a correlation between BNP and troponin I and echocardiographic LV strain measures;¹¹⁴ however, correlation does not prove causation. Other studies have failed to demonstrate any such relationship.^{117,129} A

CMR study performed post endurance event in athletes with persistently raised serum troponin concentrations (up to 3 days), did not reveal any evidence of myocardial oedema or LGE to suggest myocardial inflammation or damage¹¹³ A further small study of 17 endurance athletes with troponin levels above the cut-off level for MI also found no evidence of myocardial inflammation on CMR.¹³⁰ By contrast, Gaudreault *et al* reported myocardial oedema and decreased LV function and perfusion in 20 runners immediately after a marathon, with more pronounced abnormalities in less-trained runners.¹³¹

There are several proposed mechanisms for raised serum troponin associated with intense exercise. The most feasible is that mechanical and oxidative stress and electrolyte shifts associated with acute endurance exercise cause cellular wounds, consequently increasing membrane permeability, with leakage of unbound troponin.¹³² Aengevaeren *et al* speculated that the finding of increased mean myocyte diffusibility identified on CMR in athletes, which correlated with troponin, provided evidence for this mechanism.¹³³

Alternative proposed mechanisms include increased degradation of troponin complexes and release of membranous vesicles secondary to ischaemia and increased cardiomyocyte apoptosis, necrosis and cell turnover.^{134,135}

Aengevaeren *et al* published the only noteworthy study of raised troponin levels amongst endurance event participants and subsequent mortality. In a cohort of 725 individuals walking 30-55km (mean age 66 years), they detected 9% of participants with a troponin level above the 99th centile and a 27% prevalence of an all-cause mortality and MACE composite end-point amongst these participants, compared to 7% with a troponin below the 99th centile, at 43-month follow up, suggesting that elevated troponin in the context of

endurance exercise is not a benign phenomenon and indeed a marker risk of future mortality and MACE.¹³⁶ However, the small numbers and limited follow-up period in this preliminary study are too small to draw any clinically meaningful conclusions. Furthermore, the individuals with raised serum cardiac troponin were considerably older, heavier and had more established risk factors for CAD compared with individuals without raised troponin. No study to date has demonstrated causation between cardiac biomarkers and long-term deleterious cardiac effects.¹¹⁷ Overall, the association between cardiac troponin levels, acute changes in cardiac structure, long-term damage and the impact on morbidity and mortality remains speculative, with further research needed.

1.7.1.1.2 Structural Changes

Several small studies have examined the acute changes in cardiac structure and function associated with endurance exercise. Studies suggest a 6-hour threshold at which endurance athletes develop abnormal parameters of LV function. These include impairment of EF, LV strain, twist, tissue doppler parameters and diastolic function, all of which contribute to the reduction in SV observed.^{114,137–139} This finding was originally attributed to changes in loading conditions resulting in reduced circulating volume and increased flow to the skin for thermoregulation.¹⁴⁰ However, this was subsequently disproved when a reduction in SV was demonstrated despite preserved blood volume. This led to the first description of exercise induced cardiac fatigue (EICF) represented by an acute reduction in myocardial contractility in conditions of intense prolonged endurance exercise.¹⁴¹ These abnormalities of LV function largely resolve within 24-48 hours of cessation of exercise.¹⁴² A meta-analysis of 23 studies including 372 athletes, demonstrated a reduction in LVEF immediately following endurance exercise, affecting in particular, highly trained athletes participating in ultra-

endurance (4%) and 'untrained' runners performing moderate duration exercise (5.5%).¹⁴³ Further analysis of the dose-response effect has identified that highly trained athletes and those exercising over longer distances, have more significant impairment of LV systolic function.^{137,138} Some studies have reported that the RV is more significantly dilated and impaired than the LV in the period immediately after exercise.^{144,145} Echocardiography performed in 14 runners immediately after a 163 km mountain race showed increased RV dimensions and reduced RV fractional area change, but preserved LV systolic function.¹⁴⁶ In another study, echocardiography performed on 40 athletes participating in an ultra-triathlon showed that RV function was impaired for up to 1 week after the event, whereas LV systolic function was preserved.¹⁴⁷ Levels of BNP and troponin I were also correlated with the RV dysfunction.

There are a number of proposed mechanisms for EICF; however, a combination of factors is likely at play. Prolonged exposure to high levels of catecholamines may reduce cardiac beta adrenoceptor sensitivity and thus reduce function, as well as the oxidative stress of exercise causing direct cardiomyocyte damage. How these abnormalities translate in terms of long-term sequelae in the context of chronic repetitive insults remains unknown.

1.7.1.2 Long-Term Cardiovascular Abnormalities

There are a growing number of life-long endurance athletes revealing cardiac abnormalities that include CAD, MF, RV dysfunction and atrial and VAs, the consequences of which are unknown.

1.7.1.2.1 Coronary Artery Disease

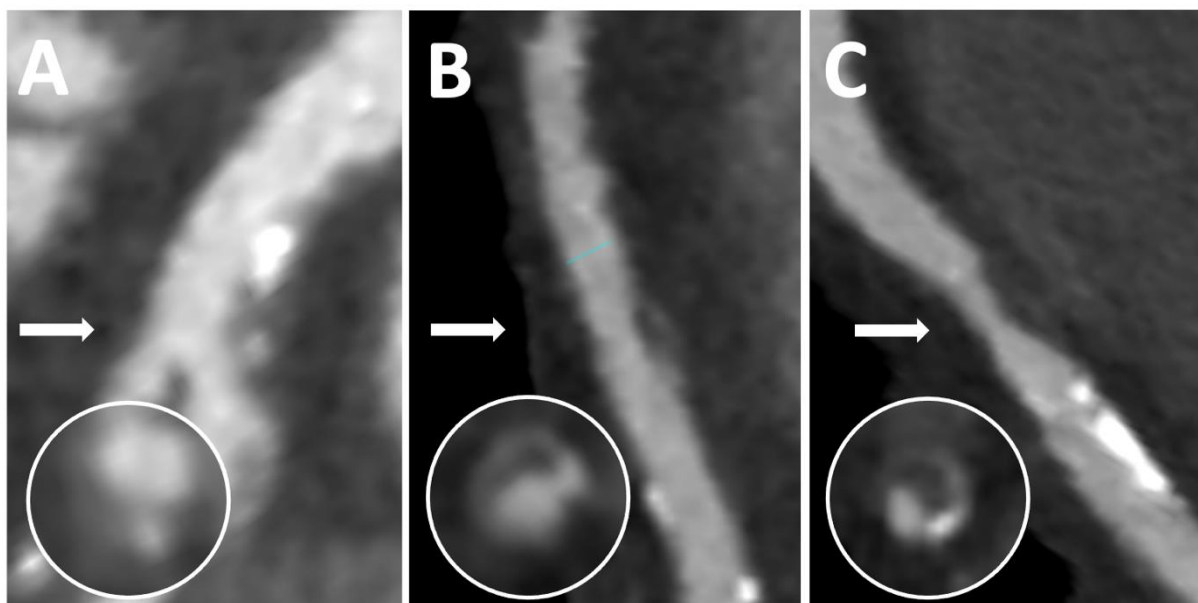
1.7.1.2.1.1 CT Evaluation in Athletes

CAC scoring is the first of two computed tomography (CT) imaging techniques currently used to identify coronary atherosclerosis in athletes. The CAC score is a surrogate for atherosclerotic volume, a strong predictor of future adverse coronary events and a powerful adjunct to conventional CVD risk factors used in coronary risk stratification in the non-athletic population.^{148–150} It is therefore used for intensifying therapy when CVD risk factors are identified. The CAC score, measured in Agatston units (AU), is achieved by quantifying the volume of calcium above a certain density (>130 Hounsfield units (HU)) within the coronary artery wall. Despite the strong correlation between CAC score and burden of atheroma, as the calcified plaque density increases the CVS risk is in fact reduced.¹⁵¹

CT coronary angiography (CCTA), is the second CT technique used to evaluate the coronary arteries and offers greater disease characterisation, providing an incremental benefit alongside CAC¹⁵² CCTA permits identification of the number, location and morphology of plaques, identification of high-risk plaque features, quantification of PCAT, a marker of coronary inflammation and quantification of stenotic disease. Plaque morphology is characterised as calcified, partially calcified and non-calcified, with non-calcified predisposing to the highest risk of plaque rupture. Specific features within each plaque that are associated with a higher risk of rupture include 'spotty' calcification (presence of lesions <4mm in length and containing an arc of calcification <90°), 'napkin ring' sign (high-attenuation around a coronary plaque with attenuation of the ring higher than those of the adjacent plaque and no >130 Hu, suggesting a thin fibrous cap), low attenuation plaque (LAP) (quantified as <30 HU) and positive remodelling (compensatory expansion of the

vessel outer wall and lumen due to atherosclerosis) (figure 1.10); all these high-risk features being predictive for major adverse cardiovascular events (MACE) in the general population,¹⁵³ with LAP representing the strongest predictor amongst them.¹⁵⁴

Figure 1.10 CCTA Images of Plaque Vulnerability Markers Including (A) Plaque Rupture (contrast pool within plaque) (B) Positive remodeling and low attenuation (C) Napkin ring sign and spotty calcification on CCTA.



PCAT is a novel non-invasive CT marker of coronary inflammation and predictor of high-risk coronary lesions which provides risk stratification in addition to plaque vulnerability data, given that there is only a 3% overlap in the predictive power of PCAT and plaque vulnerability markers.¹⁵⁵ Pro-inflammatory cytokines in the arterial wall signal the peri-coronary adipose tissue, inhibiting local adipocyte lipid accumulation which in turn stimulates angiogenesis in the coronary lumen.¹⁵⁶ Inhibition of adipose lipid accumulation shifts the CT attenuation of this tissue from a more negative lipid dense state to a less

negative, aqueous state.¹⁵⁵ The cut off value for PCAT that predicts all cause and CVS mortality is ≥ -68.2 HU.¹⁵⁵

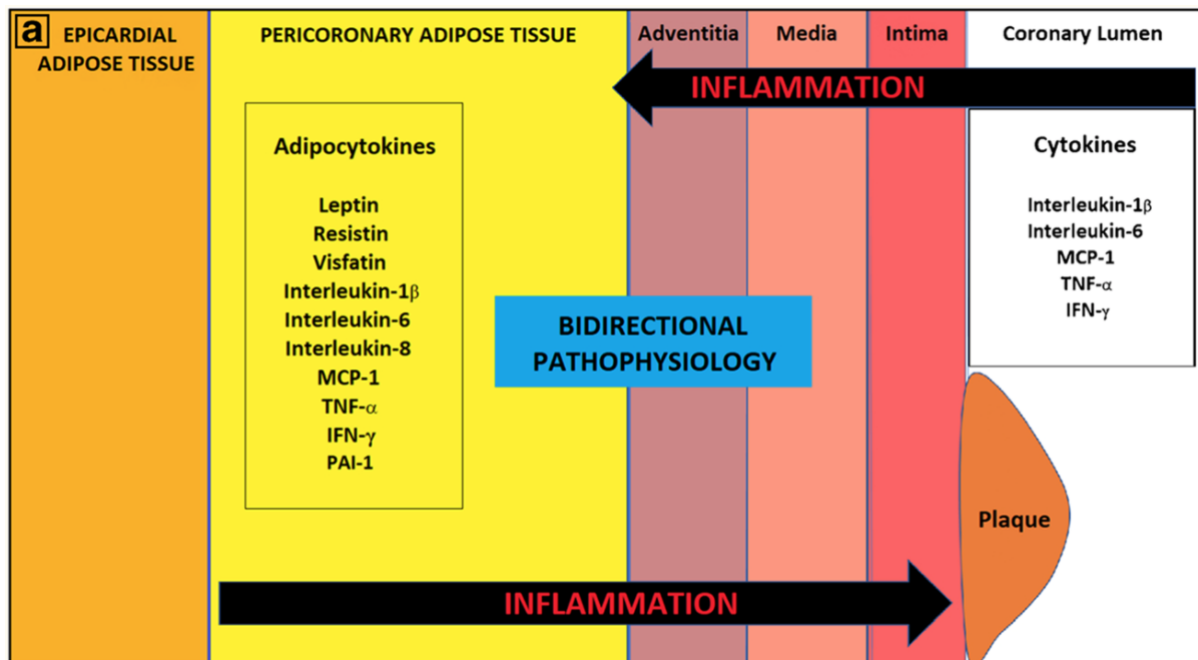


Figure 1.11 Demonstrating the bidirectional inflammatory signalling between the coronary

lumen and peri-coronary adipose tissue.¹⁵⁶ Inflammatory cytokines excreted into the coronary lumen send signals outwards to the peri-coronary adipose tissue, stimulating the release of adipocytokines which in turn drive the inflammatory response in coronary plaque, rendering them more prone to rupture and thus predisposing the individual to acute coronary syndrome (ACS).

The main limitation of CCTA is its spatial resolution, which results in over-reporting of the severity of stenotic lesions, the inability to identify vulnerable thin-capped plaques, and differentiate between medial and intimal calcification.

Despite the reduction in atherosclerotic risk strongly associated with endurance exercise, male master endurance athletes have a higher prevalence of high CAC scores (>100 AU) on CCTA compared with age and CVS risk matched controls.^{6,157,158} In a study of 108 ostensibly healthy male athletes aged 50-72 who had run at least five marathons, a CAC score of >100 AU was reported in almost one third of athletes.¹⁵⁸ Marathon runners had a median CAC score threefold higher than that of age and Framingham-matched controls.¹⁵⁸ It is noteworthy however, that the cumulative CVS risk may have been underestimated as more than 50% of athletes were ex-smokers, whom may have only taken up exercise in later life. In the Measuring Athlete's Risk of Cardiovascular events (MARC) study of 318 middle-aged, male endurance athletes with a predominantly low ESC risk score, >50% had CAC, and 16% had a CAC score >100 AU.¹⁵⁹ Merghani *et al* compared 152 master endurance athletes (aged 54.4 ± 8.5 years) with a low Framingham risk score (FRS) who had exercised for a mean of 31 ± 12.6 years, versus 92 controls of a similar age and with a similar FRS.⁶ Almost 20% of male athletes had a CAC score >100 AU, and 11% had a CAC score >300 AU, compared with none of the male controls. The lower prevalence in the more contemporary cohorts is likely due to the lower overall CVS risk of the athletes. Male athletes had twice the number of coronary plaques compared with male controls (44% versus 22%) and a greater proportion of morphologically stable atherosclerotic plaques i.e., calcified plaques, and therefore, less prone to rupture (72% versus 31%; $P < 0.001$).⁶

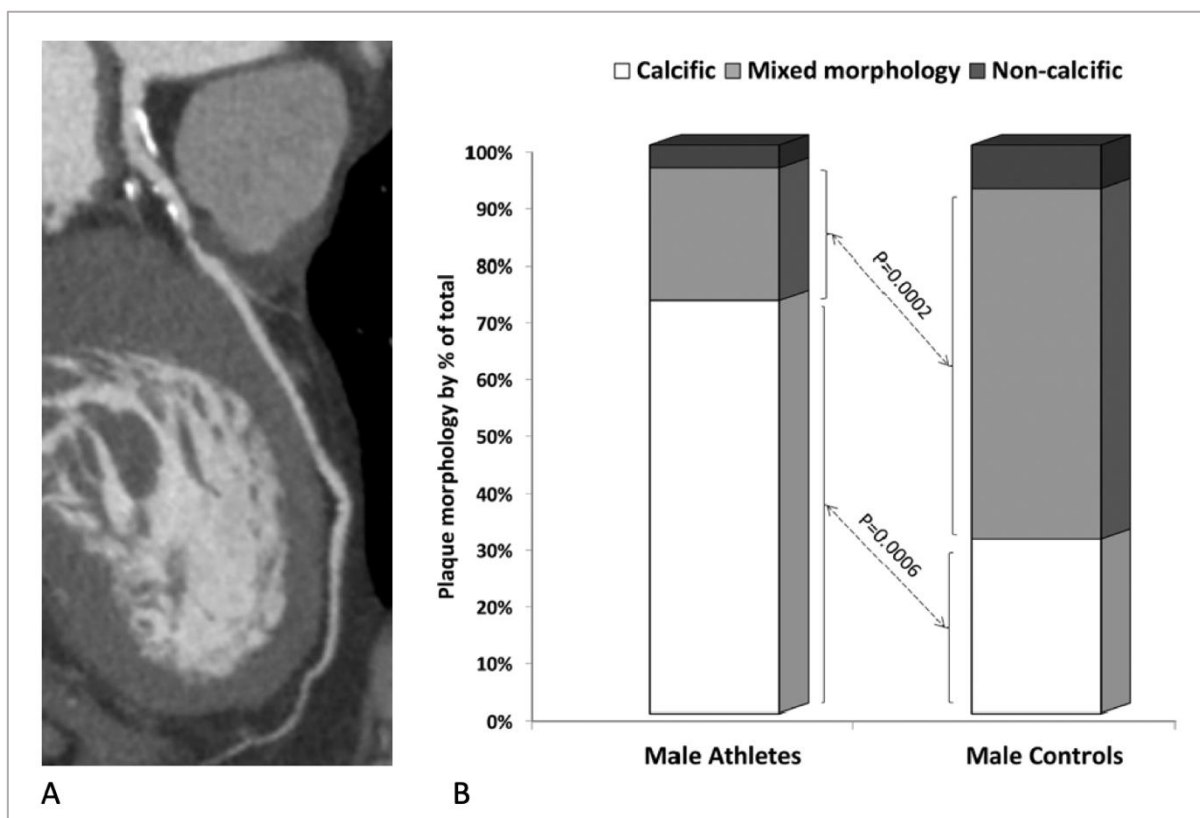


Figure 1.12 (A) CCTA demonstrating partially calcified plaque in the LAD in a male master endurance athlete participant. (B) Data from a study by Merghani *et al* showing a breakdown of coronary plaques according to plaque morphology i.e., calcified, partially calcified and non-calcified, demonstrating a greater prevalence of calcified disease amongst athletes.⁶

The MARC study investigators used their data to evaluate the relationship between coronary atherosclerosis and exercise dose (MET-minutes/week) in 284 men. Athletes were categorised as exercising for <1000, 1000 to 2000, or >2000 MET-minutes per week. Athletes with the highest dose of exercise had a significantly higher prevalence of abnormal CAC scores and more atherosclerotic plaques, but equally had the greatest proportion of calcified morphology (as opposed to, partially calcified and non-calcified) plaques.⁷

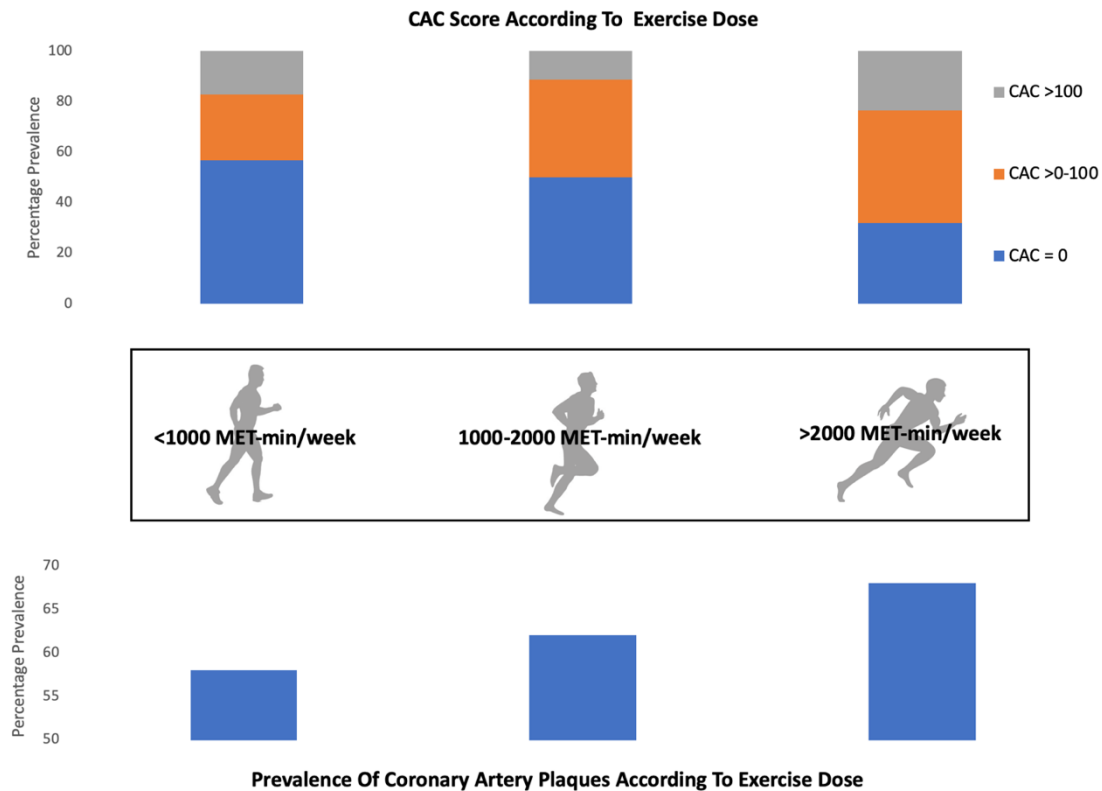


Figure 1.13 Key findings of the study of coronary atherosclerosis and exercise dose by the MARC study investigators; demonstrating higher CAC scores and greater prevalence of coronary plaques, as exercise dose increases.

The relationship of both exercise dose and sporting discipline to CAD will be further explored in chapter 4.

1.7.1.2.2 Mechanisms of Coronary Atherosclerosis

There are several proposed mechanisms to explain the development of predominantly calcified atherosclerotic coronary plaques amongst male master endurance athletes; however, overall, it remains largely unknown. The currently proposed mechanisms of vascular calcification in the general population are complex and also poorly understood;

however, it is recognised that there are 2 distinct types of calcification occurring in the coronary artery wall in adults that differ both anatomically and physiologically.

The first type is intimal calcification which occurs at the site of pre-existing atherosclerotic plaques, that are vulnerable to rupture, resulting in an ACS. Plaques undergo a process similar to endochondral ossification and consequent lamellar bone formation.⁴⁸ The second type of calcification arises in the medial layer of the artery wall and occurs independent of any atherosclerosis, as part of the process of arteriosclerosis, also known as 'Monckeberg's sclerosis'¹⁶⁰. It is commonly recognised in conditions including diabetes mellitus, chronic kidney disease and ageing, secondary to smooth muscle cell oxidative stress and apoptosis. Medial calcification increases vascular stiffness but does not pose any risk of rupture or thrombosis.

Current CCTA sequences cannot differentiate between intimal and medial calcification¹⁶¹ and therefore medial calcification must be considered a possibility in explaining the finding of increased calcification in athletes as it purports very different prognostic implications.

The Structure of an Artery Wall

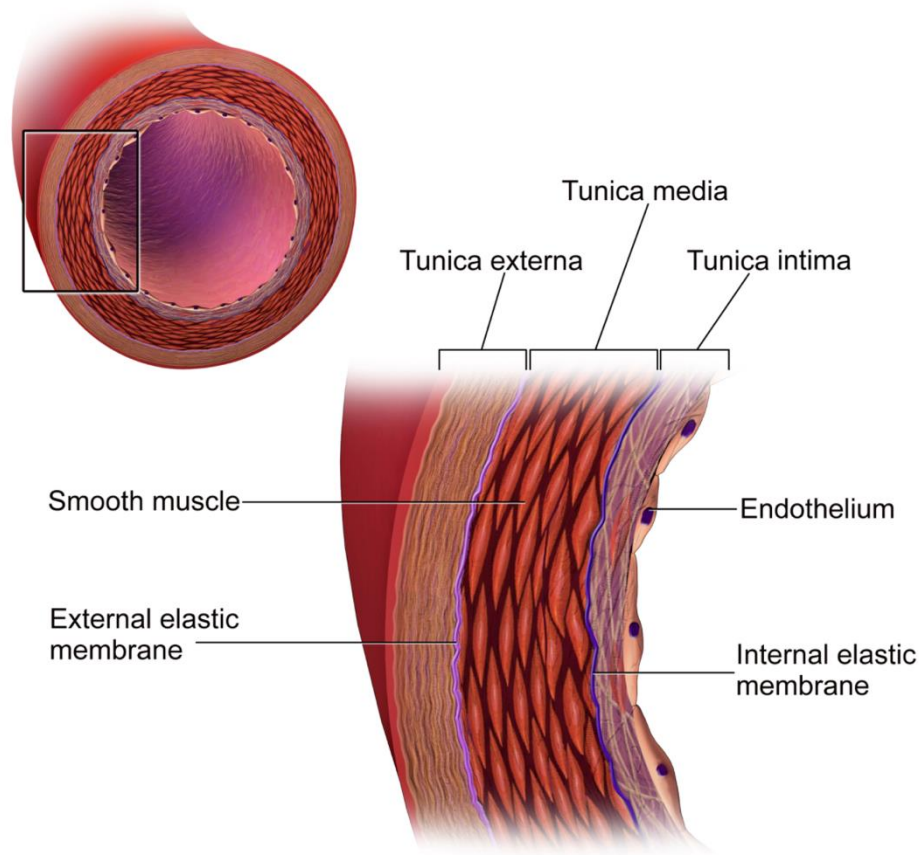


Figure 1.14 Summary image of the layered anatomy of the coronary artery wall.¹⁶² The 2 anatomical sites of coronary calcification formation i.e., tunica media and intima are indicated.

Exercise may be directly responsible for the increased prevalence of CAC amongst master endurance athletes. It is known that atherosclerosis has a predilection for forming at artery branch points where there is a disruption of laminar flow and it has been proposed that the prolonged and repetitive mechanical stress from flexing of the epicardial coronary arteries during vigorous cardiac contraction further disrupts laminar flow. This, compounded by a significant rise in systolic BP and the acute inflammatory response provoked during exercise,^{163–165} may result in damage to the endothelium, which when accompanied by

inadequate recovery, and therefore healing time, could result in formation of calcified atheroma.^{6,158,166} Another proposed explanation for increased calcification in endurance athletes may be as a sequelae of silent plaque rupture, a phenomenon that may be more common amongst this cohort due to effective ischemic pre-conditioning.¹⁶⁷ The chronic anti-inflammatory effects of endurance exercise may also contribute to the accelerated calcification of pre-existing coronary plaques, such as has been demonstrated with statin drugs.^{168–171} Finally, the presence of increased parathyroid hormone levels, recognised in some athletes,¹⁷² and genetic predisposition are also potential contributors to the presence of CAC in males master endurance athletes.

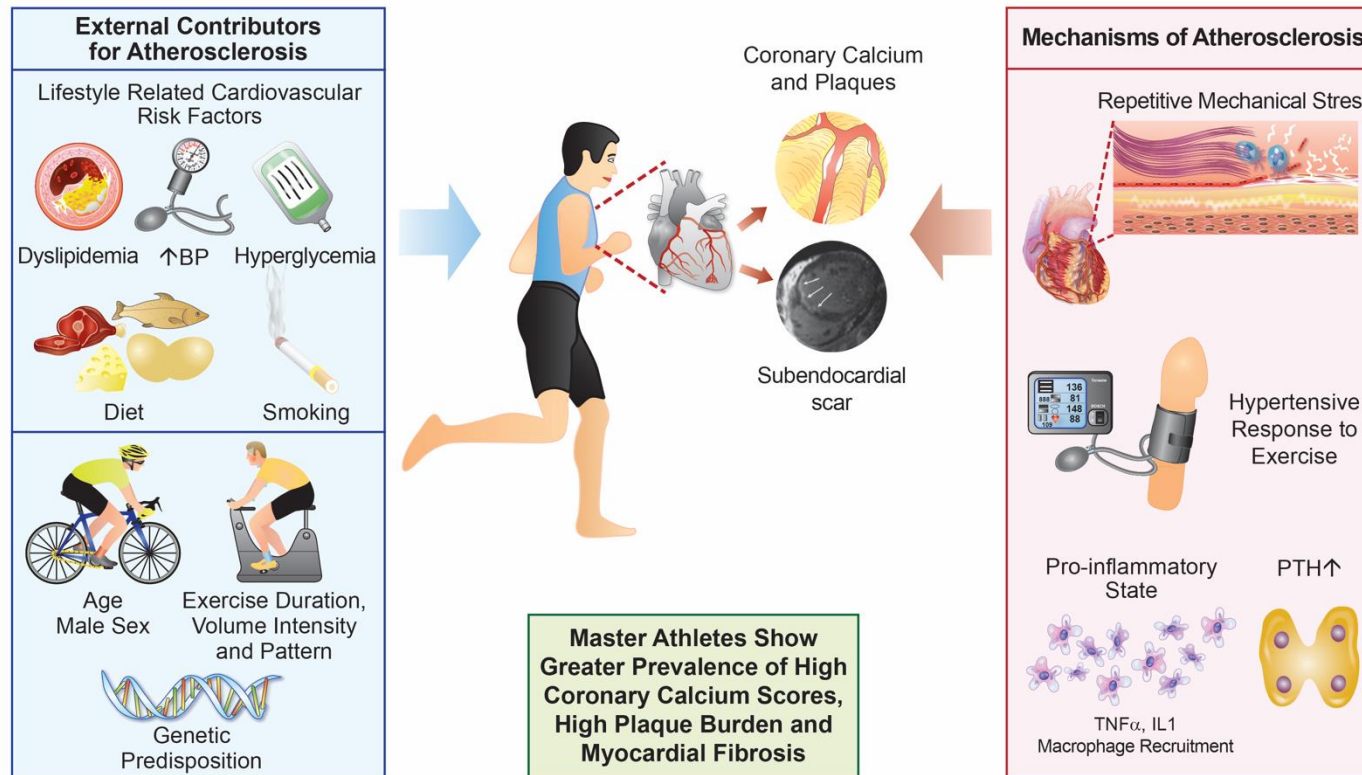


Figure 1.15 Summary of proposed contributory factors, mechanisms, and consequences of chronic endurance exercise.¹⁷³ Life-long middle-aged male endurance athletes demonstrate increased prevalence of high CAC scores and coronary plaques. Contributing factors include genetic predisposition, ageing, exercise dose and recognised CVS risk factors. Additionally, exercise is associated with mechanical flexing of the arteries, coronary inflammation and some athletes demonstrate a hypertensive response to exercise. Consequences for some include ischaemic scar and increased risk of VAs; however, longitudinal studies are necessary to investigate this further.

Assuming that exercise does increase the extent of intimal calcification and thus overall lesion density, the traditional CAC score may overestimate the burden of atheroma in endurance athletes and thus equally overestimate the prognostic significance of such calcification compared to the general population, upon which the scoring system and its interpretation is based.

Some athletes demonstrate non-calcified coronary plaque on CCTA. Lin *et al* found 4 athletes out of 8 who underwent CCTA before and after participating in the race across America had an increase in non-calcified plaque volume after compared to before the race and a concomitantly raised highly sensitive C-reactive protein (hs-CRP); all of whom also had pre-existing coronary atherosclerosis and risk factors, provoking questions with regards to the impact of acute exercise on non-calcified coronary plaque.⁵⁸

Some further findings amongst athletes that may stabilise coronary plaques include increased collagen and elastin plaque content, increased thickness of the fibrous cap and a reduction in necrotic area size and overall plaque burden,¹ therefore even those with non-calcified plaques on CCTA may not carry the same prognostic risk as in the general population.

As demonstrated, there are several potential differences between the pathophysiology and progression of CAD in athletes compared with the general population, which may limit the interpretation of conventional markers in terms of risk and prognosis. Guidelines currently recommend the same management as for the general population, highlighting the urgent need for more informative data in this area.

1.7.1.2.2.1 Prognostic Significance of CAD

The long-term outcomes of athletes with CAD are unknown; however, medium-term studies indicate a favourable prognosis. The Cooper Centre Longitudinal study evaluated CRF, CAC score and MACE over an 8.4-year follow-up period in a cohort of 8,425 men.¹⁷⁴ Higher CRF attenuated the risk of CVS events when adjusted for CAC score. For each 1-MET increase in CRF (across all CAC scores and adjusted for risk factors), the CVS event rate was reduced by 11%.¹⁷⁴ Although highly active men who performed >3,000 MET-min of exercise per week were more likely to have CAC, there was no associated increase in all-cause mortality compared with those who performed <1,500 MET-min of exercise per week.¹⁷⁵ These data suggest that higher levels of CRF diminish the prognostic significance of a raised CAC score.

1.7.1.2.3 Myocardial Fibrosis

Male master endurance athletes have a greater prevalence of MF than controls.⁶ Currently the standard techniques for the detection of MF using CMR include LGE for focal fibrosis, T1 mapping for diffuse fibrosis and extracellular volume for quantifying the amount of fibrosis. Fibrosis can also be diagnosed on myocardial biopsy; however, this technique is limited as it can only evaluate a few small areas of the myocardium, potentially missing areas of disease.

Studies to date have identified that seemingly healthy, male master endurance athletes engaging in marathon running or triathlons have a prevalence of MF of between 11 and 17%.^{8,9,176,177} The pattern of MF in master athletes is heterogenous, and helps determine the most likely aetiology, be that hypoxic ischaemic injury, hypertensive overload, inflammation or other. The distribution of fibrosis and likely aetiology also differs from that found in the

general population suggesting there are athlete specific factors influencing the presence, pattern, and prognosis of MF in athletes.

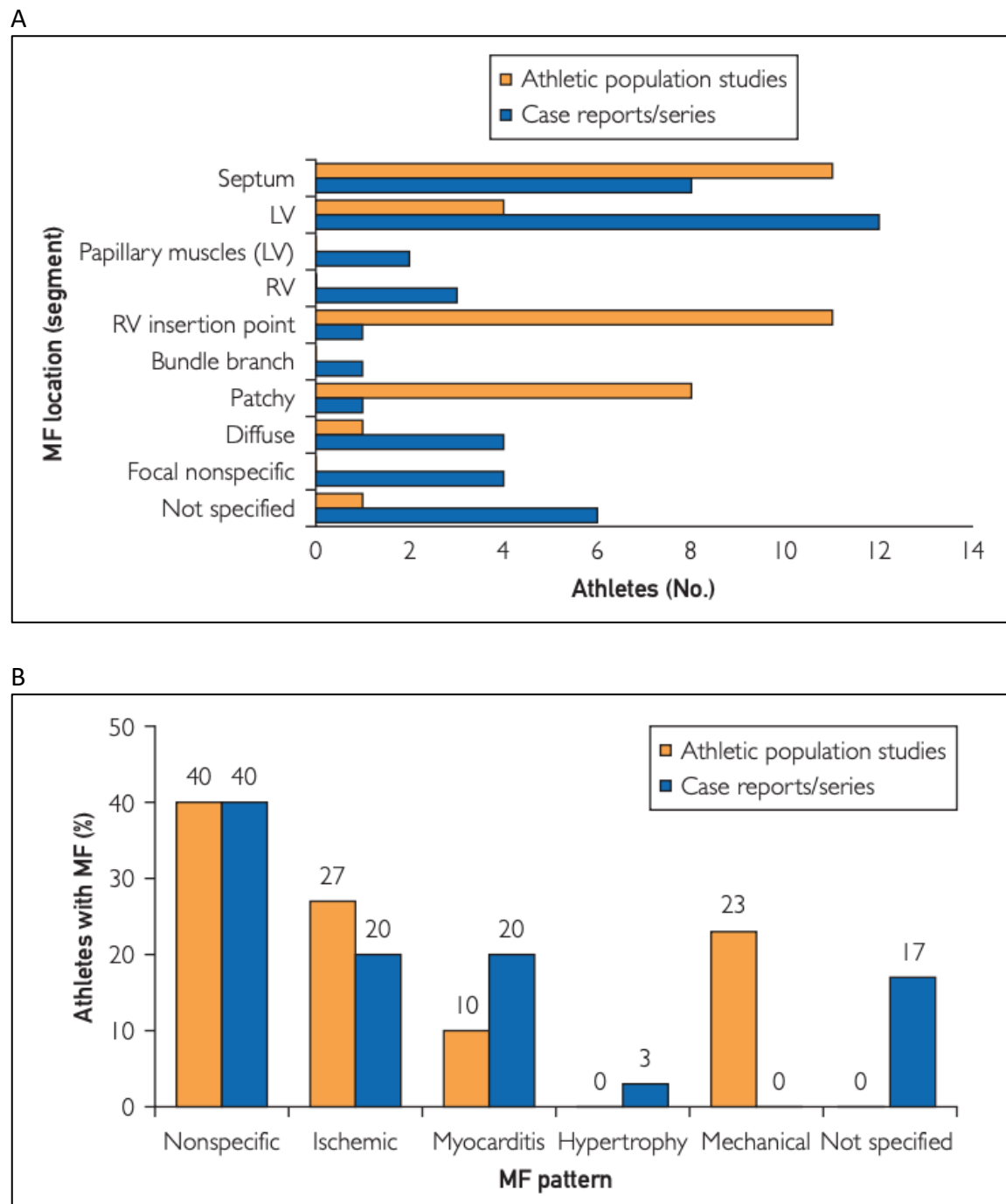


Figure 1.16 Distribution of the pattern and causes of myocardial fibrosis amongst athletic population studies and case reports/series.¹⁷⁷ (A) According to this data septal, RV insertion point and patchy fibrosis are the most common patterns seen amongst endurance

athletes. **(B)** Forty percent of MF in athletes is non-specific followed by 20-27% ischaemic and 10-20% consistent with a pattern of myocarditis.¹⁷⁷

Twenty to thirty percent of athletes have mid wall fibrosis at the RV insertion or hinge point, which is exercise dose dependent and considered a benign consequence of sustained repetitive RV pressure and volume overload, with similar findings in pulmonary hypertension. Forty percent of MF in athletes is isolated to small non-specific patchy areas,¹⁷⁷ a finding present in only 4% of the general population with no known prognosis.^{178,179} More pathological appearances, including subendocardial ischaemic and subepicardial and extensive mid-wall fibrosis account for 20-27% and 10-20% of MF patterns in athletes respectively, and are considered pathological until evidence suggests the contrary.^{8,177} A small number of athletes also show diffuse fibrosis as detected by native T1 mapping and ECV.

Merghani *et al* identified focal MF on cardiac MRI in 14.2% (n=15) of male master endurance athletes compared with none of the controls, of whom one third revealed fibrosis compatible with previous MI. Of the athletes with scar compatible with MI only half had a stenosis in the relevant coronary artery and in each case the stenosis was <50%. This finding suggests that master athletes may sustain sub-clinical MI from demand ischaemia, micro-emboli due to the pro-coagulant nature of exercise and coronary spasm, in addition to plaque rupture. The remaining two thirds of athletes had fibrosis with a non-ischaemic mid-wall or subepicardial in distribution. This pattern is often characteristic of acute or healed myocarditis, possibly due to the continuation of training by athletes whilst harbouring

infections,¹⁷⁹ although an exercise-induced cardiomyopathic process also merits consideration. Breuckmann *et al* reported a 12% prevalence of MF in 102 asymptomatic male master marathon runners, compared to 4% of controls.¹⁷⁶ Five runners had a subendocardial distribution of LGE consistent with myocardial ischaemia but a greater proportion (n=7) had mid-myocardial or sub-epicardial LGE. Finally, La Gerche *et al* also found LGE in the interventricular septum of 5 out of 39 (12.8%) endurance race participants¹⁴⁷ possibly secondary to prior myocarditis, however these results have not been revealed in any other data sets.

Current limited data suggests that there may be a dose-response association between endurance exercise and MF. An increased prevalence of LGE, consistent with a non-ischaemic pattern of MF, was reported amongst 83 asymptomatic, middle-aged, competitive triathletes. Race distances, specifically longer cumulative swim and cycle distances, and a higher peak systolic BP on exercise testing were predictive of the presence of MF⁹. A further study of 12 athletes over the age of 50 years who had participated in endurance sports for at least 35 years demonstrated significantly more LGE on CMR compared to both their younger counterparts and age-matched controls. Four athletes had a non-specific pattern of MF, one had fibrosis compatible with myocarditis and another had fibrosis compatible with MI. LGE appeared to be significantly related to years of training and number of endurance events completed, with similar findings from Möhlenkamp, who found that the presence of significant LGE in marathon runners over the age of 50 was associated with number of marathons completed and a higher CAC score and percentile¹⁵⁸ which is likely to be driven by those cases with ischaemic MF which made up 42% of the athletes with LGE. Follow-up data from Möhlenkamp demonstrated 3 athletes with LGE

requiring revascularisation within a 21-month follow-up period, compared to only one athlete without LGE.¹⁷⁶ The prevalence of coronary events at 6-year follow-up was 57% amongst those with LGE versus 8% in those without,¹⁸⁰ suggesting that the presence of LGE in addition to CAC is predictive for adverse outcomes.

MF is an important finding due to its association with VAs and increased mortality in the general population.^{181,182} There is little known about the association between MF and arrhythmias in master athletes. Our, relatively limited experience of arrhythmias in male master athletes reveals that those with an ischaemic pattern of fibrosis have a higher prevalence of non-sustained ventricular tachycardia (VT) than those without (43% v 7%). Additionally, in this data set 3 of the athletes with VT revealed a $\geq 50\%$ stenosis in the left anterior descending (LAD) artery.⁶ Several published cases of SCD in master endurance athletes have reported isolated MF that is not consistent with recognised patterns of pathological fibrosis, suggesting there may be an interaction between exercise-related factors and pathology.

The arrhythmic and SCD risk associated with MF in athletes is unknown. Limited studies to date have not demonstrated any greater prevalence of VAs amongst athletes compared to controls¹⁸³ nor any direct association between MF, VAs and MACE in master athletes;¹⁵⁸ however, large longitudinal follow-up studies are warranted. One study of 7 young asymptomatic athletes with either T-wave inversion (n=4) or VAs (n=3) on exercise testing, were found to have sub-epicardial LGE (predominantly lateral wall) on cardiac MRI. Of the three athletes with non-sustained ventricular tachycardia (NSVT), 2 had a LVEF of $<50\%$ without contractile reserve on exercise. During the 3 ± 1.5 year follow up of the remaining 4

athletes with MF, two had symptomatic VT and 1 developed progressive LV dysfunction. Thus, in 6 out of 7 cases of young athletes with significant MF, its presence was associated with adverse outcomes, necessitating exclusion from competitive sport¹⁸⁴. Zorzi demonstrated that athletes with both non-ischaemic fibrosis and VAs have a greater prevalence of malignant arrhythmic events than those with arrhythmias and no fibrosis, which may imply some association.¹⁸⁵

Overall, the exploration of MF in male master athletes is limited and its characterisation and relationship to exercise dose merits further examination. Further large-scale longitudinal studies are required to investigate the precise impact of myocardial scar in athletes.

1.7.1.2.4 Exercise-Induced Right Ventricular Cardiomyopathy

The right and left ventricles are subjected to the same volume of venous return during exercise, however, the reduction in the pulmonary vascular resistance is considerably smaller than the reduction in systemic vascular resistance, resulting in an exponential rise in pulmonary artery pressure with exercise. Indeed, a >30-fold increase in RV wall stress occurs with exercise,¹⁸⁶ which might explain why some studies have shown transient dilatation and systolic impairment of the RV following endurance events. Some endurance athletes, particularly cyclists, can develop more persistent abnormalities of RV size and function that may be associated with palpitations, syncope, VAs and even aborted SCD. In a study of 46 athletes (median age 45 years) with complex RV arrhythmias, almost 25% had RV abnormalities during invasive ventriculography, nearly 50% had regional wall motion abnormalities on CMR, and almost 90% fulfilled criteria for arrhythmogenic right ventricular cardiomyopathy (ARVC).¹⁸⁷ In a further study of 27 endurance athletes with RV arrhythmias,

82% had angiographic RV abnormalities, including reduced EF and reduced fractional shortening, with 27% meeting task force criteria for ARVC.¹⁸⁸ This phenomenon is poorly understood but is often referred to as 'exercise-induced ARVC'. It has been proposed that endurance exercise may either directly result in ARVC in individuals harbouring unrecognised desmosomal mutations or unmask the condition in athletes with an otherwise quiescent genetic predilection in an epigenetic fashion. Studies of mice with mutations in genes encoding desmosomal proteins, exposed to endurance training showed either an acceleration of pre-existing RV abnormalities¹⁸⁹ or the development of new changes,¹⁹⁰ all resembling the human ARVC phenotype, whereas sedentary mice underwent no changes. Studies of human carriers of mutations in desmosomal genes have also shown earlier phenotypic manifestation of disease and an increased risk of VAs among individuals participating in vigorous and/or competitive sport.^{191,192} La Gerche *et al* tested for pathogenic variants in genes encoding desmosomal proteins in 47 athletes with complex RV origin VAs and either a possible (36%) or definitive (51%) ARVC phenotype, according to task force diagnostic criteria.¹⁹³ Only 12% of athletes had pathogenic variants associated with ARVC, compared with 40% of affected individuals from the general population. Furthermore, Sawant *et al* studied 82 individuals with ARVC, 39 of whom had pathogenic variants in genes encoding desmosomal proteins, and 43 had no pathogenic variants. Individuals without an identified pathogenic variant were more likely to be endurance athletes, had done more intensive exercise and were less likely to have a family history of the condition (9% versus 40%; $P < 0.001$) compared with athletes who had an identified pathogenic variant.¹⁹⁴ Together these studies demonstrate that the manifestation, pathophysiology and progression of ARVC amongst athletes is different and is directly influenced by exercise training. The SCD risk and prognosis associated with this abnormality

remains unknown. Given this data, individuals with pathogenic variants (even in the absence of an overt phenotype) and those with phenotypically overt ARVC are advised to cease competitive sport and pursue only light exercise.¹⁹⁵ Adhering to the current WHO/ESC recommendations for exercise does not seem to increase the risk of accelerating the severity of the ARVC phenotype,¹⁹⁴ and the risk is particularly low among individuals exercising at an intensity of <6 METS.¹⁹⁶

1.7.1.2.5 Atrial Arrhythmias

Low to moderate doses of exercise protects against AF^{116,197,198} and may confer a lower risk of developing AF in later life, through modification of CVS risk factors.¹⁹⁹ However, chronic endurance exercise training increases the risk of developing AF by up to five-fold, with men aged <60 years being at greatest risk.^{116,200} A large meta-analysis of 22 studies including a total of 656,750 individuals reported that moderate physical exercise protects both women and men against AF¹⁹⁸ however, intense exercise increases the risk of AF in men but is protective in women.¹⁹⁸ Mont *et al* identified that 63% of patients attending an AF clinic participated in regular sports compared to only 15% amongst the general population.²⁰¹

The research suggests a positive correlation between AF risk and exercise dose and intensity.^{202,203} In a study of 134 Swiss former elite male endurance cyclists and age-matched golfers, the prevalence of AF was significantly higher among the former cyclists (4% versus 0%)²⁰⁴ A cut-off duration of 1,500 lifetime-hours has been proposed as the threshold at which sporting participation increases the risk of AF.¹¹⁶

Data exploring the underlying mechanisms of AF in athletes is limited. The effect of increased vagal tone in inducing AF is thought to be the greatest contributor, and rat models suggest that this effect is secondary to increased baroreflex responsiveness and myocyte sensitivity to cholinergic stimulation.²⁰⁵ A recent small study of 20 middle-aged athletes who had exercised more than 15 hours per week for an average of 29 years, and age-matched non-athletic controls, demonstrated that athletes had not only significantly larger atria but also a greater percentage of atrial fibrosis ($15.5\% \pm 5.9$ vs $9.6\% \pm 4.9$), which is associated with increased adverse events in the general population.²⁰⁶ In addition, McNamara *et al* studied non-athletic individuals who were exposed to a 2-year high intensity training programme and although there was significant mechanical atrial remodelling, there were no non-invasive markers of electrical remodelling, implying that the development of atrial fibrosis is likely to result from prolonged repetitive exposure over many years.²⁰⁷ The interaction of high vagal tone, age, male sex, height and exercise dose as well as LA remodelling from chronic repetitive atrial stretch and atrial fibrosis, produce a sufficient substrate for some athletes to develop AF.^{208–211}

A study of 208,654 cross-country skiers provides the first insights into the risk of CVS events in athletes with AF.²¹² Female skiers had a 37% lower risk of AF than non-skiers, independent of performance and number of races completed. By contrast, the incidence of AF was slightly higher in male skiers than in non-skiers, and the number of races completed, and faster finishing times were determinants of an increased incidence of AF, implying a dose-response effect as previously described above. Overall, skiers had a 30% lower incidence of stroke than non-skiers. Skiers with AF had a greater incidence of stroke than skiers and non-skiers without AF (7.6% versus 0.6% versus 1.2%) but a lower incidence of

stroke than non-skiers with AF (9.7%).²¹² These data suggest that athletes who develop AF are at increased risk of stroke and should be treated according to conventional anticoagulation guidelines. Substantial gaps in the research of AF in athletes remain.

1.7.1.2.6 Ventricular Arrhythmias

Approximately 10% of young athletes and up to 30% of master athletes have >10 isolated ventricular premature beats (VPBs) on 24 -hour ECG monitoring.^{183,213} Several small studies suggest that the prevalence of VPB's is not greater than in non-athletes.^{183,214,215} Zorzi compared young, competitive athletes aged 16–35 years with healthy, lifelong endurance athletes aged >30 years and age-matched controls and revealed no significant difference in the number of VPBs on 12-lead, 24-hour ECG monitoring between athletes and controls, and neither age nor exercise dose had a significant effect on the prevalence of VA's.^{183,213} Conversely, there are a small number of studies demonstrating an increased prevalence of VAs in master endurance athletes; however, there remains no evidence to date of any adverse events.^{204,216} Former elite Swiss cyclists performing >4 hours of extreme exercise per week had a significantly greater prevalence of non-sustained VT (15% versus 3%) compared with age-matched golfers; however, the precise origin of the VT was uncertain from the single-lead Holter monitors.²⁰⁴ There is no data supporting an increased prevalence of adverse events associated with VAs amongst master endurance athletes with normal hearts or those with RV abnormalities, including exercise induced ARVC.^{147,194,204,214,217} There is emerging evidence suggesting that it is the morphology of VPB's that is crucial in determining their clinical significance. Most VPBs in athletes originate from the RV outflow tract or the LV fascicles, which are common sites for benign ectopy. VPB's conducting with a wide RBBB pattern and superior axis that are exacerbated by

exercise should be investigated further, because emerging reports indicate that these characteristics are associated with LV scar²¹³ and potentially greater risk.

1.7.1.2.7 Sinus Node Dysfunction

Sinus bradycardia and sinus pauses are common in endurance athletes. Suppression of the sinoatrial node owing to high vagal tone is a widely accepted explanation for this finding, although modern studies in animals suggest that a reduction in the *If* funny current channels could be in part responsible for bradycardia through intrinsic sinus node changes.²¹⁸

Evidence suggests that these *If* channel changes persist despite de-training²⁰⁴ and autonomic blockade.³⁸ These observations have led to speculation that lifelong endurance exercise might promote adverse remodelling of the conduction system through fibrotic changes that manifest in athletes with increasing age. In one study, 40% (n=20) of athletes had evidence of sick sinus syndrome on 24-h monitoring.²¹⁵ In a further study, former cyclists had a higher prevalence of sinus node disease (16% versus 2%) and greater need for pacemaker implantation for bradyarrhythmia (3% versus 0%) than relatively sedentary golfers.²⁰⁴ Finally, a study of 52,755 participants in the Vasaloppet 90 km cross-country skiing event reported that athletes who had participated in more races and had faster finishing times had a higher risk of pathological bradyarrhythmia, including sick sinus syndrome or third-degree atrioventricular block,²⁰² implying there is a possible dose–response effect pattern of sinus node dysfunction amongst endurance athletes.

1.8 Sudden Cardiac Death in Athletes

We have already established that regular physical exercise purveys a significant reduction in mortality and mortality; however, exercise can acutely increase the risk of SCD in individuals

harbouring underlying cardiac disease. The overall incidence of SCD during endurance exercise is estimated at 1 in 50,000 participants;^{12,219,220} however, this is likely to be an under-estimate due to global under-reporting. Compared with females, males have a 9:1 and 20:1 risk of SCD in competitive and recreational sports respectively.

1.8.1 Young Athletes and Inherited Cardiac Conditions

In young athletes (aged <35 years), most exercise-related SCD is attributable to inherited cardiomyopathies and channelopathies or congenital coronary anomalies.^{221–223} Until recently, hypertrophic cardiomyopathy was considered the most common cause of SCD among young athletes,^{221,222,224} although one small registry reported that ARVC was the predominant cause.²²³ However, a paradigm shift resulting from two large studies demonstrated that sudden arrhythmic death syndrome, defined as SCD in the absence of structural heart disease, was the leading cause of SCD in young athletes.^{225,226}

1.8.2 Master Athletes and Sudden Cardiac Death

SCD during endurance exercise predominantly affects middle-aged men, who constitute >40% of participants in mass endurance events.^{5,227} A study of SCD and resuscitated cardiac arrests during triathlon in the US demonstrated 85% of cases were male and SCD risk increased significantly with age. With each decade between 40, 50 and 60 years of age, the risk increased from 6.1 to 9.6 to 18.6 per 100,000 respectively. In addition, the majority (67%) of events occurred during the swim section of the race and 44% had underlying cardiac pathology at autopsy.²²⁰

CAD accounts for approximately 80% of SCD in master athletes⁵ with a high male preponderance.^{10,228,229} Exercise acutely increases the risk of plaque rupture and resultant MI by up to ten-fold.^{228,230,231} The risk of acute MI and SCD during exercise is inversely related to the amount of habitual exercise performed, and previously sedentary individuals have a 50-fold greater risk of MI and a 7-fold greater risk of SCD during exercise than individuals who have exercised habitually.^{11,228,231} However, even the most highly trained and seemingly healthy athletes are not immune from atherosclerotic-associated SCD^{228,231,232} and more than 50% of athletes victim to MIs and sudden cardiac arrests during events are free of pre-existing symptoms or cardiac disease.^{233,234}

The common endpoint in atherosclerotic related SCD is VA; however, the underlying trigger is poorly understood. The most commonly proposed mechanism is a combination of endothelial erosion resulting in plaque rupture, neuro-hormonal activation, triggering coronary vasospasm and hypercoagulability.^{10,11} However, plaque rupture is not the only mechanism by which atherosclerosis exacerbates SCD under these circumstances. In a large case series of SCD during marathons in the United States, there was no evidence of thrombus or plaque rupture found; however, many survivors had atherosclerotic plaques with marked luminal narrowing, indicating that fatal arrhythmias may also occur due to demand ischemia from subclinical coronary artery stenosis.¹² Acute electrolyte and metabolic shifts likely also contribute to lowering arrhythmia threshold and afford some explanation for the major proportion of SCD occurring in the final quarter of a marathon.

Although the acute physiological effects of exercise appear to lower the VA threshold, regular exercise training may increase it. In a study of canines with easily inducible ischemia

driven ventricular fibrillation, a 6-week exercise programme reduced the incidence of VF by 100%, likely secondary to the anti-arrhythmic effect of increased vagal tone.²³⁵

Despite the acute increase in MI risk associated with endurance exercise, it is likely that in the long term the physiological effects of endurance exercise afford a protective effect on the myocardium thus potentially attenuating the overall risk of arrhythmic cardiac arrest. These physiological effects include pre-ischaemic conditioning, lower levels of chronic inflammation and a greater vasodilatory capacity, which offers some explanation for the greater longevity amongst endurance athletes already described.

1.8.3 Performance Enhancing Drugs

The failure to disclose use of performance enhancing drugs (PEDs) by athletes introduces confusion into the understanding of the CVS adaptation to endurance exercise. Knowledge of the direct harmful impact of PEDs is limited; however, indirectly, the fact that using PEDs will permit an athlete to potentially train longer and harder with shorter recovery periods would likely affect the extent of cardiac adaptation and may also increase the risk of arrhythmias such as AF. The most data exists for anabolic steroid use which has CVS effects including dyslipidaemia, cardiac conduction abnormalities, coagulation problems including MI as well as features that overlap with hypertrophic cardiomyopathy i.e., increased myocardial mass and LV wall thickness, impairment of ventricular systolic and diastolic function and MF.^{236–240} The possibility of PED use must be considered when clinically evaluating any athlete.

1.9 Sex Differences

Female athletes tend to be smaller and have a lower muscle mass and are therefore unable to achieve the same workloads as males. As such, the adaptations to endurance exercise in the hearts of female athletes are qualitatively similar but quantitatively less than those in the hearts of male athletes.^{95,241} In studies of elite female athletes only 1% had an LV end diastolic diameter measuring >60mm compared with 14% of males,¹⁹⁵ and no females demonstrate an abnormal LVWT^{241,242} compared to males in whom up to 2% of Caucasians and 12.4% of Black athletes demonstrate an abnormal LVWT.^{90,243} Female athletes also have a lower LV mass corrected for bodyweight. The occurrence of SCD in women during exercise is also exceptionally rare,^{5,221,244} consequently, the female athlete is under-represented in research data with only a few studies of cardiac biomarkers including large numbers of women, and very few studies of CAD, MF and RV dysfunction. Recognising that adaptation is less profound in female athletes is important in order that findings are not overlooked during their clinical assessment for potential cardiac disease. However, based on the available data, female endurance athletes do not seem to exhibit the increased prevalence of CAC or MF that is observed in male athletes.^{6,176} Knowledge of the pattern of CAD specifically in the female master athlete is scant. A study of 26 life-long female marathon runners, having run at least 1 marathon per year for 10-25 years, showed a lower CAC burden and less plaques compared with controls; however, the athletes also had a lower CVS risk factor profile. Athletes with plaques tended to be older and were amongst those who had been running marathons for the most years. Jafar *et al* assessed the effect of exercise dose in 56 athletes including 19 females, over the age of 45. They found that women running in longer endurance races had higher CAC scores compared to sub-marathon runners²⁴⁵ suggesting a dose-response effect. Merghani *et al* compared 46 female

master endurance athletes with 38 non-athletic age and FRS-matched controls. There was no significant difference in CAC score or plaque morphology observed and none of the female athletes had clinically significant narrowing of the coronary arteries.⁶ In contrast to male athletes, female athletes also seem to be protected from developing AF.¹⁹⁸

The participation of female master athletes, particularly in endurance sports, is rising rapidly with female participation in the 2020 Tokyo Olympic games estimated to reach the largest proportion of any games yet at 48.8%.²⁴⁶ There is therefore a call for the scientific community to better define the physiological adaptations in this cohort and provide a molecular explanation for the differences between the sexes. It is important to highlight the 10-year lag in CVS risk seen in women compared to men up to the point of menopause, which may explain some of this difference; however, there is currently no data to support this. Comparisons between low-risk premenopausal women and age-matched men have suggested that the protective effects of oestrogen or the deleterious effects of testosterone are responsible, but further studies are needed.²⁴⁷

1.10 Screening in Athletes

1.10.1 Cardiac Screening in Young Athletes

Some young athletes have undiagnosed inherited cardiomyopathies and channelopathies as well as coronary artery anomalies that can both worsen with intense exercise and put the athlete at increased risk of SCD, particularly during intense exercise. Thus, there is a vested interest in developing a screening programme that can identify those at risk in order that effective risk management strategies can be implemented. Currently, the role of pre-participation screening in young athletes remains controversial with many of the recognised

criteria defining an effective screening programme being unmet. Examples include knowing the incidence of cardiac events that might have been prevented with screening and the effectiveness of screening in altering the clinical outcome. Due to the inadequacies in screening techniques with respect to the Wilson's screening criteria²⁴⁸ the department of health does not currently fund a screening programme in the UK.²⁴⁹ The charitable organisation Cardiac Risk in the Young and its donors, fund a free UK wide screening programme for 14-35 years old athletes, using a health and family history questionnaire and 12-lead ECG, with follow on transthoracic echocardiogram if there is sufficient concern of a potential underlying cardiac abnormality.

1.10.2 Cardiac Screening in Master Athletes

Given that CAD accounts for the majority of SCD in master athletes, the objective of screening is primarily to identify those at significant risk of coronary events, to permit appropriate and aggressive risk factor intervention where needed and consider implementing exercise restrictions. Current clinical guidance for the pre-participation evaluation of endurance athletes is controversial, largely expert consensus driven and limited in its evidence base.¹⁶ There are several published recommendations from the ESC and American College of Cardiology (ACC) providing guidance for the evaluation of all older (>35 years) individuals participating in or planning to participate in physical activity.^{16,250} The latest (2020) European guidance recommends assessment of CVS risk using the SCORE-2 calculator, consideration of intensity of exercise, clinical evaluation including history of symptoms, physical examination and an ECG. Asymptomatic athletes with a low to moderate risk i.e., SCORE <5%, warrant no investigation and can continue exercising at high intensity. For those with a score $\geq 5\%$ or other high-risk features, participating in high or very

high intensity exercise, a maximal exercise test is recommended to assess for myocardial ischemia unless the ECG is uninterpretable. The exercise test is also deemed helpful to detect exercise induced arrhythmias, BP response to exercise and a blunting of exercise performance, which can be a subtle and early manifestation of coronary ischaemia. If there is availability, additional imaging such as stress echocardiography should be included. If the exercise test is positive for ischaemia or the stress imaging test demonstrates evidence of high-risk features ('SPECT: area of ischaemia $\geq 10\%$ of the LV; stress echocardiography: ≥ 3 of 16 segments with stress-induced hypokinesia or akinesia; stress CMR: ≥ 2 of 16 segments with stress perfusion defects or ≥ 3 dobutamine-induced dysfunctional segments; CCTA: three-vessel disease with proximal stenoses; left main disease; proximal LAD disease'),¹⁶ the athlete should proceed to undergo invasive coronary angiography as per the ESC guidelines for the investigation of chronic coronary syndromes (CCS),²⁵¹ to confirm the presence, extent and severity of disease. If these stress tests are equivocal/inconclusive, further functional imaging such as stress MRI, SPECT or CCTA is recommended. If the test is normal, significant CAD can be excluded.

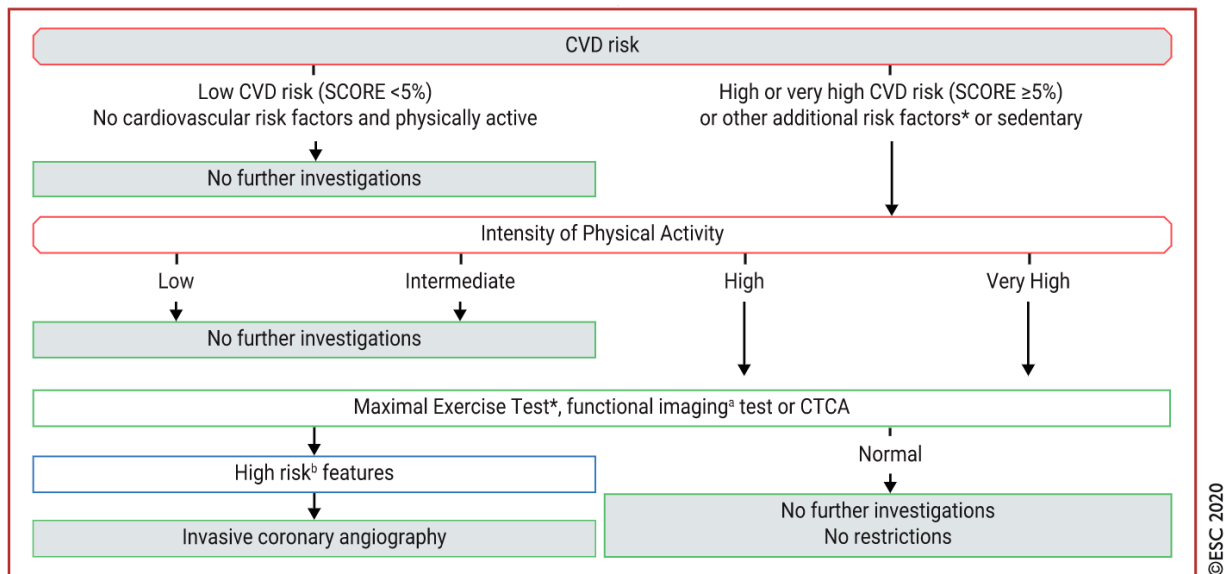


Figure 1.17 Algorithm from the ESC recommendations for pre-participation CVS evaluation of asymptomatic athletes over the age of 35 years.¹⁶

The most recent American guidance from the 2007 ACC update is less specific and recommends history, assessment of risk factors using the 12-point evaluation, and selective exercise testing for those athletes with 2 or more risk factors for atherosclerosis or 1 or more very abnormal risk factors, with a positive test warranting further investigations.²⁵⁰

Medical history*
Personal history
1. Exertional chest pain/discomfort
2. Unexplained syncope/near-syncope [†]
3. Excessive exertional and unexplained dyspnea/fatigue, associated with exercise
4. Prior recognition of a heart murmur
5. Elevated systemic blood pressure
Family history
6. Premature death (sudden and unexpected, or otherwise) before age 50 years due to heart disease, in ≥1 relative
7. Disability from heart disease in a close relative <50 years of age
8. Specific knowledge of certain cardiac conditions in family members: hypertrophic or dilated cardiomyopathy, long-QT syndrome or other ion channelopathies, Marfan syndrome, or clinically important arrhythmias
Physical examination
9. Heart murmur [‡]
10. Femoral pulses to exclude aortic coarctation
11. Physical stigmata of Marfan syndrome
12. Brachial artery blood pressure (sitting position) [§]
*Parental verification is recommended for high school and middle school athletes.
†Judged not to be neurocardiogenic (vasovagal); of particular concern when related to exertion.
‡Auscultation should be performed in both supine and standing positions (or with Valsalva maneuver), specifically to identify murmurs of dynamic left ventricular outflow tract obstruction.
§Preferably taken in both arms. ³⁷

Figure 1.18 Twelve-point medical history recommended by the AHA for the pre-participation cardiovascular evaluation of competitive athletes.

Standard exercise tolerance testing is often more widely used in pre-participation evaluation due to its availability; however, caution must be exercised with respect to its limitations i.e., low positive predictive value and high false positive rate with ischaemic ECG changes developing only at an advanced stage of the ischaemic cascade resulting in only haemodynamically significant coronary stenoses being revealed. Fifty percent of plaque rupture resulting in arrhythmic SCD in the general population occurs in subclinical coronary lesions which remain unidentified by the standard exercise test or other functional tests.²³³

There are also several drawbacks to all functional testing modalities in athletes. Firstly, athletes tend to have supra-normal coronary reserve due to ischaemic pre-conditioning and

collateral growth, which may mask the severity of a lesion. Secondly, there are numerous other factors at play during intense exercise as previously discussed, that alter the physiological threshold for ischemia and plaque rupture, that are not re-produced during functional testing. CT CAC scoring and/or CCTA may be favoured in future for mass screening given its strong negative predictive value compared with current methods and ever diminishing radiation doses. The MARC study group, calculated that the number of athletes needed to screen using either CAC scoring or CAC scoring plus CCTA, to prevent one cardiovascular event within 5 years, were 183 (95% CI: 144-236) and 159 (95% CI: 128-201), respectively.¹⁵⁹

The main overall drawback of a pre-participation screening process in middle-aged athletes is that there is currently no evidence that CAD screening in older athletes reduces the toll of MACE and exercise related SCD and therefore it remains difficult to justify both the financial and personal costs.

1.11 Management of Athletes with Asymptomatic Coronary Artery Disease

Despite the differences in CVS physiology between athletes and non-athletes, current recommendations state that an athlete with CAD should be managed in the same manner as a non-athlete, with additional individualised advice regarding exercise participation.

Therefore, management of CVS risk factors including BP therapy and statin use is advised, with the addition of conventional anti-thrombotic therapy. This has a consequence for athletes participating in high impact sports as they are advised against participation while taking anti-thrombotic therapy.

An individual athlete-centred approach with shared decision making should always be adopted when managing these individuals. Athletes at risk of CAD or who are asymptomatic with CAD detected at screening i.e., subclinical CCS, should have aggressive management of risk factors but only have restrictions imposed where there is a high risk of an adverse event, as indicated by functional tests or on detection of disease progression on serial follow-up, and should be individually tailored. Such individuals should be re-evaluated using functional testing on an annual basis.¹⁶

An athlete with established CCS is considered at low risk of MACE if they are free from symptoms, inducible ischaemia and arrhythmias on exercise or functional testing and have preserved LV function and can participate in most intensive exercise programmes with some exceptions for those sports imposing the greatest cardiovascular demand and for older athletes, although regular review and risk stratification is warranted. Athletes with inducible ischaemia should undergo invasive coronary angiography which allows for further determination of risk and revascularisation where possible. Factors that would classify such an athlete as at risk include a critical coronary stenosis >50% in the LMS or LAD or $\text{FFR} < 0.8$ / $\text{iFR} < 0.9$, 2 or 3 vessel disease with >50% stenosis, >90% stenosis in any vessel. The possibility of revascularisation, LVEF, presence of exercise induced arrhythmias and level of remaining symptoms are key determinants in the subsequent exercise recommendations of these individuals (see figure 1.19). Once revascularized they may return to sport in a graded fashion after 3-6 months, following a normal maximal exercise or functional study.

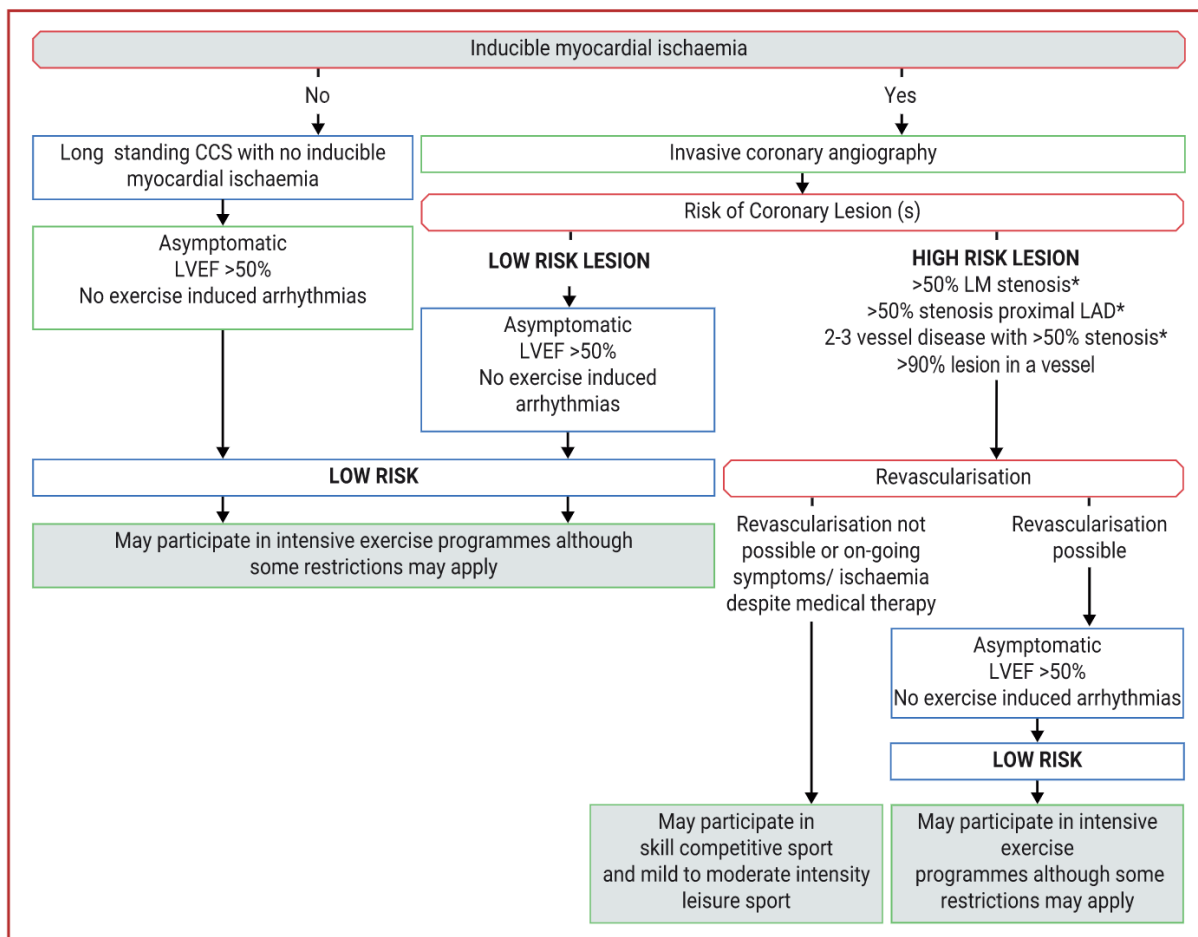


Figure 1.19 Algorithm for Further Management of Athletes with Inducible Ischemia from the ESC Recommendations for Pre-Participation Cardiovascular Evaluation of Asymptomatic Athletes over the Age of 35 Years.¹⁶

CCS, chronic coronary syndrome; LM, left main; LVEF, left ventricular ejection fraction.

1.12 Original hypothesis

The development of CAD and ischaemic MF in ostensibly healthy male master athletes, without known conventional CVS risk factors for CAD, is attributable largely to a greater cumulative exercise dose and compounded by modern lifestyle factors including subclinical hypertension, age and a pro-inflammatory diet.

1.12.1 Rationale for study

Ostensibly healthy middle-aged male endurance athletes with an otherwise low CVS risk develop CAD and ischaemic MF that in the general population would confer an adverse prognosis for MACE, the cause of which is currently unknown.

1.12.2 Research Question

Is there an association between the presence of CAD as defined by CAC score or CCTA findings including plaque morphology, plaque vulnerability markers and PCAT, and 1) exercise dose, 2) sub-clinical hypertension, 3) a pro-inflammatory diet and/or a combination of factors, to explain why some seemingly low-risk male master endurance athletes develop CAD?

Is there an association between the presence of MF and CAD to explain why some low-risk male master endurance athletes develop MF? And are 1) exercise dose, 2) sub-clinical hypertension, 3) a pro-inflammatory diet and/or a combination of factor's contributory?

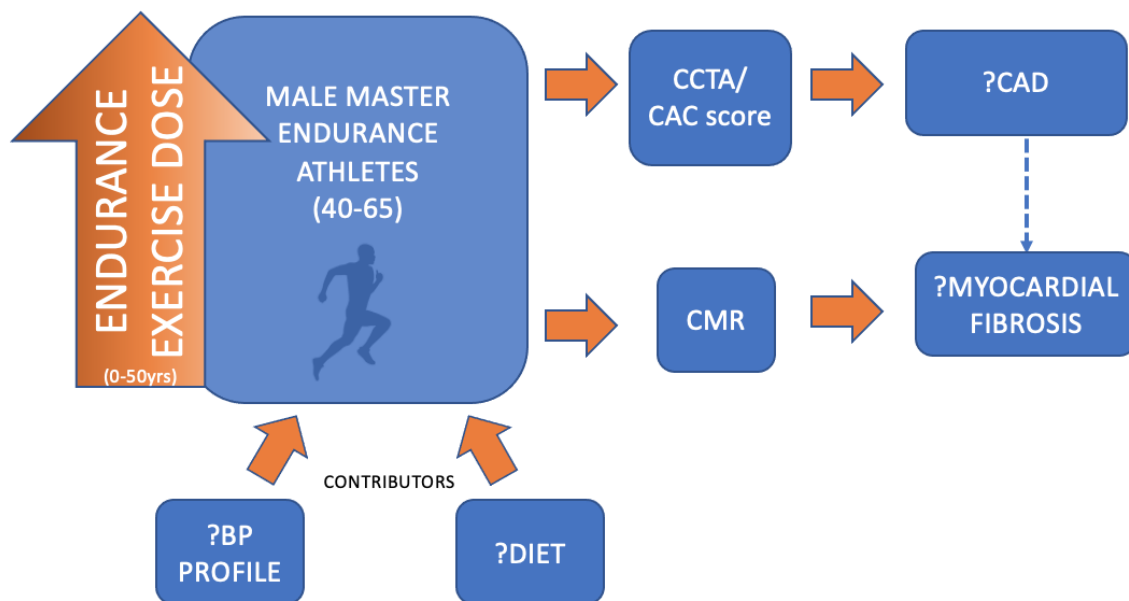


Figure 1.20 Summary image of overall research question.

1.12.3 Aims

- Evaluate the relationship of BP profile, lifetime exercise endurance exposure, sporting discipline and a pro-inflammatory diet to the presence, pattern, and characteristics of CAD.
- Assess the impact of BP profile, lifetime exercise endurance exposure and sporting discipline on the prevalence and patterns of MF.

Collectively, this work aims to (i) improve the understanding of why and which endurance athletes develop CAD and MF and (ii) provide further insights into the debate surrounding the potential deleterious effects of lifelong endurance exercise and thus guide recommendations and the clinical evaluation of healthy recreational male master athletes. The wider population implication being that with increasing knowledge, reassurances can be

provided to allay fears surrounding the risk of exercise participation amongst the general population.

1.13 Primary Objective

- To investigate the relationship between exercise dose and the presence and patterns of significant CAD in male master endurance athletes.

1.14 Secondary Objectives

- To investigate the relationship between presence and patterns of CAD and
 - 1.) Peak exercise BP
 - 2.) Resting 'office' BP
 - 3.) Ambulatory BP
 - 4.) Sporting Discipline
 - 5.) A pro-inflammatory diet
- To investigate the relationship between LGE consistent with both ischaemic and non-ischaemic patterns and ECV and
 1. Exercise Dose
 2. Peak exercise BP
 3. Ambulatory BP
 4. Sporting Discipline
 5. A pro-inflammatory diet

2 Study Setting, Techniques and Methods

2.1 Study Design

Cross-sectional Observational Study

2.2 Participants

2.2.1 Study Population

Asymptomatic male endurance athletes aged 40-65 and free of known modifiable CVS risk factors who have been participating in endurance sport defined as long distance running, cycling or multi-endurance i.e., any combination of running, swimming and/or cycling, for a minimum of 6 hours per week.

2.2.2 Sample Size and Power Calculation

This was a single-centre study including 220 participants. The approximate sample size was calculated on the assumption that the prevalence of significant CAC (CAC score ≥ 100 AU) in this population is $\sim 18.8\%$.^{6,7} The main independent variable was exercise dose. Given the observational nature of the study, the confounders of age, sporting discipline and BP profile have been taken into consideration. Assuming that the chosen 4 explanatory variables explain most of the variability in the outcome and given the nature of this binary outcome, for a robust multiple logistic regression, the study should collect 10-16 cases of significant CAC per variable, i.e., for a power of at least 80%, equivalent to a type 2 error of less than 20, a minimum of $4 \times 10 = 40$ such cases would be required.²⁵²⁻²⁵⁴ Therefore, we aimed to recruit a minimum of $(40 \times 100) / 20 = 200$ participants, and 220 allowing for 10% missing data.

2.2.3 Exclusion Criteria

Individuals were excluded for the following reasons;

- current or previous smoking
- known hypertension
- diabetes mellitus
- chronic kidney disease ($\text{eGFR} < 90\text{ml/min/1.73m}^2$)²⁵⁵
- previous cardiac disease
- other chronic systemic or inflammatory conditions
- cardiac symptoms including chest pain, shortness of breath, palpitation, cardiogenic syncope or pre-syncope
- recent deterioration in exercise capacity
- contraindication to CT or CMR
- refusal of consent to sharing of abnormal results with the general practitioner.

2.2.4 Participant Recruitment

As a consequence of the sports cardiology unit at St George's University Hospital and the reputation of the primary supervisor, we have direct links with endurance sports clubs, the British Master Athletics Federation and British triathlon, who disseminated the official advertisement (appendix 1) to their members and were the primary source of recruitment.

Advertisements containing essential data invited interested participants to complete an online eligibility questionnaire via. an online link (appendix 2).

2.2.5 Preliminary Screening Health Questionnaire

The screening questionnaire collected the following data:-

- Personal details including name, date of birth, height and weight, ethnicity, email address and telephone number.
- Any history of cardiac symptoms, conditions, other chronic diseases or known risk factors including smoking status past and current
- Full drug history
- Allergies
- Family history of cardiac disease
- Type of exercise undertaken
- Number of hours of exercise per week on average
- Details of prolonged periods without training and reasons

Questionnaires were manually evaluated for eligibility. When there was any ambiguity in responses, athletes were contacted by email or telephone to confirm or reject inclusion.

2.2.6 Participant Scheduling

Every athlete who was deemed eligible was invited to participate in the study and was sent the patient information sheet including an example consent form, in anticipation of attendance for testing. Those wishing to participate were advised to book a convenient time slot using an online scheduling programme. Athletes were then sent a confirmation email of their appointment time and date along with further instructions for day 1 of testing (appendix 3). Once athletes had completed day 1 and abnormal glucose tolerance and severe hypercholesterolaemia were successfully excluded, participants were invited to book

appointments for subsequent testing for CAC scoring and CCTA (day 2) and CMR (day 3), via the same online process, with these appointments again being confirmed by email and full instructions including necessary preparations (appendix 4 and 5), relevant safety questionnaires for CT (appendix 6) and CMR (appendix 7), and maps and directions to the study site locations provided. Where athletes booked their appointments a considerable time ahead, reminder emails were sent to optimise attendance. If athletes wished to change their appointments, they were asked to make contact via email as early as possible so appointments could be re-distributed to another participant, and they were subsequently offered a new booking.

2.2.7 Participant Consent

Having had the opportunity to read the information sheet (appendix 8) and consent form (appendix 9) ahead of attending for the first day of testing, participants provided written informed consent following a detailed explanation of the investigation protocol and opportunity to have any queries answered by the study lead or appropriate delegate, on the first day of testing. Participants were offered a copy of the consent form for their own record keeping.

2.3 Ethical Approval

Ethical approval from the Health Research Authority (HRA) was obtained with the submission of 2 significant amendments to previous approval obtained for the 'Veteran athlete's heart study' in 2011, primarily updating consent forms, information sheets, advertisements, inclusion/exclusion criteria, CT location and dates including follow-up periods (appendix 10 and 11).

2.4 Study Setting

Investigations took place over 3 visits at 3 locations on 2 sites. Testing was arranged as follows;

2.4.1 Day 1 - Cardiac Investigations, Youde Room, St George's University Hospital, London.

This site is a tertiary centre hospital adjoined to the university and hosts the internationally renowned sports cardiology centre headed by Professor Sanjay Sharma and part funded by the charitable organisation Cardiac Risk in the Young.

On day 1 of testing athletes underwent the following investigations in the following order; venous blood sampling, anthropometry (height and weight), 12-lead ECG, 2D transthoracic echocardiography, resting 'office' blood pressure and cardio-pulmonary exercise testing (CPET). At this point athletes were offered a shower followed by fitting of 24-hour Holter and ambulatory BP monitoring (ABPM). Athletes were provided with paid, addressed protective postage bags in which they were instructed to return the 2 monitoring devices after 24 hours of monitoring.

Appointments took place around clinical work within the Youde Room, often early mornings and evenings and numerous weekends.

2.4.2 Day 2 - CT Imaging Department, St George's University Hospital, London.

Athletes underwent CT calcium scoring and CCTA. Scanning took place on weekend days only, due to scanner availability. Scans were undertaken by 2 expert CT radiographers with

assistance from the study lead (Gemma Parry-Williams) for consenting, clinical support, venous cannulation, and logistical management.

2.4.3 Day 3 – The Barts Heart Centre, St Bartholomew’s hospital.

Athletes underwent cardiovascular magnetic resonance imaging. Scanning took place on weekend days due to limited availability of scanners. Two scanners were run simultaneously as per the St Bartholomew’s method of scanning for research. This resulted in large number (48) of scans being performed over a weekend but limited the appointment options for participants which made it difficult for some to attend. Scans were undertaken by expert CMR radiographers with a research fellow from St Bartholomew’s on stand-by for any site-specific concerns. Consenting, cannulation, overseeing and logistical management were performed by the study lead (Gemma Parry-Williams).

In total over 600 appointments were arranged, with the addition of cancellations, non-attendances, and re-arrangements.

2.5 Cardiovascular Risk Factor Evaluation

Data from the resting BP, serum cholesterol and glucose on day 1 of testing and family and smoking history as detailed on the questionnaire along with demographic data provided, were used to calculate the ESC endorsed and updated version (SCORE2) of ‘HeartScore®’ and Framingham Risk Score. By analysing these risk scores data can be provided that is applicable across countries and continents.

2.6 Investigations

2.6.1 Dietary Questionnaire

Participants were provided with a personal anonymised login and detailed instructions that permitted them access to an online system where they completed a UK specific, EPIC-Norfolk food frequency questionnaire. The questionnaire took approximately 20-25 minutes to complete. Analysis of the response data from each questionnaire permitted the calculation of a dietary inflammatory index (DII) (Connecting Health Innovations, USA), a score graded between -5 and +5 that reflects the inflammatory level of the athlete's diet with a more positive score correlating with a more inflammatory diet. DII is further discussed in the methods section of chapter 7.

2.6.2 Dose Questionnaire

There is no gold standard for quantifying an athlete's exercise dose; however, it is recognised that duration, frequency, and intensity should ideally be accommodated. Dose data was collected using an online questionnaire detailing life-long exercise dose (appendix 14).

The following data was collected:-

- Principal sporting discipline
- Competition types and personal bests
- Number of days per week exercising
- Number of months in a year training intensively
- Total number of years of endurance training

- Average hours per week of each sport
- Time spent exercising at a specific intensity in Watts e.g., 2 hours cycling at 30-50 Watts. This was measured using the 2011 compendium of physical activities.^{256,257}

Full details of the Compendium can be found in appendix 15.

By totalling the hours per week spent at the given intensities, total METS per week were calculated. From this lifetime MET-hours could be determined using the following formula;

Lifetime MET-Hours =

METS/week x hours per week x no. months of year endurance training x total number of years endurance training

2.6.3 Biochemistry

Non-fasted venous samples were obtained for lipid profile and glucose, to calculate CVS risk and exclude master athletes with diabetes (random glucose ≥ 11.1 mmol/l) and severe hypercholesterolaemia (LDL > 4.9 mmol/l); renal profile to enable safe use of contrast agents and full blood count to exclude anaemia for precise CPET interpretation.

2.6.4 Anthropometry

Height and weight were recorded without shoes using a standard standiometer and analogue scales.

2.6.5 Blood Pressure Profile

2.6.5.1 Resting 'office' Blood Pressure

Measurement was performed manually using a mobile sphygmomanometer, by a single operator (Gemma Parry-Williams), following a 15-minute period of semi-recumbence and calm (during ECG and echocardiography), with the arm at heart level, using an appropriately sized cuff (i.e., bladder of cuff encircling at least 80% of the arm)²⁵⁸ and having removed any restrictive clothing. Measurements were repeated 3 times and of the three measures taken, the mean of the latter 2 was used.²⁵⁹ The definitions for hypertension, high normal blood pressure and grades of hypertension are detailed in table 2.1.

Table 2.1 ESC/ESH definitions of hypertension 2018²⁶⁰

Resting Blood Pressure	Systolic (mmHg)	Diastolic (mmHg)
High Normal BP	130-139 and/or	85-89
Hypertension	≥140 and/or	≥90
- Grade 1	140-159 and/or	90-99
- Grade 2	160-179 and/or	100-109
- Grade 3	≥180 and/or	≥110
Ambulatory Hypertension (any of following on 24-hour monitoring)		
- 24 hour or	≥130 and/or	≥80
- Diurnal or	≥135 and/or	≥85
- Nocturnal	≥120 and/or	≥70
Hypertensive Response to exercise	≥220	-

2.6.5.2 Ambulatory Blood Pressure

Twenty-four-hour ABPM (ABPM 1700, Welch Allyn, NYC, USA) was performed. Athletes were encouraged to continue usual day-to-day life activities, excluding exercise or anything requiring vigorous movement, during the investigation and advised to keep their recording arm still when the device activated to increase the chance of a successful measurement. Measurements were made using an automated system with a protocol of hourly measurements from 06h-09h and 21h-01h and measurements every 20 minutes 09h-21h and 01h-06h, to obtain sufficient data for interpretation according to the latest European Society of Hypertension (ESH) practice guidelines,²⁶¹ whilst minimising discomfort and inconvenience to the athlete. The instruction sheet provided to athletes can be found in appendix 12. Athletes removed and returned the device by post. On arrival data was downloaded using the Welch Allyn software and transferred immediately to a database.

2.6.6 Electrocardiogram

A standard 12 lead ECG was performed using a MAC 5500 digital resting ECG recorder (GE Medical Systems, Milwaukee, WI, USA). ECG recordings were made with internationally accepted lead placements in a 45-degree semi-recumbent position. A standard 10-second 12-Lead ECG acquisition was obtained at a sampling rate 500 samples/second and amplitude resolution of 4.88 mV.

2.6.7 Holter

Twenty-four-hour ambulatory ECG monitoring (Lifecard CF Holters, Spacelabs Healthcare, USA) was performed to identify supra-ventricular and/or ventricular tachyarrhythmias and bradycardias. Athletes were encouraged to continue usual day-to-day life activities

excluding exercise during the investigation. Athletes removed the devices themselves after 24-hours and posted them back for downloading onto the Spacelabs computer software system for analysis. Data was analysed offline to produce a comprehensive report which was subsequently databased. The instruction sheet provided to athletes can be found in appendix 12.

2.6.8 Echocardiogram

2D transthoracic echocardiography with tissue Doppler and speckle-track imaging was performed using a GE Vivid I (Tirat, Israel) with the subject at rest, laid in the left lateral recumbent position with simultaneous single-lead ECG displayed. Standard views were obtained including measurement of cavity sizes, LV wall thickness, valvular function, parameters of systolic and diastolic function and strain imaging, in accordance with current protocols specified by the British Society of Echocardiography.²⁶²

2.6.9 Cycle Ergometry Cardiopulmonary Exercise Test

Cycle ergometry CPET was used to evaluate current level of physical fitness according to VO_2 max (ml/kg/min) and the BP response to exercise. The assessment was performed in an upright position with a COSMED E100Watt cycle ergometer (Rome, Italy) using a ramp protocol of 25-30 Watts/min and was based on the athlete's exercise history and height. Participants were encouraged to exercise to maximal volitional exhaustion. Breath-by-breath gas exchange analysis was performed using a dedicated COSMED Quark CPEX metabolic cart (Rome, Italy). Continuous 12-lead ECG monitoring was displayed throughout and captured for printing at 2 min intervals using a Quark C12x ECG recorder (Rome, Italy). A printout of VO_2 (l/min), VCO_2 (l/min), respiratory exchange ratio (RER), heart rate

(beats/min) and work rate (Watts), were obtained and averaged at 10 second intervals to obtain a smooth graphical representation. Graphs of VCO_2 versus VO_2 were used to estimate anaerobic threshold (AT). BP was recorded manually whilst supporting the weight of the athlete's arm, at intervals of 3 minutes throughout the test, at peak exercise and for 6 minutes of recovery.

Evaluation of the data for an exaggerated BP response was undertaken using maximal systolic BP and binary analysis for a hypertensive response to exercise (HRE) using a cut-off of 220 mmHg.

Cycle ergometry CPET was selected in favour of the treadmill because there is less movement required during cycling, making it easier to obtain high-quality ECG and BP measurements. It is noted that VO_2 max values are 5-15% lower than on the treadmill and subject to physical conditioning, leg strength and motivation. Given the cohort consisted of cyclists, triathletes and runners this may have favourably biased the cyclists over the runners who were frequently limited due to leg fatigue before cardiovascular exhaustion.

2.6.10 Coronary Evaluation

2.6.10.1 CT Coronary Angiography and CAC Scoring

CT coronary angiography was performed using a wide area detector 320 slice Revolution GE scanner (GE Healthcare) and prospective gating using a commercially available protocol (SnapShot Pulse, GE healthcare), capable of single rotation full cardiac coverage. The estimated total radiation dose was 2-5mSv. The following scanning parameters were utilised: a scout scan was performed followed by a prospectively gated calcium score scan

(gantry rotation time of 270 ms, 120kVp and ~124mA) with 16cm z-axis coverage from the tracheal bifurcation to the diaphragm (field of view, 25 cm). CCTA was acquired with prospective gating and a 0.63 x 0.63mm resolution, using a medium-soft tissue convolution kernel (standard), and individual size adapted kVp, mAs, and iterative reconstruction settings to achieve minimum diagnostic dosimetry. Participants were to receive intravenous Metoprolol 5-30mg where necessary to achieve a heart rate of <60 bpm; however, none required this. All participants received two 400 mcg doses of sublingual Glyceryl trinitrate. For the angiographic part of the scan, 100 ml of iohexol (Omnipaque 350 mg I/ml) contrast, at a flow rate of 5 ml/s followed by 100 ml of saline solution, was injected into an antecubital vein via an 18-gauge peripheral venous catheter. Bolus tracking was used with a region of interest placed in the ascending aorta. Image acquisition was then commenced once signal intensity reached a predefined threshold of 100 Hounsfield units (HU). All images were transferred to an external workstation (ADW 4.5, GE Healthcare) for analysis. CAC score was plotted according to percentiles for age and luminal stenosis and plaque morphology was visually assessed using established guidelines.^{263–265} Standard clinical reporting of the studies including CAC score, stenoses and plaque morphology, were co-reported by 2 expert coronary CT radiologists.

2.6.10.2 Coronary Plaque Vulnerability

In addition to reporting of the standard clinical features, analysis was performed for markers of plaque vulnerability. This included conventional makers of napkin ring sign, spotty calcification, plaque rupture, positive remodelling and low attenuation plaque. In addition, we assessed thin capped fibroatheroma (TCFA) by quantifying the necrotic core/fibrous plaque ratio (NC/Fi), which is a novel technique, conceived by the collaborator Dr Daniel

Obaid. The NC/Fi is a measure comparable to virtual histology-intra vascular ultrasound measured TCFA, a technique performed during invasive coronary angiography that has been demonstrated in prospective studies to predict plaques at increased risk of MACE.²⁶⁶

2.6.10.3 Peri-Coronary Adipose Tissue

Quantitative assessment of PCAT density was performed using a clinically validated, standardized semiautomatic software (Autoplaque, Version 2.5, Cedars-Sinai Medical Center).²⁶⁷ Three-dimensional layers within radial distance from the outer coronary wall, equal in thickness to the average diameter of the vessel were constructed from the CCTA. We quantified the weighted PCAT after adjustment for technical parameters. PCAT density was defined as the mean attenuation within contamination-free volumes of interest. Within the predefined volume of interest, voxels with tissue attenuation based on the attenuation histogram ranging from -190 up to -30 HU^{156,268} were considered as adipose tissue. Neither myocardial tissue adjacent to the vessel wall nor the coronary branches originating from the vessel of interest were included in the automated analysis. We defined peri-coronary fat as the adipose tissue within a radial distance from the outer vessel wall equal to the diameter of the vessel. These measurements were performed in all coronary lesions and in a reference region of the PCAT surrounding the proximal and mid-right coronary artery (RCA), as described recently.^{156,268} We traced the proximal 40 mm segments of the three major epicardial coronary vessels (for RCA starting 10 mm distal to the ostium, whilst for the LAD artery and circumflex artery starting normally at the ostium), whether there was plaque detected or not. PCAT values reported in the results are taken from the proximal RCA segment.

2.6.11 Cardiovascular Magnetic Resonance Imaging including Late Gadolinium Enhancement, T1 mapping and Extra-Cellular Volumes.

Participants underwent CMR using a 1.5T magnet (Aera, Siemens Medical Solutions).

Chamber dimensions and volumes, LV and RV function, aortic dimensions, and myocardial mass (excluding papillary muscle mass) assessed by cine steady-state free precession sequences using machine learning analytic approaches, to maximise yield. Delayed contrast enhancement images were obtained 5-10 mins after intravenous bolus injection of gadolinium-diethylene triamine penta-acetic acid (Gd-DTPA) (0.1mmol/kg Dotarem) to identify regional MF. Inversion times were adjusted to null normal myocardium. State-of-the-art custom MOCO LGE sequences were used. T1 mapping for ECV was performed. These tissue characterisation techniques were used to identify diffuse MF and myocardial oedema. Mid-ventricular short axis native and post-contrast (15 minutes post IV bolus of 0.1 mmol/kg gadoterate meglumine, Dotarem, Guerbet, LLC), T1 maps by MOLLI were acquired. MOLLI T1 maps (pre: 5s(3s)3s, post: 4s(1s)3s(1s)2s) with motion correction were used. A full CMR protocol is detailed in appendix 13.

2.7 Statistical Analyses

Statistical analyses were performed using SPSS statistics V27 (IBM Corp, NY). All variables were assessed for normality both visually using normality histogram plots and the Shapiro-Wilk test, and skewness and kurtosis were also examined. When normally distributed, continuous variables were reported using mean $\pm$ standard deviation (SD) and using median with interquartile range (IQR) when not normal. Categorical data were reported as proportions. Preliminary analysis and graphics were used to understand the data structure, the nature of the variables and the appropriateness of the subsequent tests and analyses. A

crude analysis assessed the strength of association between the outcomes (CAC, stenosis >50%, plaque vulnerability markers, TCFA, plaque morphology, PCAT, LGE and ECV) and potential explanatory variables (age, resting 'office' systolic BP, peak exercise BP and ambulatory systolic BP, years of endurance exercise and sporting discipline). The relationships of the binary and categorical dependent variables (CAC, stenosis >50%, plaque vulnerability markers, TCFA, plaque morphology and LGE) to the outcome of sporting discipline were explored using χ^2 -test and Fisher's exact tests. The relationship of the continuous dependent variables PCAT and ECV to sporting discipline was explored using the Kruskal -Wallis test and to age, resting 'office' systolic BP, peak exercise BP and ambulatory systolic BP and years of endurance exercise using Pearson's and Spearman's rank correlation.

Following preliminary exploration of the data univariate logistic regression, including multinomial regression, was used to explore the outcomes of CACs ≥ 100 AU, stenosis >50%, plaque vulnerability markers, TCFA and plaque morphology, giving p-values, and unadjusted odds ratios (ORs) and relative risk ratio (RRR), respectively and their 95% confidence intervals. Univariate linear regression was used for PCAT to obtain unstandardised B values and the 95% confidence intervals. Subsequently multiple regression was performed using the a priori variables of age, sporting discipline and years of endurance exercise in addition to, the 3 BP variables of resting systolic 'office' BP, ambulatory systolic BP and maximum exercise systolic BP, to obtain adjusted p-values, ORs, RRRs or B coefficients and their respective 95% confidence intervals. An alpha level of 0.05 was adopted as the cut-off for a statistically significant p-value. Penalized-likelihood criteria such as AIC or BIC were used to choose between possibly non-nested models. Goodness of fit tests such as Hosmer-

Lemeshow were used to assess how the models fit to the data. A p-value of <0.05, indicated a poor fit to the data. Multiple imputations using chained equations were applied for missing data that were accompanied by a sensitivity analysis to missing at random assumptions.²⁶⁹ An interim analysis allowed for identification of inconsistencies and discrepancies in the data.

2.8 Database

Study data was collected using excel and lime survey software and stored using the recommended St George's University secure server and an encrypted hard drive. Any paper copies were kept in a locked cupboard within a locked area of the department with access available only to the study lead and primary investigator.

2.9 Funding and Support

The study was jointly funded by the British Heart Foundation with a clinical research fellowship grant (FS/19/5/34080) awarded for £238,271 (for CT and MRI scans and years 2-4 of the PhD) and a fellowship grant from the charitable organisation Cardiac Risk in the Young, for years 1-2 of the PhD.

Recruitment support was provided by British triathlon and the British Master Athletes Federation. Letters of support can be found in appendix 16 and 17.

All scheduling and screening were undertaken by the study lead (Gemma Parry-Williams) and reporting and testing of all 3 days of investigations was led by the study lead also. A

team of support from St George's University of London, St Bartholomew's University Hospital and other organisations contributed to the study as follows;

Day 1 testing was supported by dedicated expert cardiac physiologists in the field of sports cardiology funded by Cardiac Risk in the Young, Paulo Bulleros and Zephryn Fanton, for echocardiography and CPET. Other contributors included research fellows Dr Maximiliano Moreira and Dr Athanasios Bakalakos who offered CPET support at weekends. Jacki Anglin and Shams Wahid, expert cardiac physiologists, provided 24-hour Holter reporting.

Day 2 CT testing was supported by CT radiographers Hitesh Patel, May Patel, Amrit Loyal and others at St George's University Hospital. CT reporting was supported by Dr Ioannis Vlahos and Dr Joanna Moser. Plaque Vulnerability was reported with support from Dr Daniel Obaid and PCAT was reported in collaboration with Dr Nicola Gaibazzi and Dr Domenico Tuttolomondo.

Day 3 testing was supported by dedicated CMR radiographers Cheelo Simaanya, Shino Kuriakose, Sunita Chauhan and others at St Bartholomew's University Hospital. CMR set-up and reporting was supported by Professor James Moon, Dr Rebecca Hughes, Dr Joao Augusto, Dr Alex Kasiakogias and Dr Zhafik Khoury.

2.10 Outcome measures

Primary Outcome Measure

- CAC Score

Secondary Outcome Measures

- On CCTA
 - Stenosis >50% in a proximal coronary artery
 - Coronary plaque morphology (partially calcified and non-calcified)
 - Presence of plaque vulnerability markers including TCFA
 - PCAT density

- On CMR
 - Presence of LGE on CMR imaging including sub-endocardial, mid-wall and subepicardial distributions, with the following sites that are considered normal: RV insertion points, trabeculae, RV free wall or papillary muscles.
 - ECV

2.11 Measures of Exposure

Exposures

1. Lifetime 'dose' of endurance training
2. Sporting discipline
3. BP Profile
 - a. Resting 'office' BP
 - b. Maximum systolic BP during CPET
 - c. 24-hour ABPM
4. Pro-inflammatory diet

2.12 Timeline

Recruitment took place over a period of 14 months. There was a 40% exclusion rate following the eligibility questionnaire, measurement of the blood glucose and lipid profile, therefore approximately 580 individuals were assessed to recruit 220 study participants. Recruitment rate was approximately 4 participants per week. Figure 2.1 demonstrates the timeline of the study.

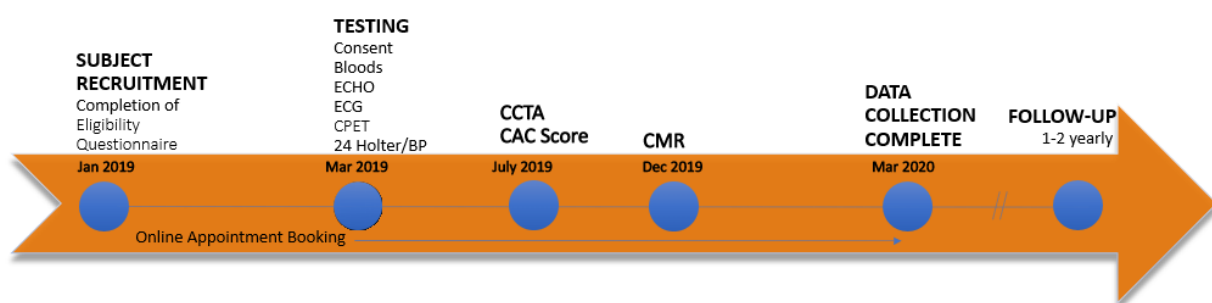


Figure 2.1 Timeline of study including opening of recruitment, testing periods for 3 testing days and completion date.

2.13 Follow-up and Loss to Follow-up

Participants with study findings that required further action or follow-up were referred to their GP with all the relevant clinical information and recommendations provided, to be appropriately managed or referred on for appropriate speciality care.

2.14 Reporting of Clinically Significant Findings

Athletes with any abnormality that was considered potentially distressing, important, or requiring explanation, were either spoken to on the day of testing, where results were immediately available, or called directly. Following this all athletes were informed of the

results and further recommendations in writing either by email alone or email and postal letter, along with their GP.

The ESC guidelines for sports cardiology and exercise in patients with CVD¹⁶ currently advise on the course of action with regards to exercise prescription in the presence of hypertension and hypercholesterolaemia; however, they fail to provide specific recommendations for further evaluation of newly recognised BP and cholesterol in an athlete advising that treatment should be as for the non-athlete. An extensive review of the current evidence by leading experts in 2020 made recommendations regarding management of hypercholesterolaemia amongst athletes.²⁷⁰ As with all guidance the foremost recommendation is that all decisions are made on an individual basis based on the individual's overall risk and using a patient led, informed decision-making process. In accordance with the AHA guidance for the management of hyperlipidaemia, statin therapy is recommended for a CAC score ≥ 100 AU or $\geq 75^{\text{th}}$ percentile and for a CAC score of 1-99 AU in those over the age of 55 years²⁷¹. This is in accordance with the data showing that statins reduce MACE if the CAC score is ≥ 100 AU but equally shown to be of no benefit in a CAC of zero.²⁷² Statins should also be recommended in the presence of a non-calcified plaque, and in high dose in the context of a CAC score ≥ 400 AU.

Recent review of current literature for the approach of asymptomatic CVD by Martinez *et al*²⁷³ recommends for a CAC score ≥ 400 AU athletes should be prescribed lipid lowering therapy in the form of a statin and aim for an LDL < 1.4 mmol/l and consideration should be given to initiate a statin in those with a CAC score ≥ 100 AU and/or $\geq 75^{\text{th}}$ centile, after discussing the limitations in evidence and increased side effects in this cohort. Athletes must

also be advised against undergoing repeat CAC score testing once taking statin as they are known to increase the score and could result in unwarranted additional investigations and treatment in certain circumstances.

Based on the available evidence and recommendations available, including guidelines for the management of CCS in the general population,²⁵¹ the following recommendations were made to the athlete's GP;

- An athlete with evidence of CAD was advised to cease training immediately should they begin to experience new cardiac symptoms including chest pain, disproportionate shortness of breath, palpitations, syncope or pre-syncope and undergo further investigation.
- An athlete with evidence of myocardial ischaemia on CPET and significant coronary disease on CCTA was recommended referral for invasive coronary angiography.
- An athlete with a stenosis >75% in a proximal coronary vessel was recommended referral to a cardiologist for consideration for coronary angiography and advised to cease intense and/or competitive training until further evaluation was undertaken.
- An athlete with a stenosis of 50-75% in a proximal coronary vessel was recommended referral to a cardiologist for consideration of functional imaging or invasive coronary angiography.
- An athlete with a stenosis greater than 50% in a non-proximal artery but one supplying a significant area of myocardium was recommended referral to a cardiologist for consideration of functional imaging.

- An athlete with non-calcified coronary plaque was recommended for consideration of statin therapy.
- An athlete with a CAC score ≥ 100 AU or $\geq 75^{\text{th}}$ percentile, and LDL ≥ 1.8 mmol/l was recommended for consideration of statin therapy and in the case of a CAC ≥ 400 AU, at a high dose.
- An athlete demonstrating hypertension on ABPM was recommended for dietary $\pm$ medical management.
- An athlete demonstrating resting hypertension but normal ABPM or high normal resting BP or an isolated hypertensive response to exercise was recommended annual monitoring.²⁶⁰
- An athlete demonstrating grade 3 hypertension was recommended to cease intense/competitive exercise until the BP had been controlled.
- An athlete with a dilated aortic arch or aneurysm was recommended referral to a cardiologist for further evaluation, monitoring and exercise advice.
- An athlete with significant valvular heart disease was recommended referral to a cardiologist for further evaluation and monitoring.
- An athlete with impaired cardiac function was recommended referral to a cardiologist for further evaluation and monitoring.

To minimise loss, all athletes consented to the use of their NHS number to obtain their contact details via the GP should they be uncontactable using the details they initially provided.

A sample of the letter provided to the athlete's GP can be found in appendix 18.

3 Cohort Descriptive and Baseline Results

3.1 Hypothesis

Extensive examination of the male master endurance athlete cohort reveals findings consistent with the existing data and understanding of the adaptive and potentially pathological changes amongst this demographic.

3.2 Study Population

A total of 582 male master endurance athletes were screened for eligibility and 214 of the original 220 recruited completed the study, which is above the anticipated attrition rate of 20% (n=200). Two athletes withdrew following initial testing as it was no longer convenient, 2 declared new sinister symptoms on initial testing and were excluded, 1 later disclosed he was not an endurance athlete and 1 had wrongly declared his age and was out of range. A summary figure of dropouts and loss to follow-up is provided in appendix 19.

3.2.1 Demographics of Athletes

The mean age of athletes was 51 ± 7.06 years (range 40-65 years). The median height and weight of participants was 178 cm (range 155-198 cm) and 75 kg (range 49-110 kg), respectively. Ninety-three percent of participants were white with the remaining athletes diverse in their ethnicities.

3.2.2 Cardiovascular Risk Profile of Athletes

Overall athletes had a low CVS risk with a median FRS of 3.2% (1.8-5.8) and Qrisk®3 score of 3.5% (2-6.1). None of the athletes by nature of the age range of 40-65 years, had a low

HeartScore® and the median HeartScore® was 3%. Only 2 (0.9%) athletes had a very high HeartScore® i.e., greater than or equal to 10% (maximum HeartScore® 11%), 57 (26%) had a HeartScore® of 5-10% with the majority (72%) at moderate 10-year risk of fatal CVS disease. The mean total cholesterol was 5.1 mmol/l (SD 0.85) with an LDL of 2.7 mmol/l (SD 0.77) and HDL 1.8 mmol/l (SD 0.45). The mean non-fasted glucose was 4.9 mmol/l (SD 0.83).

3.2.3 Exercise Exposure

Over half (n = 132, 61.7%) of athletes were participating in multi-sports i.e., any combination of 2 or 3 of endurance swimming, cycling and running. The remainder of the cohort consisted of 49 (22.9%) runners and 33 (15.4%) cyclists. One hundred and fifteen (54%) athletes had completed at least one full marathon with a mean time of 3:16 hours and 36 athletes had run a sub-3-hour marathon. Fifty-one (24%) of the athletes had completed at least one ironman and 29 (14%) an ultra-marathon. Fourteen competed at international level, of whom 6 were national age-group champions.

Athletes exercised for a median of 8.5 hours per week (range 6-26 hrs) with a cumulative exposure to endurance exercise of 15 years (range 2-26 years). The median exercise dose was 97 (IQR 75-140) MET-hours per week and over a lifetime, 2.1 (0.9-4.5) lifetime MET years. If one assumes that all athletes are spending a major proportion of time exercising at at least moderate intensity, then it would also seem reasonable to assume that the whole cohort was exercising at least 3 times the WHO recommendation of 150 minutes of moderate aerobic exercise per week. Some athletes are likely to be exercising 10-20 times this, an exercise 'dose' far beyond what is currently considered the dose for mortality benefit of 3-5 times these recommendations.^{64,109,110} Whilst there was no difference in

number of years of endurance exercise between sporting disciplines, cyclists had a greater overall lifetime exposure to exercise compared to runners, (1.37 vs 2.91 lifetime MET years, $p=0.04$) and exercised for longer and more intensively than runners (82.9 vs 117.2 MET hours per week, $p=0.06$). Although exercise doses of cyclists were higher than triathletes it did not meet the cut off for significance, i.e., 1.37 vs 2.12 lifetime MET years, $p=0.50$, and 82.9 vs 102.9 MET hours per week, $p=0.36$.

There was a positive correlation between increasing age and the number of years of endurance exercise (r 0.48) as well as lifetime MET hours (r 0.42) and MET hours per year (r 0.16).

3.3 Echocardiographic Characteristics in Master Athletes

All 214 athletes underwent 2D transthoracic echocardiography. Details of these findings are summarised in table 3.1.

Amongst the mean values for echocardiographic parameters of cardiac size and function only indexed LA volume was outside of the normal range for the general population.

However, there were a proportion of athletes with values outside of the normal range i.e., 78% and 45% had enlarged LA volume and RA area, respectively, 10% had a dilated LV by LVIDd and 40% by EDV, 3% had an increased MWT and up to 42% had increased RV dimensions and 12% had reduced fractional area change.

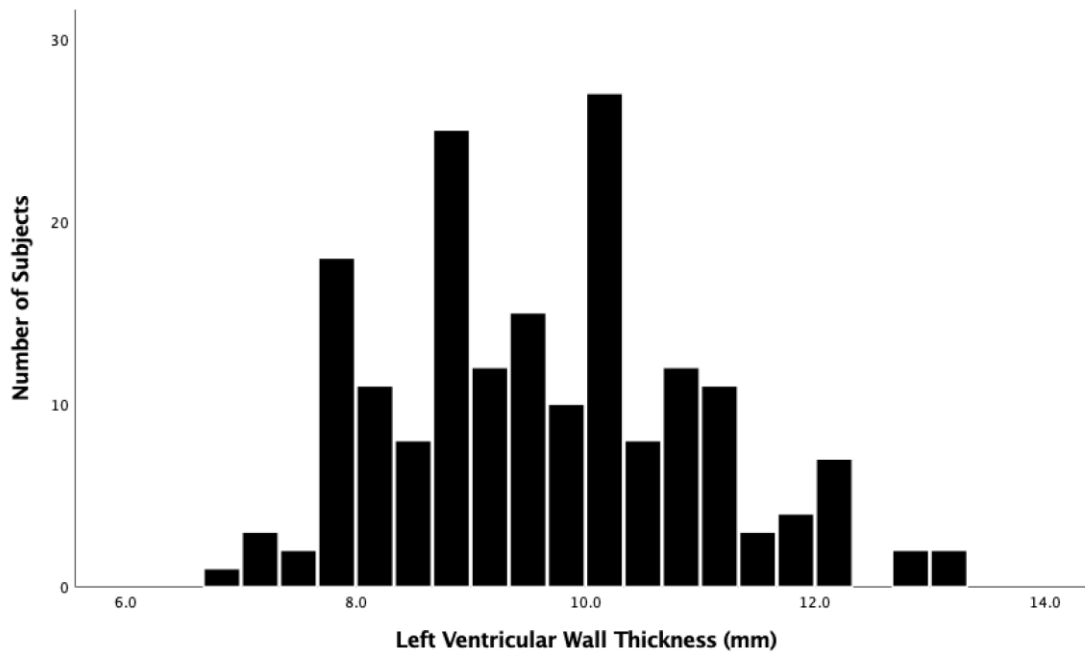


Figure 3.1 Chart Demonstrating Distribution of LVWT.

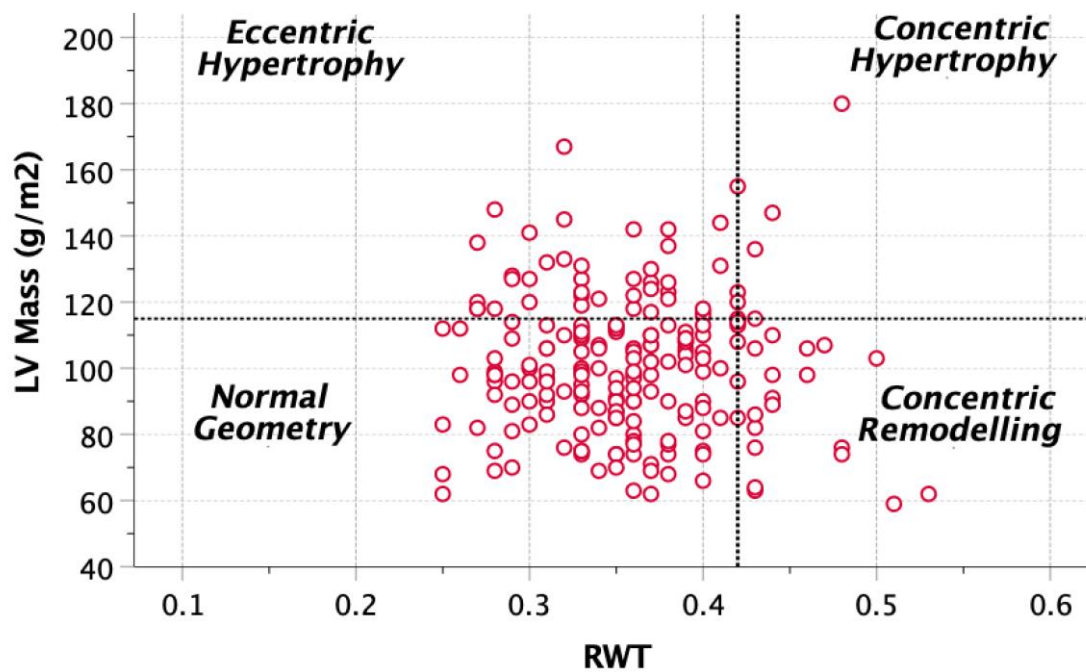


Figure 3.2 Scatter Plot of Distribution of LV remodelling Patterns.

Table 3.1 Summary of 2D Transthoracic Parameters of all Participants.

Left Ventricle		Left Ventricle	
LVIDd, mm	50 (4)	LVIDd >56mm, n (%)	22 (10)
LVIDs, mm	34 (4)	LVIDs >41mm, n (%)	5 (2.4)
Maximum wall thickness, mm	9 (2)	Maximum wall thickness >12mm, n (%)	6 (2.9)
LV mass indexed, g/m ²	103 (32)	LV mass indexed >110 g/m ² , n (%)	66 (31)
Relative Wall thickness	0.41 (0.42)	LV Geometry	
LVEDV, ml	148 (28)	Concentric Remodelling, n (%)	16 (7.9)
LVESV, ml	58 (13)	Concentric Hypertrophy, n (%)	13 (6.4)
LVEF (Simpson's biplane), %	61 (5)	Eccentric Hypertrophy, n (%)	42 (21)
GLS, %	-19 (2)	LVEDV >156 ml, n (%)	70 (40)
E/A ratio	1.4 (0.4)	LVESV >62 ml, n (%)	68 (33)
E/e' ratio	5.8 (1.6)	LVEF (Simpson's biplane) <55%, n (%)	20 (10)
Mitral S', cm/s	12 (3)	<50%, n (%)	1 (0.5)
Right Ventricle		Mitral S' <5.7cm/s, n (%)	2 (0.9)
RVD 1, mm	42 (5)	Right Ventricle	
RVD 2, mm	33 (5)	RVD 1 >43 mm, n (%)	87 (42)
RVD 3, mm	84 (13)	RVD 2 >35 mm, n (%)	53 (26)
RVOT 1, mm	33 (5)	RVD 3 >87 mm, n (%)	78 (38)
RVOT 2, mm	23 (4)	RVOT 1 >47 mm, n (%)	2 (1.0)
FAC, %	45 (9)	RVOT 2 >28 mm, n (%)	18 (9)
TAPSE, mm	26 (5)	FAC, <35%, n (%)	23 (12)
RV S' wave, cm/s	14 (2)	TAPSE <17 mm, n (%)	2 (1.0)
TR Vmax, cm/s	10 (11)	RV S' wave, <9 cm/s, n (%)	1 (0.5)
Atria		Atria	
LAVi, ml/m ²	42 (11)	LA Volume indexed, >34 ml/m ² , n (%)	142 (78)
RA area, cm ² /m ²	22 (4)	RA area >22 cm ² /m ² , n (%)	95 (45)

FAC, Fractional Area Change; GLS, Global Longitudinal Strain; LAVi, Left Atrial Volume Indexed; LVEDV, Left Ventricular End Diastolic Volume; LVEF, Left Ventricular Ejection Fraction; LVESV, Left Ventricular End Systolic Volume; LVIDd, Left Ventricular Internal

Diameter End Diastole; LVIDs, Left Ventricular Internal Diameter End Systole; RA, Right Atrium; RV, Right Ventricular; RVD, Right Ventricular Diameter; RVOT, Right Ventricular Outflow Tract; TAPSE, Tricuspid Annular Plane Systolic Excursion; TR, Tricuspid Regurgitation. Data are expressed as mean (SD).

3.4 Blood Pressure Profile

All 214 athletes underwent resting 'office' and exercise blood pressure measurement on day 1 of testing. Ambulatory BP data was available for 207 athletes; 4 athletes did not undergo monitoring as there was no monitor available on day 1 and they then failed to subsequently attend for day 2 CT scanning and concurrent monitor fitting, and the remaining 3 had insufficient data to allow meaningful interpretation.

The mean resting 'office' BP was 129 (SD 14) / 79 (SD 8) mmHg and almost a quarter (23%) of athletes met criteria for being resting 'office' hypertension ($\geq 140/90$ mmHg) i.e., following a 15-minute period of semi-recumbence and calm, taking the mean of the latter two of three measurements. The majority (78%) of athletes with raised 'office' BP met criteria for grade 1 hypertension. Sixty-five athletes (30%) met criteria for a high normal 'office' BP ($\geq 130-140/85-90$ mmHg) and therefore in total more than half (53%) of the athletes met criteria for an abnormal 'office' resting BP. This data is summarised in Table 3.2

Table 3.2 Prevalence of Resting ‘Office’ Hypertension according to ESC Guideline

Classifications.

Grade of hypertension	N (%)
Total Abnormal, <i>n</i> (%)	115 (53.7)
Total Hypertensive, <i>n</i> (%)	50 (23.4)
High Normal, <i>n</i> (%)	65 (30.4)
Grade 1, <i>n</i> (%)	39 (18.2)
Grade 2, <i>n</i> (%)	10 (4.7)
Grade 3, <i>n</i> (%)	1 (0.5)

Abnormal ‘office’ blood pressure defined as $\geq 130/85$ mmHg, hypertensive defined as $\geq 140/90$ mmHg, high-normal ‘office’ BP defined as 130-139/85-89 mmHg, grade 1 defined as 140-159/90-99mmHg, grade 2 defined as 160-169/100-109mmHg and grade 3 defined as ($\geq 180/110$ mmHg).

Average 24-hour ambulatory blood pressure was 118 (SD 11) / 76 (SD 6) mmHg with a diurnal mean of 123 (SD 9) / 80 (SD 7) mmHg and nocturnal mean of 106 (SD 10) / 66 (SD 7) mmHg. Thirty eight percent (79/207) of athletes met the diagnostic criteria for ambulatory hypertension. Of these athletes, 24% (49/207) met the criteria for masked hypertension i.e., met criteria for ambulatory hypertension but had a resting BP $< 140/90$ and 14% (28/207) of these met the diagnostic criteria for ambulatory hypertension and had a high normal blood pressure at rest. Finally, 22 athletes (11%) met the ESH criteria for the white coat hypertension i.e., a raised resting ‘office’ BP $\geq 140/90$ mmHg but an average ambulatory monitoring BP $< 130/80$ ²⁶⁰ and 32 (15%) had a high normal BP in the absence of ambulatory hypertension, accounting for almost half of both these groups. The demographic features

and CVS risk profile of athletes with ambulatory hypertension and athletes without ambulatory hypertension are summarised in table 3.3.

The average maximum exercise BP during CPET was 207 (SD 23) / 78 (SD 9) mmHg with 35% of athletes demonstrating a hypertensive response to exercise as defined by a systolic BP ≥ 220 mmHg.

Table 3.3 Baseline Demographics and Cardiovascular Risk Profile in Athletes with and without Criteria for Ambulatory Hypertension.

	Normal Ambulatory BP N = 128	Ambulatory Hypertension N = 79	P value
Demographics			
Age, y	51.20 (6.68)	51.44 (7.72)	0.81
Height, cm	178.25 (174.25-183)	178.00 (173-181)	0.09
Weight, kg	74.61 (9.29)	75.78 (8.18)	0.38
Ethnicity			
Caucasian	119 (92.97)	74 (93.67)	0.85
Exercise History			
Sporting Discipline			
Multi-Endurance	80 (62.5)	48 (60.75)	Reference
Running	31 (24.22)	17 (21.52)	0.80
Cycling	17 (13.28)	14 (17.72)	0.43
Years Endurance Exercise, y	16 (10-30)	15 (7-30)	0.96
MET-hours/week	95.20 (74.35-128.13)	107.50 (75.02-147.75)	0.94
Lifetime MET-years	2.09 (1.00-4.54)	1.97 (0.84-5.12)	0.65
VO ₂ Max, ml/kg/min	50.03 (7.13)	50.1 (6.47)	0.99

VO₂ Max Percentage Predicted, %	154 (20.58)	155.10 (17.02)	0.65
Max CPET Heart Rate, %	95.86 (6.57)	97.60 (7.14)	0.08
Cardiovascular Risk			
Total Cholesterol, mmol/l	5.10 (0.88)	5.10 (0.76)	0.95
LDL Cholesterol, mmol/l	2.71 (0.81)	4.75 (1.39)	0.60
HDL Cholesterol, mmol/l	1.82 (0.48)	1.78 (0.41)	0.81
Random Glucose, mmol/l	4.80 (0.77)	5.15 (0.89)	0.005*
Framingham Risk Score, %	3 (1.53-4.78)	3.7 (2-6.1)	0.15
HeartScore®, %	3 (2-4.4)	3 (2-5.5)	0.05

MET, metabolic equivalent; PCAT, peri-coronary adipose tissue attenuation; VO₂, volume of oxygen consumed; y, years

Data are presented as mean (SD), median (interquartile range) or n (%).

*p<0.05, n = 207

3.5 CT Coronary Calcium Scoring and CCTA

A total of 203 (95%) athletes successfully completed CAC scoring and CCTA. The mean radiation dose was 2.73mSv (SD 1.55). A CACs ≥100 AU was present in 16.2% of athletes with over a quarter (26%) lying above the 75th centile for the general population. Forty four percent of all athletes had evidence of coronary plaques. Fourteen percent had either or both partially calcified and non-calcified (12%) and/or non-calcified plaque (2%) and 30% had calcified plaque(s). The majority (40%) of plaques were found in the left anterior descending (LAD) artery with 28% specifically in the proximal LAD. There was a total of 15 stenoses greater than 50%, in 11 (5%) athletes, all of whom had a lesion either within the

proximal (n=4) or mid (n=7) LAD. Thirteen percent of the cohort had evidence of plaque vulnerability markers; the most prevalent marker was spotty calcification (11.3% of athletes, 12.9% of all plaques) followed by positive remodelling (8.9% for both), low attenuation plaque (3.9%) and napkin ring sign (2%) (see figure 3.3). Eleven percent (11.4%) had evidence of TCFA. Sixty athletes (28%) had a PCAT $\geq$ -68.2 Hounsfield Units (Hu) and the median PCAT was -72.64 Hu (IQR -79.98- -67.21).

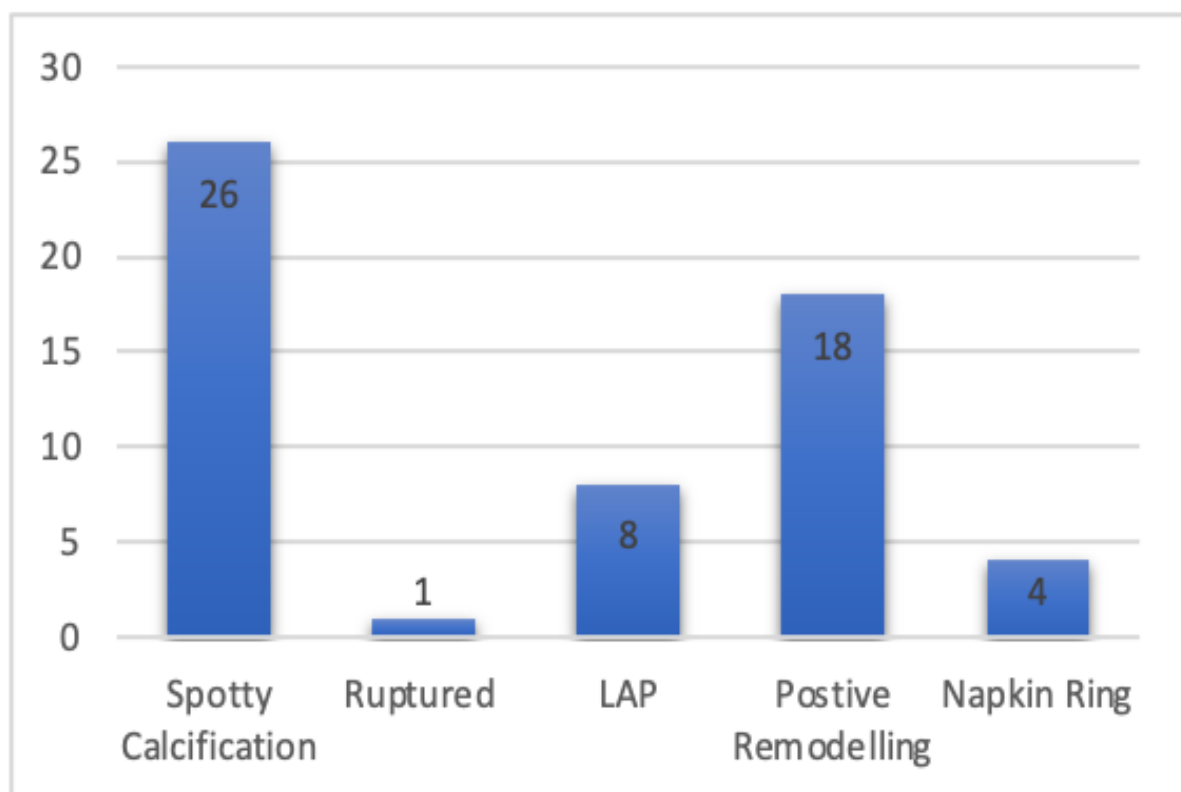


Figure 3.3 Bar Chart showing prevalence of specific plaque vulnerability markers amongst all athletes. Data is derived from assessment of plaques on CCTA (n=202).

Four athletes underwent coronary intervention because of the CCTA findings. Three athletes required percutaneous coronary intervention (PCI) to the LAD or its branches for a severe stenosis, 2 of which were FFR guided. One athlete with partially calcified morphology disease had a blocked LAD, severe disease in the first diagonal and first and second obtuse

marginal branches and evidence of prior infarction on cardiovascular MRI with good viability, was deemed to warrant coronary artery bypass surgery.

Chapters 4, 5 and 7 provide an extensive analysis and discussion of the CT findings and their relationships to explanatory factors.

3.6 MRI

Of the 214 eligible athletes who completed day 1 of testing, 181 (85%) were eligible to continue and attended and successfully completed cardiovascular MRI scanning. Scanning was abandoned in one athlete due to claustrophobia. Of the remaining 32 missing participants, 25 athletes were unable to attend during available scanning sessions, 3 athletes ceased to respond to correspondence, 1 athlete withdrew having developed a prostate malignancy, one other withdrew as following CT scan he was found to have a blocked LAD and underwent bypass surgery, 1 moved abroad and one had undergone CMR as part of another study and did not wish to travel for a repeat scan.

As demonstrated in the table below, athletes exhibited lower LV and RV mass and volumes and higher LV and RV ejection fractions compared to the reference values offered by D'Ascenzi *et al.*²⁷⁴

Table 3.4 MRI characteristics of ventricular size and function with reference ranges for endurance athletes.

Left Ventricle		Normal Range for Endurance Athlete²⁷⁴
LV Mass, g	126 (31)	142 ± 4 (95% CI 134-151)
LV mass Indexed, g/m ²	65 (16)	72 ± 2 (95% CI 68-76)
LVEDV, ml	200 (63)	208 ± 6 (95% CI 195-220)
LVESV, ml	70 (19)	74 ± 2 (95% CI 68-79)
LVEDV Indexed, ml/m ²	103 (33)	111 ± 4 (95% CI 104-121)
LVESV Indexed, ml/m ²	36 (10)	49 ± 2 (95% CI 45-55)
LVEF, %	65 (6.1)	59 ± 1 (95% CI 58-61)
LV Stroke Volume, ml	123 (28)	125 ± 4 (95% CI 116-135)
LV Stroke Volume Indexed, ml/m ²	64 (15)	63 ± 6 (95% CI 45-79)
Right Ventricle		
RVEDV, ml	196 (34)	230 ± 7 (95% CI 214-245)
RVESV, ml	74 (24)	101 ± 4 (95% CI 91-110)
RVEDV Indexed, ml/m ²	101 (18)	120 ± 3 (95% CI 113-126)
RVESV Indexed, ml/m ²	38 (12)	55 ± 2 (95% CI 49-61)
RV Stroke Volume, ml	121 (28)	123 ± 4 (95 % CI 112-134)
RV Stroke Volume Indexed, ml/m ²	62 (15)	65 ± 2 (95% CI 52-56)
RVEF, %	63 (7.2)	54 ± 1 (95% CI 52-56)

LVEDV, Left Ventricular End Diastolic Volume; LVEF, Left Ventricular Ejection Fraction;

LVESV, Left Ventricular End Systolic Volume; RVEDV, Right Ventricular End Diastolic Volume;

RVEF, Right Ventricular Ejection Fraction; RVESV, Right Ventricular End Systolic Volume.

LGE was present in 32% of athletes with RV insertion point LGE identified in 23% and pathological LGE in 11% i.e., non-insertion point subendocardial, subepicardial or mid wall enhancement. Four athletes (2.2%) had evidence of LGE in an ischaemic pattern and 15 (8.3%) exhibited non-ischaemic i.e., 13 mid-wall and 2 subepicardial MF. The distribution of non-ischaemic LGE was limited to the basal to mid lateral (n=12), inferior walls (n=2), and basal septal walls (n=1) and 2 of these athletes exhibited accompanying LV systolic dysfunction. None of these athletes with LGE demonstrated any VA on rhythm testing. Further details and analysis of the MF and scar data is provided in chapter 6.

There were no additional onward referrals required for MRI findings over and above those already made for abnormalities detected by investigations performed earlier in the study.

3.7 Electrocardiogram

All 214 athletes underwent 12-lead ECG, which were of high quality allowing precise interpretation. The mean heart rate was 54 beats per minute (BPM). Details of all ECG findings are provided in table 3.5.

Table 3.5 Findings of 12 lead resting ECG.

ECG Feature	N (%)
Sinus Rhythm	213 (99.5)
Sinus Arrhythmia	3 (1.4)
Sinus Bradycardia (HR<60bpm)	160 (74.8)
Junctional Rhythm (V>A)	1 (0.5)
1st Degree AV block	39 (18.2)
2nd Degree AV block	0 (0)
LBBB	3 (1.4)
RBBB	2 (1)
Interventricular Conduction Delay	3 (1.4)
Atrial Ectopics	6 (2.8)
Ventricular Ectopics	2 (1)
Pre-excitation	1 (0.5)

Of the 3 athletes with LBBB, one had evidence of an aneurysmal LV despite normal coronaries, the second had a CAC score of over 800 with non-calcified plaque and multiple plaque vulnerability markers and the third had no evidence of any cardiac disease apart but revealed ambulatory hypertension. Forty-three athletes met the criteria for LVH. Only 1 athlete demonstrated pathological q waves who was found to have a blocked LAD and underwent bypass surgery and 1 athlete demonstrated pathological T wave inversion (V5-V6, II and aVL) with no evidence of any cardiac abnormality detected despite the full spectrum of testing. The six athletes who showed atrial and 2 athletes with ventricular ectopics (VEs) had no cardiac substrate identified on testing. The 1 athlete who demonstrated ECG features of pre-excitation i.e., short PR interval and delta wave and was asymptomatic with otherwise normal investigations.

3.8 24-Hour Holter Monitoring

Holter monitoring data was successfully collected from 209 athletes. One monitor failed in-situ and 4 athletes did not undergo monitoring as there was no monitor available on day 1 and subsequently failed to attend for day 2 CT scanning and concurrent monitor fitting.

All athletes were in a predominantly sinus rhythm with 36 demonstrating sinus arrhythmia. The mean minimum heart rate was 43 BPM (SD 6). Two athletes showed an intermittent junctional rhythm with retrograde p-waves. First degree AV block was frequent in 192 athletes and 16 demonstrated episodes of Wenckebach. There was no evidence of any higher degree AV block. None of the athletes had evidence of AF.

Thirty nine percent of athletes had >10 VEs. Three athletes had a 5-10% frequency of VEs but none of the athletes had more than 10%. One of these athletes demonstrated 8 beats of non-sustained VT at a rate of 176bpm with a narrow RBBB morphology and an inferior axis suggestive of a left anterior fascicular origin. The athlete had a structurally normal heart on echo and CMR, a normal CAC score and no evidence inducible myocardial ischaemia on CPET. The second athlete had VEs also on CPET, with a LBBB morphology, early transition, and inferior axis suggestive of an RVOT origin, that increased with exercise in the context of a normal CAC score, no coronary stenosis, and no scar on MRI. The third athlete had VEs with a LBBB pattern with late transition and an inferior axis, suggestive of a RV free wall origin. The CCTA showed no coronary abnormality, and the MRI was free of MF; however, he was found to have ambulatory hypertension. One athlete demonstrated 5 beats of NSVT on Holter at a rate of 134 bpm with an RV free wall morphology. There was no evidence of

ischaemia on CPET, the CAC score was zero and no scar on MRI; however, this athlete also demonstrated ambulatory hypertension.

3.9 CPET

All 214 athletes underwent exhaustive cycle ergometry CPET. Athlete's fitness levels measured by CPET revealed a mean VO_2 max of 49ml/kg/min (SD 7) giving a mean percentage predicted of 154% for age and size (SD 19). They achieved a mean Wattage of 331 Watts (SD 53) and 14.2 METS (SD 2.0). The average maximum percentage HR achieved was 97% (SD 7) of the maximum predicted for age. Only 1 athlete showed ECG evidence of ischaemia and was found to have an aneurysm of the left main stem (LMS) leading into the LAD on CCTA. Fourteen athletes had poor quality ECG tracings that prevented reliable interpretation.

Six athletes (2.8%) had VEs with a RBBB and superior axis morphology suggestive of LV inferior wall origin. None of them demonstrated an increase in frequency of ectopics with exercise. Three had evidence of mid wall or subendocardial lateral wall scar on MRI and 2 of these athletes plus one other with VEs but without scar, met the criteria for ambulatory hypertension.

Six athletes (2.8%) had VEs that increased in frequency with increasing exercise load. None of these athletes demonstrated ischaemic ECG changes or myocardial scar on CMR and only 1 had diseased coronary arteries with a CAC score greater than 1000 AU and a significant calcified stenosis in the proximal LAD. In addition, one of these 6 athletes had a bicuspid aortic valve with moderate aortic regurgitation, and another had a suspected healed

muscular ventricular septal defect, low normal LV function and concentric remodelling. The latter athlete also exhibited non-sustained VT originating in the RVOT at peak exercise.

Finally, a total of four athletes manifest asymptomatic non-sustained VT during exercise, 3 with a LBBB with early transition and inferior axis morphology consistent with an RVOT origin and one with a LBBB pattern with late transition and an inferior consistent with an RV free wall origin. None of these athletes had an abnormal resting ECG, a CAC score >100 AU or significant CAD or any evidence of myocardial scar on CMR. The athlete demonstrating non-sustained VT originating in the RV free wall and was found to be hypertensive.

3.10 Discussion

Overall, the cohort of athletes in this thesis is representative of the common majority of recreational male master endurance athletes in the UK, which is helpful to physicians when applying the findings to their practice in the evaluation and management of such individuals.

3.10.1 Cardiovascular Risk

Although this cohort were considered to be very low risk having been screened for any known cardiovascular risk factors and disease prior to recruitment, and excluding those with known hypertension and hypercholesterolaemia, calculation of the HeartScore® showed 26% to be at high-risk and 2 athletes (0.9%) at very high risk i.e. 10-year coronary risk $5 \leq 10$ and $\geq 10\%$, respectively; highlighting that despite declaring themselves as free of cardiac risk factors, symptoms or disease, some athletes in this cohort were not truly low-risk and warrant systematic preparticipation evaluation. D'Ascenzi *et al* also found that even

younger elite Olympic endurance athletes, although at lowest risk compared to other sporting disciplines, were not immune from cardiovascular risk with 3.8 % diagnosed with hypertension and 32% meeting criteria for dyslipidaemia.²⁶

3.10.2 Echocardiography

The echocardiographic parameters revealed in analysis of this cohort are largely consistent with known adaptive changes recognised amongst older endurance athletes, with dilatation of all 4 chambers, in particular LA dilatation in which the mean indexed volume was 24% above the upper limit with almost 80% showing volumes above the normal range.^{6,99,100,275}

The mean MWT of 9.2mm (SD 1.5) is slightly lower than that found amongst a group of young adults (mean 20 years) athletes ($10\text{mm} \pm 1.5$)²⁴³ (figure 3.4) which is contrary to the existing data showing greater MWT amongst these athletes.²⁷⁶ Possible explanations for this include that the younger cohort exercised for a mean of 14 ± 7 hours per week compared to 8.5 hours (6-12 hours) in this cohort and differences in sporting category with the younger athletes participating in mixed sports including boxing, soccer, rugby, tennis, sprinting and long distance as opposed to endurance sports.

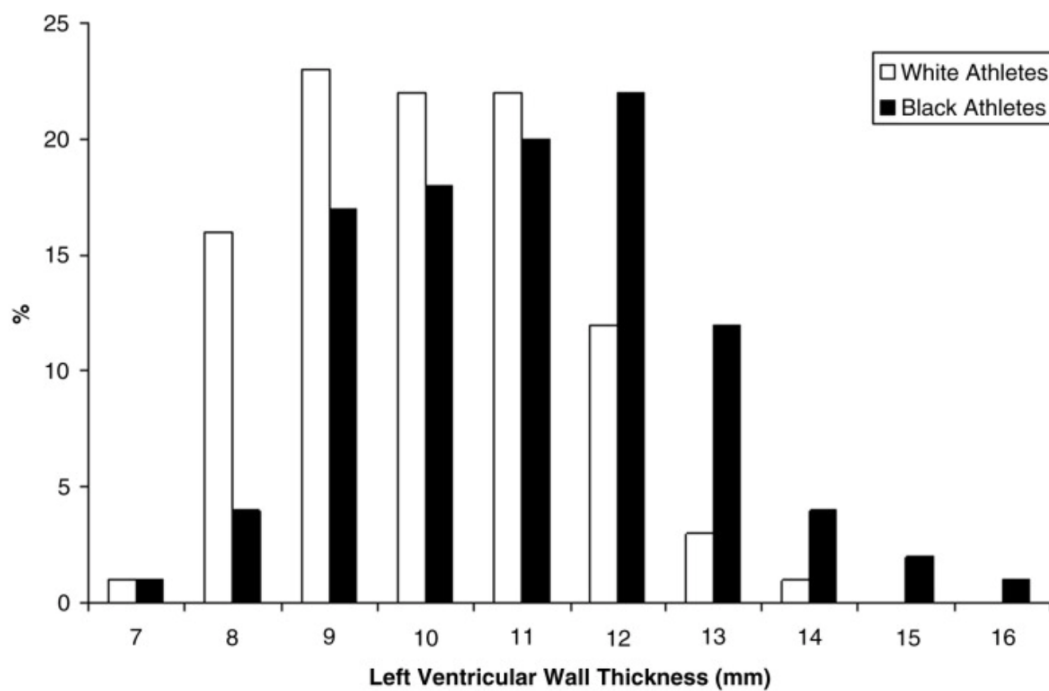
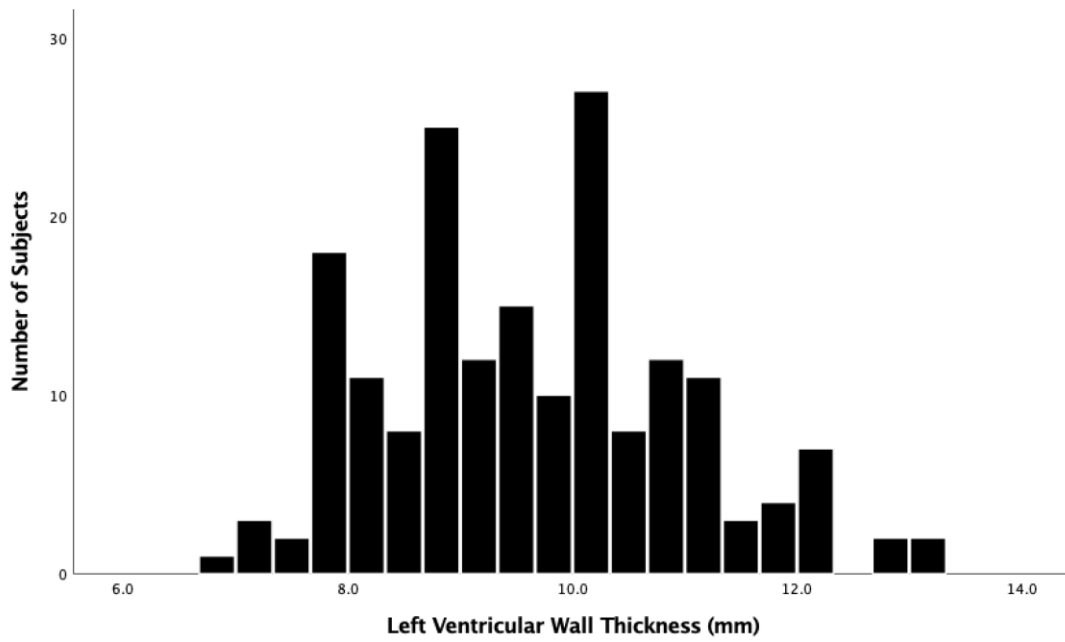


Figure 3.4 Comparative bar charts of LV MWT in this cohort (above) and 300 young adult athletes (below). (White bars represent White athletes and black bars represent Black athletes).²⁴³

Consistent with data from both young (21.8 years)⁹⁵ and older (41.6 years)¹⁰¹ male endurance athletes, eccentric hypertrophy was the commonest type of adaptive LV geometry identified i.e., 21% vs 19% vs 28.3%, respectively. Athletes with eccentric remodelling were more likely to have ambulatory hypertension compared with those athletes with normal geometry (42% vs 36%), although this finding did not meet statistical significance ($p=0.63$). Similar was found for concentric hypertrophy (54%, $p=0.19$), the commonest finding amongst hypertensive patients in the general population.²⁷⁷ The potential contribution of BP to cardiac remodelling amongst endurance athletes is worthy of exploration in future studies.

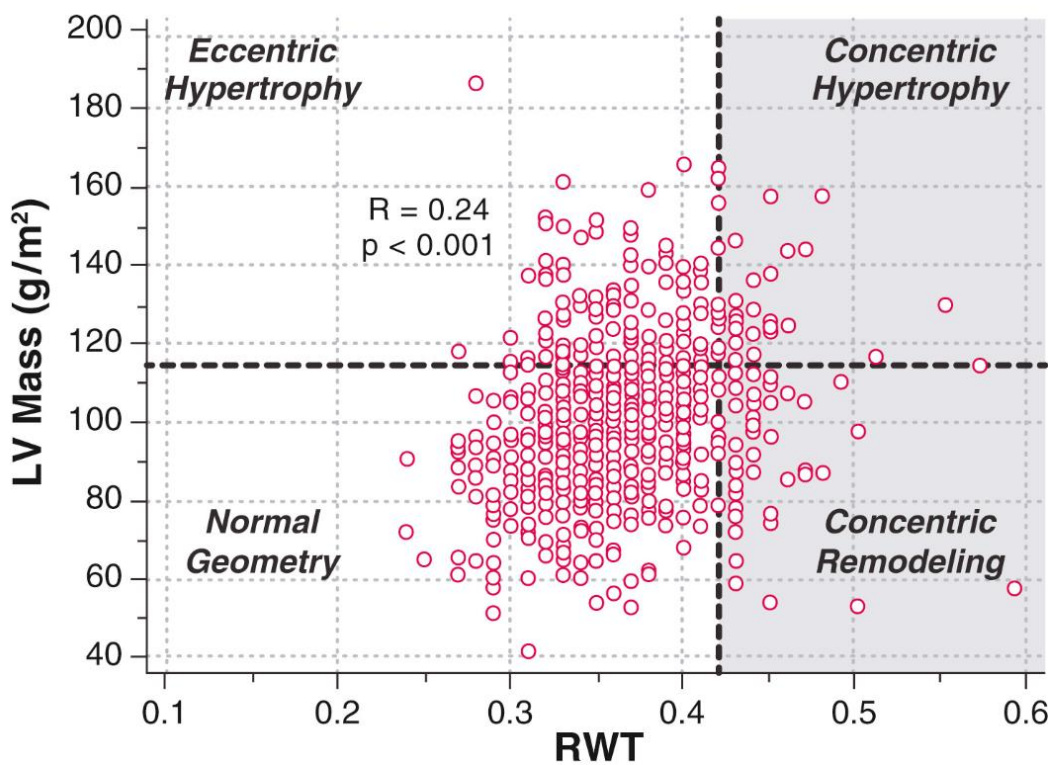
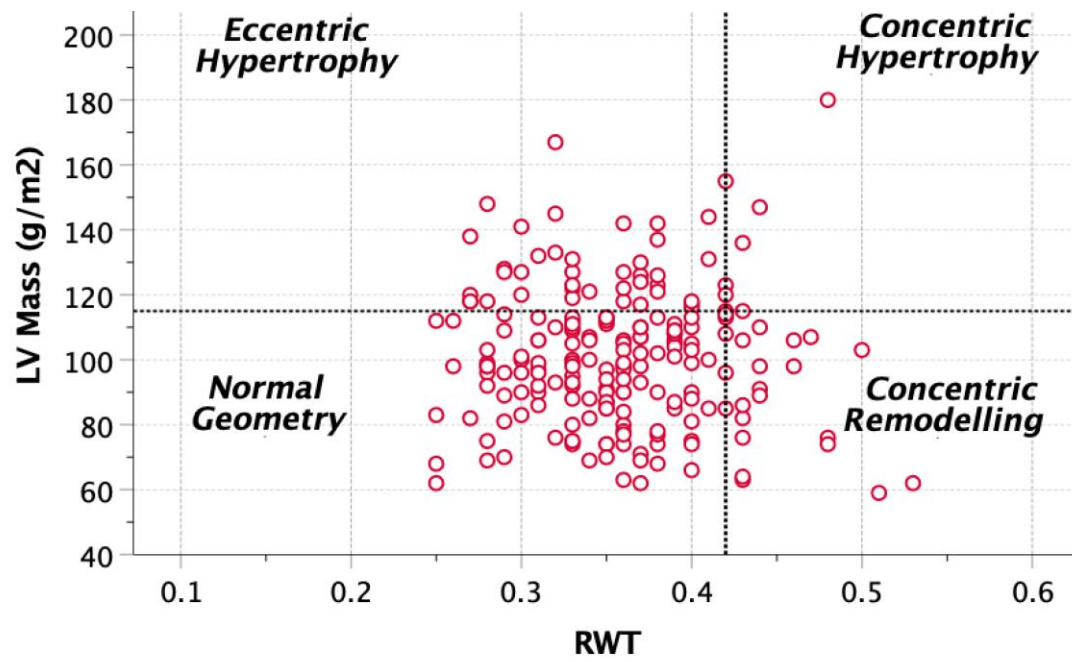


Figure 3.5 Scatter plot (above) of data from this cohort demonstrating pattern of LV remodelling and (below) data from the study of young males (21.8 ± 5.7 years) by Finocchiaro *et al.*⁹⁵

3.10.3 Prevalent Hypertension

Although endurance training reduces BP by an average of 3.5mmHg systolic and 2.5mmHg diastolic²⁷⁸ and regular moderate intensity exercise has been shown to reduce mortality by 15%;²⁷⁹ a high-normal (135-140/80-85mmHg) 'office' blood pressure (30%), resting 'office' blood pressure $\geq 140/85$ mmHg (23%), ambulatory (38%) and masked hypertension (24%), are prevalent amongst this population²⁸⁰ Despite no athlete having a known history of hypertension at recruitment, over half demonstrated an abnormal 'office' resting BP i.e., $\geq 135/80$, which in the general population would warrant at a minimum annual recording and consideration of ambulatory BP monitoring or home-monitoring to rule out masked hypertension.²⁶⁰ However, almost half of these athletes (47%) had normal ambulatory monitoring which is the gold standard diagnostic test for hypertension, suggesting the finding of a raised 'office' BP was not a true reflection of underlying hypertension but a consequence of white coat hypertension amongst these individuals, a finding which is known to be more prevalent amongst athletes.²⁸¹ As such the data for 'office' blood pressure can be assumed to be an over estimation of the true prevalence of hypertension in this cohort. Comparing this cohort to the UK male general population data by age-group, the overall prevalence of hypertension is lower amongst athletes, particularly in the older age group, but remains important. Further figures demonstrating this finding are provided in table 3.6.

Table 3.6 Comparison of Hypertension Prevalence Data from 2017 Health Survey for England (left column) and ABPM Data from this Study (right column).²⁸⁰

Age	General Population (%)	Endurance Athlete Study Participants (%)
35-44 (athletes all 40-44)	19	19
45-54	26	32
55-64	45	28

The data in **table 3.3** shows the baseline characteristics and CVS risk profile according to the presence or absence of ambulatory BP. Ambulatory BP is considered the gold standard diagnostic test for hypertension; it is an easy and non-invasive test to undertake and a better predictor for end-organ damage including coronary atherosclerosis, and morbid and fatal events including MACE and stroke,^{282–284} than office BP. Overall, athletes in the 2 groups were well matched based on their baseline characteristics with only a significant difference in random glucose found, although both values remain well below the normal range of <11.1 mmol/l.

A HRE was prevalent amongst this cohort (35%). Caution must be exercised when interpreting this information given the lack of consensus and evidence-based cut-off for HRE.

According to the latest European guidelines for the management of hypertension,²⁶⁰ 38% of the cohort required treatment for hypertension based on a diagnosis made using the gold

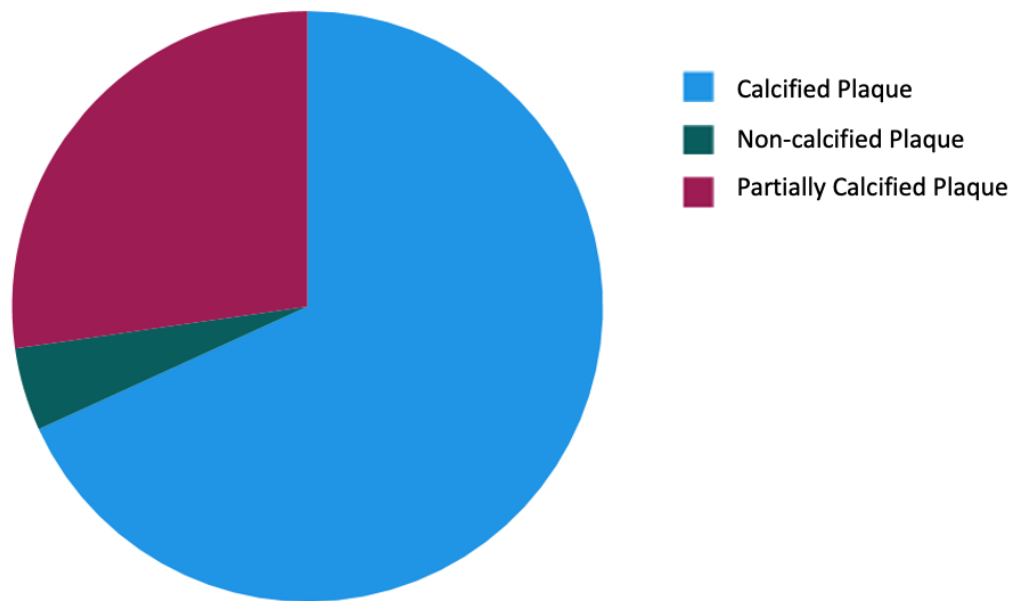
standard measurement of ambulatory monitoring. Nine percent merited further investigation using either ambulatory or home monitoring based on a diagnosis of resting 'office' hypertension and a further 21% required on-going monitoring due the finding of either a high-normal resting 'office' BP or an exaggerated response to exercise. Therefore, over half (58%) of the cohort required further action based on their screening for BP and the time and cost implications of this must be considered.

This thesis demonstrates that athletes are certainly not immune to the development of hypertension. It is novel in its identification of prevalent undiagnosed hypertension amongst male master endurance athletes. Although it is most likely that these athletes have developed essential hypertension due to a combination of lifestyle, genetic and environmental factors. The possible contribution of anabolic steroid abuse, which endurance athletes are known to use to aid strength and recovery,²⁴⁰ and damage because of overuse of NSAIDS, are also worthy of consideration. Equally, there is data suggesting that anabolic steroid use is associated with a higher volume of coronary plaque and a greater CAC score.²⁸⁵ The use of steroids is notoriously difficult to evaluate due to athletes not wishing to divulge such information and become exposed with consequences for their future competitive pursuits, as such, data relating to this was not collected as part of this thesis. Given the prognostic significance of hypertension as a major CVS risk factor in the general population, the prognostic relevance of these findings amongst athletes is worthy for further exploration.

3.10.4 Coronary Artery Disease

This study demonstrates prevalent CAC amongst male master endurance athletes (16.2%), in line with the current existing data (18.8%).^{6,7,286} Although CAC score is predictive for MACE in non-athletes,^{149,150} it is not known if this applies to endurance athletes. This is the first study to identify that seemingly low-risk master endurance athletes not only harbour a non-negligible amount of partially calcified and non-calcified morphology plaque but also a number have plaque vulnerability markers including thin-capped fibroatheroma which represent more direct measures of MACE risk. The pie chart in figure 3.6 shows the distribution of plaque morphology type and is comparable to previous studies of male master athletes.^{6,7} More than a quarter of athletes (28%) were also found to have positive RCA PCAT values, again a novel measure amongst this cohort that is suggestive of active coronary inflammation and translates to MACE risk in the general population. Given that there is a complex acute and chronic relationship between exercise and inflammation further research is warranted to explore its validity in this context, to support the potential clinical application of PCAT evaluation. These additional parameters offer further data for risk stratification of the master endurance athlete that require minimal additional post-processing time to glean the data and is therefore highly effective.

Figure 3.6 Pie Chart of Distribution of Plaque Morphology



3.10.5 Cardiovascular MRI

The mean value for the EF amongst this cohort (65%) is slightly higher than the values given in the recent data from meta-analysis from D'Ascenzi *et al*²⁷⁴ that provides CMR normal range values for an endurance athlete i.e., upper limit 59%.²⁷³ The reason for this may be the differences in the mean age of participants i.e., 31 years in the meta-analysis compared to 51 in this study. It is plausible that the relatively small LV cavity size and increase in LV stiffness with increasing age³² prevents the same magnitude of augmentation in stroke volume observed in younger athletes, that results in some young athletes exhibiting a low-normal EF.²⁸⁷

3.10.6 Electrocardiogram

The yield of clinically important abnormalities from the 12-lead ECG was low in this study with only 5 athletes found to have abnormalities requiring further investigation. The presence of a LBBB was consistent with significant CAD amongst 2 of the 3 athletes in which

it was detected, and the pathological Q waves seen in 1 athlete was consistent with prior infarction and a blocked LAD and therefore these ECG features appear to have good specificity, as seen in the general population. Overall, the 12-lead ECG added little additional information to the clinical evaluation of the male master endurance athlete over and above findings on CCTA and failed to identify most individuals (94%) in whom further management was indicated.

3.10.7 Coronary Ischaemia

CPET failed to detect evidence of coronary ischemia in the 4 athletes with significant flow-limiting CAD, suggesting that exercise testing has poor sensitivity for coronary ischaemia in the male master athlete cohort.

3.10.8 Ventricular Arrhythmia

The finding of non-sustained VT and VE's increasing with exercise detected on ECG, 24 Holter or exhaustive CPET was not sensitive for coronary abnormalities or MF, with none of the 10 athletes with these findings exhibiting MF on MRI and only 1 found to have significant CAD. Zorzi *et al* found the QRS morphology of VEs to be an important determinant of arrhythmia risk i.e., ectopics with a broad RBBB and superior axis arising from the LV myocardium that increase in frequency with exercise were associated with LV scar.¹⁸⁵ Three of the 6 athletes in this cohort had ectopics with this morphology and lateral wall epicardial, mid or subendocardial scar, however none of the 6 had an increased frequency of ectopics with exercise, 2 of the 3 were however found to be hypertensive. All athletes with ectopics that increased in frequency with exercise failed to demonstrate a morphology consistent with a left-sided origin and were free of myocardial scar. However, one had significant CAD, one a bicuspid aortic valve and the other had a suspected healed

VSD to explain this finding. Based on this study, ectopic morphology i.e., LV origin was the most sensitive parameter for the detection of myocardial fibrosis with potential prognostic consequences; however, in the absence of long-term prospective outcome data, the risk of life-threatening arrhythmias or SCD associated with VEs, amongst athletes, remains an unknown.

3.10.9 Limitations

Overall limitations of this data will be discussed in the final discussion in chapter 8.

3.10.10 Conclusion

This cohort underwent extensive cardiac examination with cardiac findings consistent with prior studies and current understanding of the master endurance athlete's heart. In addition, it demonstrates that despite declaring no symptoms, cardiac conditions or known cardiac risk factors the majority of these athletes are not low risk and confirms that the exercise test is a poor test for ischaemic in this cohort. It also demonstrates novel findings of an important prevalence of undiagnosed hypertension and high-risk plaques present amongst this cohort, which expands the current understanding of the impact of chronic high-dose endurance exercise on the heart of the male master endurance athlete.

4 The Impact of Sporting Discipline and Exercise Dose on Coronary Artery Disease

4.1 Hypothesis

Exercise dose is a predictor of CAD, and the prevalence of CAD also differs between sporting disciplines with runners demonstrating a greater prevalence of CAD.

4.2 Background

The impact of the amount, intensity and type of exercise an individual undertakes, that can be collectively described as the 'exercise dose', is well recognised to contribute to the type and extent of physiological adaptation of the heart. Associations between exercise dose and cardiac pathology including AF and CAC, have also been described. The true exercise dose of any given athlete is unique and challenging to accurately define. The 2020 ESC guidelines¹⁶ for sports cardiology and exercise in athletes with CAD attempt to delineate those factors that contribute to exercise dose warranting quantification. It defines exercise dose using the acronym 'FITT' i.e., frequency, intensity, time and type / mode. Frequency is defined as the number of sessions per week, intensity refers to the rate of energy expenditure, which in the context of endurance exercise is measured in METs, VO_2 or predicted maximum heart rate achieved. Time represents the number of minutes or hours spent exercising at the given intensity level and the duration of each session. Type refers to whether it's endurance, strength, balance etc. and can be further broken down into the individual sport, and finally mode is defined according to the metabolic type i.e., aerobic or anaerobic and muscle work

e.g. dynamic versus static, continuous versus interval and small versus large muscle groups.

Training volume can be derived from the product of intensity and time.

Although a large number of studies examine differences between exercise types i.e., static versus dynamic in varying proportions and strength versus endurance, few studies have evaluated individual sporting disciplines.^{288–290} One UK study examined mortality according to sports type using data from the Health survey for England and Scotland. The analysis included over 80,000 individuals and demonstrated that whilst swimming was associated with a reduction in risk of all-cause and CVD mortality, cycling was associated with a reduction in all-cause but not CVD mortality and running was not found to be associated with a reduction in either type of reduced mortality risk,²⁹¹ suggesting there are important differences. Most studies to date classify cycling, running and multi-endurance within the same category of endurance exercise, even though long-distance running is considered largely dynamic, whereas, cycling and multi-endurance are considered both high dynamic and high static sports, with known differences in adaptation between the 2 groups, including LV cavity size and wall thickness.²⁹⁰ Table 4.1 shows data from a study of 947 athletes and exemplifies the difference between these values.

Sport	Impact on LVIDd (mm)	Sport	Impact on Wall Thickness (mm)
1) Endurance cycling	5.91	Rowing	2.13
2) Cross-country skiing	5.41	Endurance cycling	2.02
3) Swimming	4.90	Swimming	1.71
4) Pentathlon	4.35	Canoeing	1.70
5) Canoeing	4.23	Long-distance track	1.49
6) Sprint cycling	3.97	Water polo	1.38
7) Rowing	3.87	Sprint cycling	1.35
8) Long-distance track	3.47	Weightlifting	1.23
9) Soccer	3.11	Wrestling/judo	1.21
10) Team handball	2.87	Tennis	1.00
11) Tennis	2.69	Pentathlon	0.98
12) Roller hockey	2.41	Cross-country skiing	0.98
13) Boxing	2.25	Boxing	0.94
14) Alpine skiing	2.13	Roller skating	0.88
15) Fencing	2.09	Soccer	0.76
16) Taekwondo	2.07	Roller hockey	0.69
17) Water polo	2.02	Fencing	0.63
18) Diving	1.70	Sprint track	0.54
19) Roller skating	1.68	Volleyball	0.39
20) Volleyball	1.43	Diving	0.38
21) Bobsledding	1.35	Alpine skiing	0.29
22) Weightlifting	1.32	Field weight events	0.25
23) Wrestling/judo	1.25	Taekwondo	0.23
24) Equestrian	0.43	Team handball	0.19
25) Field weight events	0.18	Equestrian	0.13
26) Yachting	0.10	Bobsledding	0.07
27) Sprint track	0.00	Yachting	0.00

Table 4.1 LV Cavity Size and Wall Thickness According to Sporting Discipline.²⁹² Highlighted in red are the sports relevant to this study cohort. LVIDd, Left Ventricular Internal Diameter.

Other factors that are likely to differ within these sports are the duration of training sessions with triathletes and cyclists generally training for longer, and consistency of effort; with running and multi-endurance being steadier paced, although with greater variety given the multiple sports in multi-endurance sports, and cycling involving periodic bursts of intense effort such as when breaking away or hill climbing. This is exemplified by the fact that a runner is more likely to succumb to SCD at the end of a marathon as opposed to cyclists who have increased risk at the points throughout the race where they are climbing hills.¹² Finally, there are distinct differences between the 3 sports in terms of the muscle

recruitment involved and therefore the CVS haemodynamics, with significantly more muscle groups involved in running than cycling and multi-endurance demanding the recruitment of extensive and differing muscles groups throughout any given event. Aengevaeren *et al* that compared cyclists, runners and mixed (non-endurance) sports (n=284) and found cyclists had less atherosclerotic plaque and a trend towards a lower CAC score compared with runners. The prevalence of partially calcified plaques was similar between cyclists and runners but cyclists were more likely to have lone calcified plaques.²⁸⁹

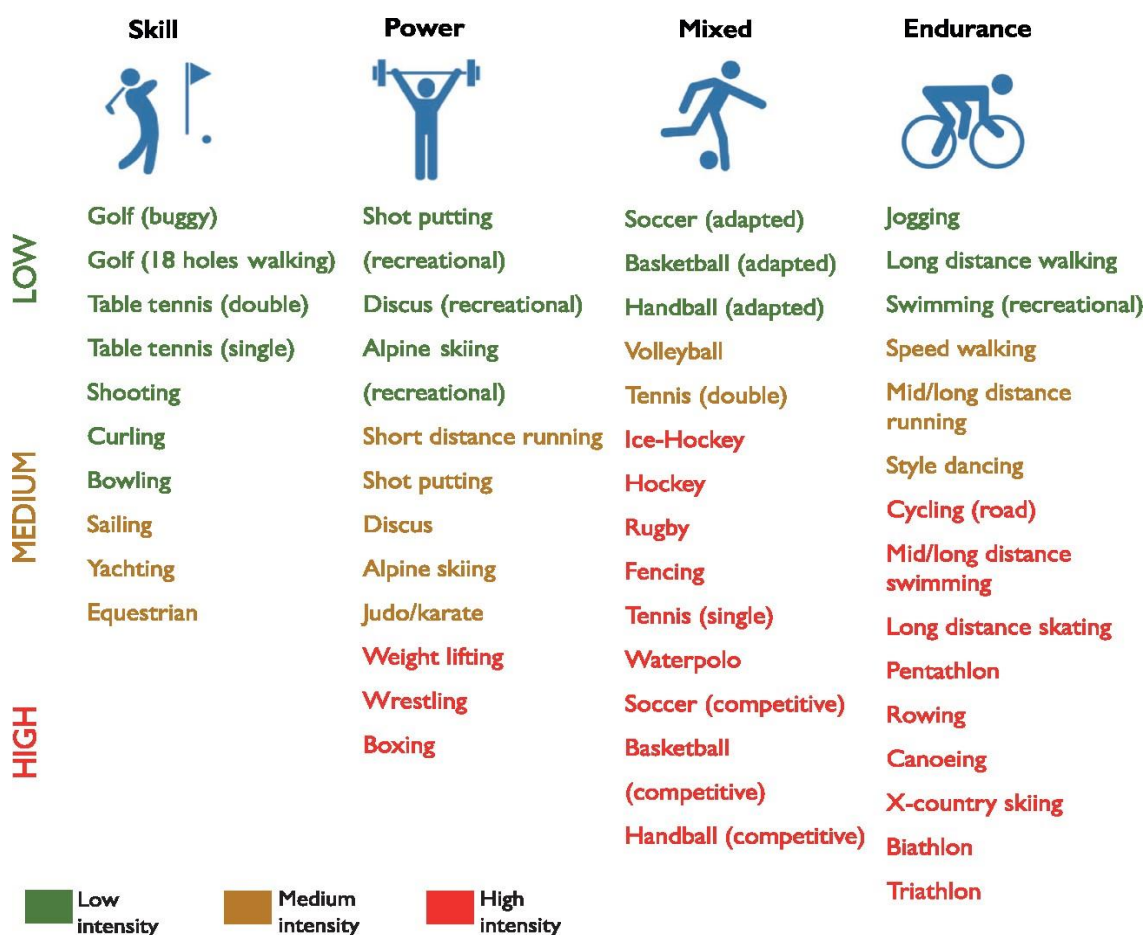


Figure 4.1 Sports Classification According to Sporting Intensity and Mode.¹⁶ Mid and long-distance running is classified as moderate and cycling and triathlon as high intensity exercise.

Two former studies have identified a significant relationship between prevalence of CAC and higher doses of endurance exercise (≥ 2000 -3000 MET-minutes per week),^{7,175} however, the presence of high-risk morphology plaque i.e., partially calcified and non-calcified was less. Aengevaeren *et al* found that despite more athletes having CAC present, there was no dose related difference in the plaque density or area, or number of lesions, and those exercising more did not have higher CAC scores than controls, which is at odds with the findings by Merghani *et al* that only athletes had a CAC score >300 AU ($p=0.009$), suggesting larger areas or increased density, compared to controls. Aengevaeren *et al* also demonstrated that intensity of exercise was a factor, with those exercising most intensively i.e., ≥ 9 METs, demonstrating a greater prevalence of CAC and coronary plaque. Cyclists also appeared to be at lower risk of coronary plaque compared to other non-endurance sporting disciplines.²⁸⁹

Without the long-term prospective data examining the outcomes of CAC in athletes its significance and risk remains unknown. This thesis is novel in its exploration of whether markers of CAD risk including plaque vulnerability markers and PCAT have the same or a different relationship to exercise dose and sporting discipline, affording a greater understanding of the nature of CAD amongst this cohort.

4.3 Methods

4.3.1 Measurement of Exercise Dose

Please refer to **Chapter 2, Section 2.6.11**

4.3.2 CT Coronary Artery Calcium Scoring and CCTA

Please refer to Chapter 2, Section 2.6.8

4.3.3 Statistical Analyses

Years of endurance exercise was used for the primary evaluation of exercise dose as preliminary analyses showed it to be a more important contributory factor than other dose measures. MET-hours per week and lifetime-MET-years may have been more important as they account for both time and intensity; however, there was significant missing data amongst these measures due to the retrospective nature by which these additional data points were collected. Following preliminary exploration of the data, univariate logistic regression, including multinomial regression, was used to explore the outcomes of CACs ≥ 100 AU, stenosis $>50\%$, plaque vulnerability markers, TCFA and plaque morphology, giving the p-values, unadjusted odds ratio (ORs) and relative risk reduction (RRR) for the given outcome, respectively. Univariate linear regression was used for PCAT to obtain unstandardised B values. Subsequently multiple regression was performed using the a priori variables of age, sporting discipline and years of endurance exercise in addition to, the 3 BP variables of resting systolic 'office' BP, ambulatory systolic BP and maximum systolic BP, to obtain adjusted p-values, ORs, RRRs or B coefficients and their respective confidence intervals. An alpha level of 0.05 was adopted as the cut-off for a statistically significant p-value.

4.4 Results

General exercise dose and sporting discipline demographics are provided in chapter 3, section 3.2.3.

4.4.1 Sporting Discipline

Overall, the demographics were similar between sporting disciplines; however, there were a small number of significant differences. Runners were significantly lower in weight and multi-endurance athletes and cyclists had significantly higher VO_2 max values and maximum heart rates on CPET testing compared to runners (table 4.2). Cyclists had a significantly greater lifetime exercise volume (Lifetime-MET-years) compared to runners ($p=0.04$).

Table 4.2 Baseline Demographics According to Sporting Discipline.

	Multi-endurance (M) N = 132	Running (R) N = 49	Cycling (C) N = 33	P value		
				M vs R	M vs C	R vs C
Demographics						
Age, years	51.65 (7.05)	51.22 (7.48)	50.27 (7.68)	0.72	0.32	0.55
Height, cm	178 (173-183)	176.91 (173-181)	180 (176.5-183.75)	0.94	0.61	0.68
Weight, kg	75 (9.01)	72.78 (9.69)	75.33 (7.74)	0.04*	0.72	0.19
Ethnicity Caucasian	123 (93.2)	45 (91.8)	31 (93.9)	0.76	0.87	0.72
Exercise History						
Years Endurance Exercise, years	16 (7.25-31.5)	14 (8.5-30)	16 (11-30)	0.34	0.92	0.53
MET-hours/week	102.9 (77.36-143.89)	82.90 (68.22-101.71)	117.2 (85.7-163.2)	0.14	0.36	0.06
Lifetime MET-years	2.12 (0.91-4.89)	1.37 (0.74-3.59)	2.91 (1.78-5.93)	0.06	0.50	0.04*
VO ₂ Max, ml/kg/min	49.69 (6.51)	47.46 (6.71)	54.21 (47.8-60.05)	0.05*	<0.001*	<0.001*
VO ₂ Max Percentage Predicted, %	154.72 (16.95)	144.59 (6.71)	166.67 (22.40)	0.001*	0.002*	<0.001*
Max CPET Heart Rate, %	95.96 (6.46)	95.61 (7.92)	101.15 (4.76)	0.75	<0.001*	<0.001*
Cardiovascular Risk						
Total Cholesterol, mmol/l	5.14 (16.95)	5.02 (0.82)	5.14 (0.76)	0.43	0.97	0.53
LDL Cholesterol, mmol/l	2.74 (0.78)	2.62 (0.73)	2.83 (0.82)	0.33	0.58	0.23
HDL Cholesterol, mmol/l	1.82 (0.46)	1.85 (0.46)	1.74 (0.43)	0.66	0.36	0.28
Random Glucose, mmol/l	4.97 (0.80)	4.76 (0.89)	5.11 (0.81)	0.13	0.40	0.07
Framingham Risk Score, %	4.97 (0.80)	4.76 (0.89)	5.11 (0.81)	0.54	0.85	0.77
HeartScore®*, %	3.67 (1.93)	3.55 (2.19)	3.56 (1.70)	0.72	0.79	0.98

*ESC Endorsed updated (SCORE2) version of HeartScore®.

cm, centimetres; CPET, Cardiopulmonary exercise test; C, Cycling; HDL, High Density Lipoprotein; Kg, kilogrammes; LDL, Metabolic equivalent; M, Multi-endurance Sports; R, Running; VO₂, Volume of oxygen consumed.

Table 4.3 demonstrates a broad array of coronary artery findings from CCTA. There was no significant difference in any of the CAC measures between sporting disciplines. Cyclists were more likely to demonstrate partially calcified plaque, a stenosis >50%, LMS and proximal LAD disease in addition to plaque vulnerability markers including spotty calcification, LAP and TCFA compared to multi-endurance athletes and more likely to demonstrate circumflex disease and TCFA compared to runners. There was no significant association found between sporting discipline and the prevalence of hypertension either at rest, on ABPM or at peak exercise.

Table 4.3 Table of Coronary Artery Findings according to Sporting Discipline

Coronary Artery Features	Multi-Endurance N = 132	Running N = 49	Cycling N = 33	P Value		
				M vs R	M vs C	R vs C
CAC Score, AU	0 (0-15.35)	0 (0-43.5)	8.65 (0-124.13)	0.34	0.10	0.07
CAC Score >100, AU	18 (14.4)	7 (15.2)	8 (25)	0.89	0.16	0.29
CAC Score Centile	0 (0-68.5)	0 (0-76)	45 (0-90.25)	0.82	0.15	0.29
Number of diseased vessels						
0	75 (60)	24 (53.3)	15 (46.9)	Reference	Reference	Reference
1	29 (23.3)	16 (35.6)	8 (25)	0.16	0.79	0.68
2	13 (10.4)	3 (6.7)	7 (21.9)	0.63	0.51	0.09
3	8 (6.4)	2 (4.1)	2 (6.3)	0.77	0.07	0.66
Total number plaques	0 (0-2.5)	0 (0-2.5)	2 (0-4)	0.82	0.12	0.15
Plaque Morphology						
None	76 (60.8)	24 (52.2)	15 (46.9)	Reference	Reference	Reference
Calcified	36 (28.8)	16 (34.8)	8 (25)	0.370	0.80	0.68
Partially calcified or non-calcified	13 (10.4)	6 (13)	9 (27)	0.49	0.02*	0.16
Partially Calcified	11 (8.8)	5 (10.2)	8 (25)	0.536	0.016*	0.15
Non-calcified	2 (1.6)	1 (2.2)	1 (3.1)	0.712	0.46	0.75
Stenosis >50%	5 (4)	0 (0)	6 (18.8)	-	0.008*	-
Coronary Plaque Site						
LMS	3 (2.4)	2 (4.4)	4 (12.5)	0.49	0.02*	0.21
LAD	46 (36.8)	19 (42.2)	16 (50)	0.52	0.18	0.50
Proximal LAD	29 (23.2)	14 (31.1)	13 (40.6)	0.30	0.05*	0.39
Circumflex	15 (12)	2 (4.4)	7 (21.2)	0.17	0.16	0.03*
RCA	18 (14.4)	7 (15.6)	5 (15.6)	0.85	0.86	0.99
Plaque Vulnerability Markers						
Spotty Calcification	15 (12)	6 (13.3)	9 (28.1)	0.82	0.03*	0.11
	13 (10.4)	5 (11.1)	8 (25)	0.89	0.04*	0.12
Ruptured Plaque	1 (0.8)	0 (0)	0 (0)	-	-	-
Low Attenuation Plaque	3 (2.4)	1 (2.2)	4 (12.5)	0.95	0.03*	0.11
Positive Remodelling	9 (7.2)	4 (8.9)	5 (15.6)	0.72	0.15	0.37
Napkin Ring Sign	2 (1.6)	0 (0)	2 (6.3)	-	0.17	-
TCFA	12 (9.6)	3 (6.7)	8 (25)	0.55	0.03*	0.03*
PCAT RCA ≥ -68.2 HU	42 (31.8)	11 (22.4)	7 (21.1)	0.25	0.23	0.85

C, Cycling; CAC, Coronary Artery Calcium; LAD, Left Anterior Descending; LMS, Left Main Stem; M, Multi-endurance Sports; PCAT, Peri-coronary Adipose Tissue Attenuation; R, Running; RCA, Right Coronary Artery; Thin-capped Fibroatheroma, TCFA.

4.4.2 Exercise Dose

A greater number of years of endurance training was associated with a CACs ≥ 100 AU, calcified plaque, TCFA and although not significant there was also a trend for the presence of plaque vulnerability markers. When adjusted for other variables in multiple regression modelling, only the association between years of endurance exercise and a CACs ≥ 100 AU remained significant. Of the other markers of exercise dose i.e., MET-hours per week, that represents exercise intensity; and lifetime-MET-years, that represents lifelong exercise volume, the only association of significance was between lifetime-MET-years and CACs ≥ 100 AU (unadjusted). Odd's ratios and p values are given in table 4.4 and demonstrated graphically in figure 4.2, where exercise dose parameters have been broken down into quartiles to aid visualisation of the data.

The bar chart in figure 4.2, top right, is suggestive that athletes above the 50th centile of years of endurance exercise have more partially calcified and non-calcified plaque compared to those in the 0-50th centile. Multinomial regression was used to explore this further and confirmed a greater prevalence of partially calcified and non-calcified plaque in these upper centiles ($p=0.035$ and $p=0.01$, for the 50-75th and 75th-100th centiles respectively); however, this finding was not upheld when corrected for age, sporting discipline and BP.

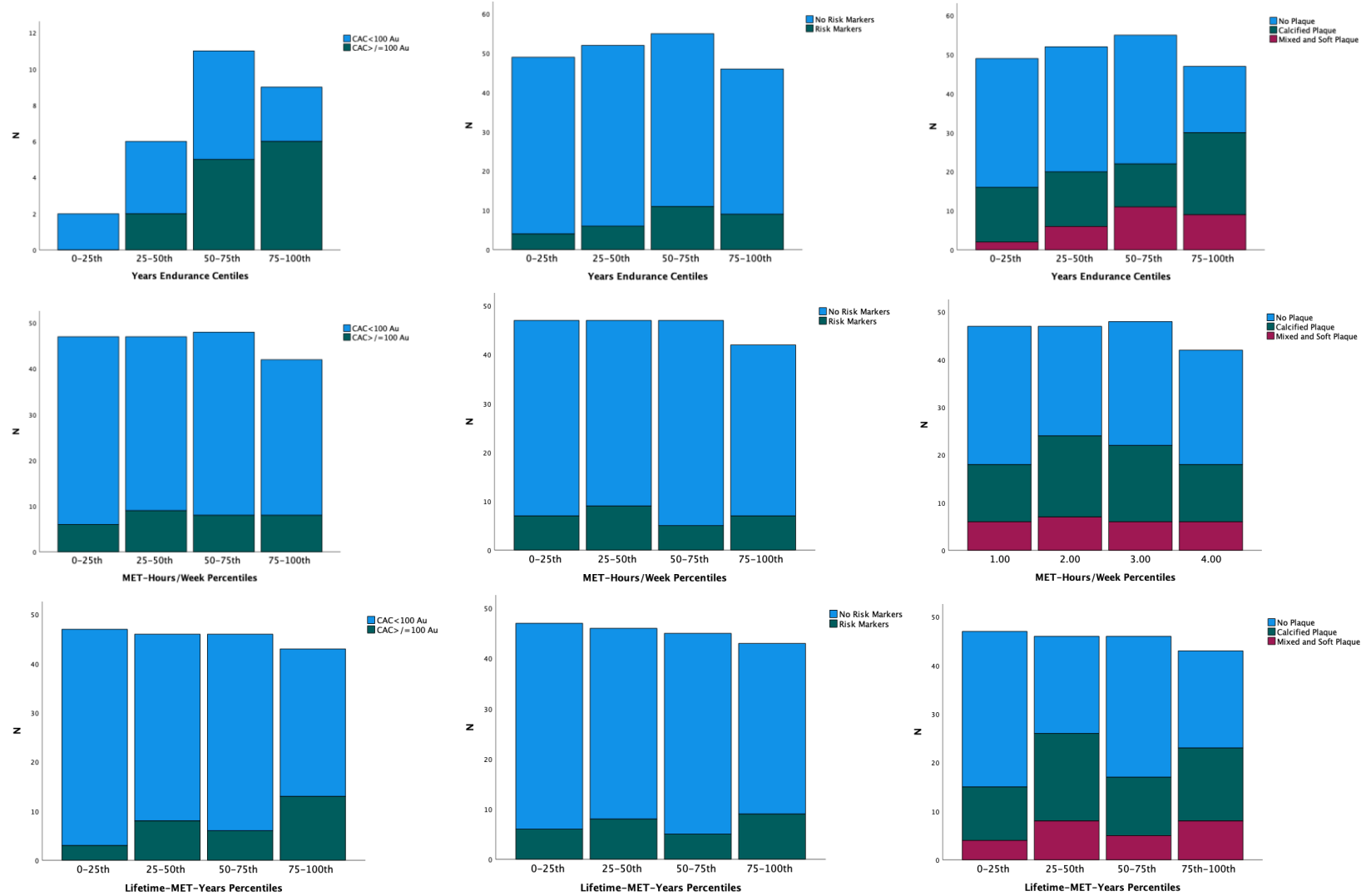
Table 4.4 Table of Coronary Artery Findings According to Exercise Dose Parameters

		Years Endurance			Adjusted Model [^] (ABP)		MET-hours/week			Lifetime-MET-years		
		Median (IQR)	OR (95% CI)	P value	OR (95% CI)	P value	Median (IQR)	OR (95% CI)	P value	Median (IQR)	OR (95% CI)	P value
CAC Score	CAC≥100	34 (9.25-40)	1.07 (1.04-1.10)	0*	1.04 (1.01-1.08)	0.02*	102 (81.43-140.88)	1.00 (0.99-1.00)	0.80	4.27 (1.68-6.29)	0.12 (1.04-1.27)	0.009*
	CAC<100	12 (8-19)					116 (80.7-144.9)			1.91 (0.83-3.90)		
Percentage Stenosis	Stenosis ≥50%	20 (15-27.5)	1.00 (0.96-1.05)	0.95	1.02 (0.98-1.06)	0.36	88 (76.93-137.08)	0.99 (0.99-1.01)	0.78	2.91 (1.26-6.20)	1.02 (0.87-1.21)	0.79
	Stenosis <50%	15 (8-30)					96 (75-137)			2.01 (0.86-4.38)		
Plaque Vulnerability Markers												
	Present	24 (12-35)	1.03 (0.99-1.06)	0.06	1.01 (0.98-1.04)	0.59	97 (74.81-137.20)	1.00 (0.99-1.00)	0.54	2.16 (1.34-5.83)	1.03 (0.92-1.15)	0.63
	Absent	15 (8-30)					97 (74.81-137.20)			2.08 (0.85-4.30)		
TCFA	Present	26 (16.5-32.5)	1.031 (1-1.06)	0.05*	1.00 (0.96-1.04)	0.91	92 (84.3-126.73)	1.00 (0.99-1.01)	0.83	2.91 (1.65-6.12)	1.05 (0.93-1.18)	0.44
	Absent	15 (8-30)					96 (74.70-137.3)			1.95 (0.85-4.33)		
		Median (IQR)	RRR (95% CI)	P value	RRR (95% CI)	P value	Median (IQR)	RRR (95% CI)	P value	Median (IQR)	RRR (95% CI)	P value
Plaque Morphology	None	15 (8-25)	Ref.	Ref.	Ref.	Ref.	96 (72-137.4)	Ref.	Ref.	Ref.	Ref.	Ref.
	Calcified	18 (10-39.25)	1.03 (1.01-1.06)	0.006*	1.02 (1.00-1.05)	0.09	100 (80.48-137.48)	1.00 (0.996-1.004)	0.96	2.08 (1.08-4.85)	1.04 (0.94-1.15)	0.43
	Partially Calcified and non-calcified	24 (15-34)	1.02 (0.99-1.06)	0.12	1.00 (0.96-1.04)	0.84	92 (82.31-126.01)	1.00 (0.99-1.004)	0.47	2.27 (1.62-5.62)	1.05 (0.92-1.18)	0.49
			B (95% CI)	P value	B (95% CI)	P value		B (95% CI)	P value		B (95% CI)	P value
PCAT		-	-0.02 (-0.12-0.09)	0.78	0.03 (-0.93-0.15)	0.66	-	-0.001 (-0.02-0.02)	0.93	-	-0.15 (-0.59-0.29)	0.50

ABP, Ambulatory Blood Pressure; CAC, Coronary Artery Calcium; CI, 95% Confidence Interval; IQR, Interquartile Range; OR, Odd Ratio; PCAT, Peri-coronary Adipose Tissue Attenuation; RRR, Relative Risk Ratio; TCFA, Thin-capped Fibroatheroma.

^ Adjusted Model refers to the odds ratios and p values for the relationship of years of endurance exercise to the given CAD parameters having adjusted for age, sporting discipline and the presence of ambulatory BP by multivariable regression.

Figure 4.2 Exercise Dose Bar Charts for CAC Score, Plaque Vulnerability Markers and Plaque Morphology.



4.5 Discussion

4.5.1 Sporting Discipline

With respect to the baseline demographic of weight, multi-endurance athletes have a significantly greater weight which is likely due to increased muscle mass but also body fat content in some of these athletes compared to runners and cyclists who tended to be leaner. This was something notably observed during the data collection process.

The use of cycle ergometry CPET testing explains why cyclists were able to achieve a higher VO_2 max and maximum heart rate, as they were less likely to be limited by leg muscle fatigue, unlike runners and multi-endurance athletes. This limitation was subjectively reported by non-cyclists during data collection.

Post-hoc analysis of the MARC study by Aengevaeren *et al* suggested cyclists appear to have a lower risk profile in terms of coronary findings with a lower prevalence of coronary plaques ($p=0.04$); and a non-significant trend towards lower CAC scores ($p=0.53$), compared with 'other' non-endurance athletes and runners, respectively. Of those athletes with plaques, cyclists more often had calcified plaques (as opposed to partially calcified and non-calcified), in comparison to runners ($\text{OR}_{\text{adjusted}} 3.59$). They suggested the reasons for this may be that runners exercised more intensively than cyclists, hence cyclists did not mount the same BP rises and were not exposed to the same coronary mechanical stresses and secondly, cycling being a non-weight bearing sport, posed different effects on bone turnover with an attenuated reduction in bone mineral density. However, classifying exercise intensity for a sporting discipline using a single MET value, as was done in this analysis, is not representative of the whole cohort participating in that discipline, hence why there is a

broad array of exercise intensities, measured in METS, proposed for each sporting discipline in the 2011 compendium of physical activities²⁵⁶ (appendix 15). The finding of this thesis does not support the hypothesis that cyclists have less plaque, lower calcium scores and a tendency to more calcified plaques than partially calcified and non-calcified. In this study no difference was found between the sporting disciplines with respect to any parameters of calcification, but cyclists were in fact significantly more likely to have partially calcified plaque morphology plaque and evidence of plaque vulnerability markers, particularly in comparison to multi-endurance athletes. Some of these findings were upheld after correction for the other relevant contributory factors of BP, age and years of endurance exercise, as seen in table 4.3. There are several possible explanations for these differences. Although both this data and Aengeavean *et al* found that cyclists had a higher lifelong exercise volume (lifetime MET hours/years) and a trend towards an increased 'intensity' (MET-hours per week); with an increased 'intensity' in their data correlating to a greater prevalence of atherosclerotic plaques, lifetime MET years was comparatively lower in this thesis i.e., 2.91 vs 6.87 lifetime MET-years, respectively. It is also worthy of mention that although there was no significant difference in traditional CVS risk factors found between disciplines by Aengeavrean, those with risk factors were included, in contrast to this study where any athlete with known CVS risk factors was excluded. Also, they only compared runners and cyclists specifically with all other non-endurance sports grouped together, and most differences identified in this cohort were in the comparison of cyclists and multi-endurance athletes (table 4.3). Overall, this data shows substantive findings to argue that cyclists exercise at higher intensity and have a greater lifetime exercise dose. This current study shows that cyclists do not exhibit more calcification but do demonstrate a higher prevalence of high-risk atherosclerotic disease. The reason for this might be the sudden

spikes of intense exertion with associated dose-response increases in systolic BP and coronary mechanical stress, potentially encouraging an acute inflammatory response, that are associated with break-aways and hill climbs in cycling, compared to the more steady and undulating level of exertion of runners and multi-endurance athletes. Additionally, cyclists tend to be exercising for longer than runners per session, resulting in prolonged periods spent with a raised systolic BP with the subsequent haemodynamic consequences to the endothelial lining of the coronary arteries that this portends. Finally, there is some data to suggest that trained cyclists can achieve a higher anaerobic threshold compared to runners, meaning that they are able to exercise at a higher intensity for more prolonged periods.

Although there was a difference in CAD prevalence between sporting disciplines, cycling as opposed to running was found to be predictive for the presence of non-calcium related CAD markers on CCTA but no differences were detected in relation to calcified disease. This is in contrast to prior data, in which runners were shown to have more calcified disease,²⁸⁹ which was instrumental in informing the original hypothesis for this chapter. The previously reported difference was hypothesised to be due the increased intensity at which runners exercised and the haemodynamic stresses of repeated pounding associated with running; however, it is noteworthy that an athlete's exercise dose was quantified using a single MET value for the intensity of each athlete's lifetime of exercise activity in this study.

It is known that a treadmill CPET versus cycle ergometry does afford a 5-15% greater VO_2 amongst untrained individuals, suggesting that higher workloads can be achieved and that overall running is of higher intensity;²⁹³ however, further studies have demonstrated amongst trained athletes, that cyclists achieve an equally high VO_2 on the cycle ergometer

as runners do on the treadmill, but cyclists will achieve a higher VO_2 on cycle ergometry compared to runners doing the same test.²⁹⁴ As discussed earlier in this chapter, data from this thesis revealed that cyclists had a significantly higher VO_2 than runners on cycle ergometry, consistent with this finding. In addition, although there was no difference in exercise dose in terms of years of endurance exercise, cyclists had a significantly higher dose in terms of lifetime-MET-hours, which is a measure of life-time exercise volume, suggesting their overall exercise exposure was greater which may have impacted upon the outcome data. Based on prior knowledge, it would therefore be expected that these athletes would have more calcified disease; however, the data does not support this finding. In fact, despite a lower prevalence of CAC, cyclists did demonstrate significantly more evidence of non-calcified markers including partially calcified morphology plaque and plaque vulnerability markers compared to multi-endurance athletes and runners. In the case of TCFA, both cyclists and runners had more than multi-endurance sports athletes. Although the mechanism for this remains unknown, considering these findings, it is important the guidance regarding the risk stratification in athletes acknowledges the greater coronary risk to which endurance cyclists appear to be exposed.

4.5.2 Exercise Dose

There was a clear association found between years of endurance exercise and CAC, consistent with current consensus and data^{6,7} that there is a dose response effect between these variables. A novel exploration of other coronary risk markers including plaque vulnerability markers and PCAT, in addition to plaque morphology, did not find such an association, although some association was found with respect to TCFA and partially calcified plaque before adjustment for other variables (table 4.4). This overall lack of

association may be due to inadequate statistical power to detect such findings, yet equally possible is that endurance exercise accelerates the development of coronary calcification in athletes compared to the general population resulting in more stable disease overall. This possibility is corroborated by the findings from the retrospective post-HOC analysis finding by DeFina *et al*¹⁷⁵, that despite higher CAC scores and higher exercise doses, athletes did not have the associated adverse prognosis found in the general population.

Although consistent with the hypothesis, increasing exercise dose was shown to predict CAD and a greater number of years of endurance exercise participation was predictive for markers of calcified CAD, exercise dose did not predict those non-calcium related markers including plaque vulnerability, partially calcified and non-calcified and PCAT. This suggests that as previously thought, a greater exercise dose plays a more protective role in the pathophysiology of CAD amongst this cohort,^{7,175} possibly driving the calcification and thus stabilisation of otherwise unstable coronary artery plaques. As such, this finding contributes to a growing narrative that can allay some of the fears surrounding the potential deleterious effects of long-term endurance exercise on this aspect of the cardiovascular system.

However, it is important not to dismiss the data suggesting exhaustive endurance exercise has an acute pro-inflammatory effect that acutely increases plaque instability and the risk of MI, supporting the argument in favour of moderation in terms of exercise dose.

4.5.3 Limitations

There is much debate surrounding how to accurately quantify the lifelong exercise exposure of an endurance athlete, considering volume and intensity throughout. The use of recall to measure a lifetime of varying exercise patterns is inevitably fraught with bias and inaccurate

data. This inaccuracy may explain why years of endurance exercise was the variable that provided most insight, given that it is most likely to have been accurately recalled. Asking an athlete to accurately recall a lifetimes exercise habit in detail including events, intensities, breaks and seasonal variability is an unrealistic demand. However, other options are limited. Using more objective measures such as current fitness level, is cross sectional and therefore does not reflect the lifetime exposure. Emerging technologies such as Strava (an app designed to record data on duration, intensity and distance of running and cycling sessions) is allowing athletes to more accurately record their exercise activity and may prove an essential tool to allow more precise exercise dose quantification in future research.

Specific to this data set is the failure of 25 athletes to complete the dose questionnaire which provided information used to derive MET-hours per week and lifetime-MET-years, thus reducing the statistical power of this data. This is a design fault as the omission in collecting this data was only corrected once the study was underway and thus the questionnaire was completed retrospective to testing and hence compliance was poor.

4.5.4 Conclusions

An increasing exercise dose predicts the presence of CAC amongst male master endurance athletes, the prognostic significance of which remains largely unknown. As such, it is important that guidelines acknowledge the increased prevalence amongst those who have been engaged in endurance exercise the longest such that these individuals are risk assessed for the possible presence of associated high-risk disease. Furthermore, cyclists appear to have a greater prevalence of non-calcified disease than runners and triathletes.

Large prospective longitudinal studies comparing coronary findings in cyclists with other sporting disciplines and consequent MACE are required to substantiate this finding.

5 The Impact of Blood Pressure Profile and Age on Coronary Artery Disease

1.1 Hypothesis

A raised BP, including resting, ambulatory and exercise BP are important determinants in the presence of CAD amongst male master endurance athletes.

1.2 Introduction

There has been a long-held societal view that athletes, in particular endurance athletes are amongst the healthiest humans on the planet. This has led to complacency amongst some athletes and led some to believe that exercise can offset the effects of poor diet and lifestyle choices. It is also possible that this information has led to a passive culture amongst physicians, where an athlete's risk is assumed to be low and thus CVS risk, such that the presence of low-grade hypertension, may be somewhat overlooked.

The recent surge in endurance exercise participation and the accompanying media coverage has brought the occurrence of SCD during sport to the fore. Research into the effects of chronic endurance exercise on the heart suggesting athletes have an increased prevalence of CAC compared to non-athletes, has made it evident that this presumed protection from CAD is not the case. Athletes like non-athletes are victim to coronary events and susceptible to CVS risk factors including hypertension and hypercholesterolaemia. As has already been explored, even the ostensibly healthy male master endurance athlete has an increased prevalence of high CAC scores, and some have plaque features recognised to portend to an increased risk of coronary events in the lay population. Despite exercise being a well-known

and effective treatment for lowering BP²⁹⁵ and athletes having an overall prevalence of hypertension that is reported to be 50% lower than the general population,²⁹⁶ hypertension remains the most common abnormal finding in the cardiac screening of athletes.^{297,298} A systematic review highlighted those male athletes and strength-trained, as opposed to endurance athletes had a greater prevalence of hypertension.²⁹⁸ The identification of a raised BP in any athlete warrants close attention given that in this context it is persisting despite exercising more than the current exercise recommendations of a minimum of 150 minutes of moderate intensity or 75 minutes of vigorous-intensity aerobic exercise per week, which is known to lower both systolic and diastolic BP.²⁵⁹

Recent developments in the hypertension literature have resulted in numerous noteworthy changes to both the AHA and ESC guidelines for the diagnosis and management of hypertension.^{260,299} The ESC guidance recommends the use of ABPM as the gold standard for diagnosing hypertension, emphasising the necessity for more aggressive treatment targets; and delineates a 'high-normal' BP category (130-139/85-89mmHg), recognising the major reduction in adverse outcomes from treating this group. ABPM has been recommended as the gold standard for several reasons. Firstly, 'office' resting BP values in the hypertensive range are a poor indicator of clinical hypertension amongst athletes, due to the high prevalence of white coat hypertension,²⁸¹ resulting in over diagnosis. A prospective study of the general population demonstrated that the presence of white coat hypertension was not associated with an increased risk of hypertension if ABPM showed an average of <130/80 mmHg; however, the risk was raised if ABPM was between 130/80 and 135/85 mmHg.³⁰⁰ Secondly, MACE predictability is comparable between sustained at rest and masked hypertension i.e., normal 'office' BP but hypertensive profile on ABPM or home

monitoring,^{300–302} and therefore ABPM prevents some important at-risk cases being missed. Data from 87 male participants in a 10-mile race with normal office BP, identified 37% had masked hypertension on ABPM. In addition, these athletes also had a higher LV mass/volume ratio and diastolic dysfunction.³⁰³ Finally, ABPM has better MACE predictability overall compared to office BP. Therefore, an athlete with a raised resting BP requires further evaluation with the ESC recommendations gold standard methodology of either ABPM or home monitoring, in order to make or refute a diagnosis and one could potentially argue that all athletes should undergo ABPM to reliably evaluate their CVS risk.²⁶⁰

A hypertensive response to exercise (HRE) is defined as an excessive rise in systolic BP during exercise, the exact cut-off value defining this however remains without consensus. In general population data HRE is a recognised predictor for masked hypertension or the future development of hypertension.^{304–307} One study of 2000 healthy middle-aged men demonstrated that HRE was also a more powerful predictor of morbidity and mortality from MI than office BP (MI mortality 58% vs 33% respectively).³⁰⁸ Caselli *et al* examined HRE in young Olympic athletes and found that endurance and mixed sports, BMI and baseline systolic BP were the strongest determinants of HRE.³⁰⁹ A 6.5-year follow-up of this cohort demonstrated that HRE was also predictive for the subsequent development of hypertension in the athletic population, with a hazard ratio of 3.6.³¹⁰ The first phase of the master athletes heart study extensively tested 152 (106 male) master endurance athletes over the age of 40 and showed that despite having normal BP at rest, 36% of athletes had a HRE (peak systolic >220mmHg). These findings did not correlate with the presence of significant coronary atherosclerosis; however, the analysis was underpowered.⁶ As exercise

tolerance testing is a simple, cheap and commonly available test for the evaluation of athletes, the possibility of HRE being predictive of coronary risk in athletes certainly warrants further evaluation.

Although hypertension is the leading CVS risk factor in the general population, not only in coronary atherosclerosis but also in LV hypertrophy and myocardial dysfunction,³¹¹ affecting more than a third of over 40-year-olds, the relationship of hypertension to coronary atherosclerosis has not previously been described in the male master endurance athlete. To date few studies have examined BP in athletes and no studies have specifically addressed the impact of the athlete's BP profile on the presence of coronary atherosclerosis in this cohort. The potential contribution of subtle sub-clinical hypertension to the development of CAD in master athletes could provide some direction to explaining the variance in prevalence of coronary atherosclerosis identified, despite equivalent exercise doses. This chapter will provide an in-depth exploration of this hypothesis.

1.3 Methods

The athlete's BP profile was evaluated using the following methods;

1.3.1 Resting 'office' Blood Pressure

Resting 'office' BP was determined by the average of 3 consecutive measures in the upright position after at least 5 minutes rest and defined according to the latest practice guidelines.^{258–260} A more detailed description of the methodology of this method is provided in section 2.6.5.1.

1.3.2 Ambulatory Blood Pressure

As described in the methods chapter (section 2.6.5.2), at the end of day 1 of testing, athletes were fitted with an ABPM for 24-hours. An abnormal ambulatory BP is defined according to the ESH as an abnormal mean BP over 24hrs of $\geq 130/80$ mmHg and/or a diurnal average $\geq 135/85$ mmHg and/or a nocturnal average $\geq 120/70$ mmHg (with a minimum of 70% valid measurements, 20 diurnal and 7 nocturnal).²⁶⁰ If the resting BP was raised a diagnosis of hypertension was confirmed; however, if the resting BP was normal the diagnosis was 'masked hypertension'.

1.3.3 Exercise Blood Pressure

As described in the methods, section 2.6.9., athletes undertook a maximal CPET during which BP was measured at 3-minute intervals throughout, at peak exercise and for 6 minutes of recovery. A hypertensive response to exercise (HRE) was defined as an excessive rise in systolic BP (>220 mmHg).

1.4 Results

5.1.1 Age

Exploration of the relationship of age to the coronary outcomes suggested that the presence of calcified disease as measured by a CACs ≥ 100 AU is more prevalent with increasing age, and this remained so even after accounting for other contributory variables including years of endurance exercise and BP. In contrast, age was not found to be a significant determinant in the other coronary measures i.e., stenosis, plaque vulnerability markers and PCAT.

Table 5.1 Relationship of Coronary Outcomes and Age by Univariate and Multivariate Regression Analysis Adjusting for Sporting discipline, Years of Endurance Training and Blood Pressure (either resting ‘office’ systolic, ambulatory systolic or maximum exercise systolic).

		Unadjusted		Adjusted Model 1 (Resting Systolic ‘office’ BP)		Adjusted Model 2 (Ambulatory Systolic BP)		Adjusted Model 3 (Maximum Exercise Systolic BP)	
		Mean Age (SD)	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)
CAC Score	CAC $\geq$ 100	57 (6.22)	1.16 (1.09-1.25)	0*	1.11 (1.03-1.20)	0.007*	1.12 (1.04-1.21)	0.004*	1.12 (1.04-1.21)
	CAC<100	51 (6.70)							
Percentage Stenosis	Stenosis $\geq$ 50%	52 (6.21)	1.02 (0.93-1.11)	0.70	1.03 (0.96-1.11)	0.42	1.05 (0.97-1.13)	0.26	1.04 (0.96-1.13)
	Stenosis <50%	53 (5.90)							
Plaque Vulnerability Markers	Present	54 (7.09)	1.06 (1.00-1.12)	0.07	1.04 (0.97-1.11)	0.29	1.04 (0.97-1.11)	0.25	1.04 (0.97-1.12)
	Absent	51 (6.07)							
TCFA	Present	55 (6.44)	1.09 (1.02-1.16)	0.014*	1.08 (0.93-1.17)	0.07	1.08 (1.00-1.17)	0.06	1.09 (1.00-1.19)
	Absent	51 (6.07)							
			RRR (95% CI)	P value	RRR (95% CI)	P value	RRR (95% CI)	P value	RRR (95% CI)
Plaque Morphology	None	49 (6.62)	-	-	-	-	-	-	-
	Calcified	54 (6.37)	1.05 (1.00-1.10)	0.04*	1.02 (0.97-1.08)	0.43	1.03 (0.98-1.09)	0.26	1.02 (0.97-1.08)
	Non-calcified	54 (6.82)	1.06 (1-1.13)	0.06	1.05 (0.98-1.13)	0.18	1.06 (0.98-1.14)	0.15	1.06 (0.98-1.13)
			B (95% CI)	P value	B (95% CI)	P value	B (95% CI)	P value	B (95% CI)
PCAT		-	-0.15 (-0.35-0.05)	0.132	-0.20 (-0.42-0.22)	0.08	-0.16 (-0.38-0.07)	0.16	-0.17 (-0.39-0.57)

CAC, Coronary Artery Calcium; CI, 95% Confidence Interval, OR, Odds Ratio; PCAT, Pericoronary Adipose Tissue Attenuation; RRR, Relative Risk Ratio; SD, Standard Deviation; TCFA, Thin-Capped Fibroatheroma.

5.1.2 Blood Pressure

Table 5.2 Relationship of CAC score ≥ 100 AU and blood pressure parameters by uni- and multivariate logistic regression adjusting for age, sporting discipline and years of endurance training.

	CAC Score									
	Unadjusted				Adjusted Model 1 (Resting Systolic 'Office' BP)		Adjusted Model 2 (Ambulatory Systolic BP)		Adjusted Model 3 (Maximal Systolic BP CPET)	
	CAC<100	CAC ≥ 100	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Resting Systolic 'Office' BP, 5mmHg	128 (14.35)	136 (15.62)	1.22 (1.07-1.37)	0.003*	0.13 (0.98-1.29)	0.09	-	-	-	-
Ambulatory Systolic BP, 5mmHg	118 (8.20)	121 (8.96)	1.23 (1.00-1.54)	0.06	-	-	1.14 (0.91-1.44)	0.25	-	-
Maximal Systolic CPET BP, 5mmHg	206 (23.07)	209 (22.98)	1.03 (0.95-1.12)	0.50	-	-	-	-	1.01 (0.92-1.10)	0.88

Table 5.3 Relationship of stenosis $>50\%$ and blood pressure parameters by uni- and multivariate logistic regression adjusting for age, sporting discipline and years of endurance training.

	Stenosis									
	Unadjusted				Adjusted Model 1 (Resting Systolic 'Office' BP)		Adjusted Model 2 (Ambulatory Systolic BP)		Adjusted Model 3 (Maximal Systolic BP CPET)	
	No significant stenosis	Stenosis $>50\%$	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Resting Systolic 'Office' BP, 5mmHg	128 (14)	142 (19.80)	1.33 (1.10-1.60)	0.003*	1.40 (1.12-1.75)	0.004*	-	-	-	-
Ambulatory Systolic BP, 5mmHg	118 (11)	127 (9.80)	1.66 (1.18-2.33)	0.003*	-	-	1.79 (1.20-2.66)	0.004*	-	-
Maximal Systolic CPET BP, 5mmHg	205 (22)	229 (26.20)	1.28 (1.10-1.48)	0.001*	-	-	-	-	1.28 (1.09-1.51)	0.003*

Table 5.4 Relationship of presence of plaque vulnerability markers and blood pressure parameters by uni- and multivariate logistic regression adjusting for age, sporting discipline and years of endurance training.

	Plaque Vulnerability Markers									
	Unadjusted				Adjusted Model 1 (Resting Systolic 'Office' BP)		Adjusted Model 2 (Ambulatory Systolic BP)		Adjusted Model 3 (Maximal Systolic BP CPET)	
	No vulnerability markers	Vulnerability Markers	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Resting Systolic 'Office' BP, 5mmHg	126 (11.72)	135 (15.96)	1.03 (1.00-1.06)	0.022*	1.13 (0.98-1.29)	0.08	-	-	-	-
Ambulatory Systolic BP, 5mmHg	118 (8.05)	122 (9.05)	1.06 (1.02-1.11)	0.01*	-	-	1.34 (1.06-1.71)	0.016*	-	-
Maximal Systolic CPET BP, 5mmHg	203 (27.50)	218 (21.36)	1.03 (1.01-1.05)	0.004*	-	-	-	-	1.14 (1.04-1.25)	0.006*

Table 5.5 Relationship of presence of TCFA markers and blood pressure parameters by uni- and multivariate logistic regression adjusting for age, sporting discipline and years of endurance training.

	TCFA									
	Unadjusted				Adjusted Model 1 (Resting Systolic 'Office' BP)		Adjusted Model 2 (Ambulatory Systolic BP)		Adjusted Model 3 (Maximal Systolic BP CPET)	
	No TCFA	TCFA	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Resting Systolic 'Office' BP, 5mmHg	129 (12.78)	137 (18.34)	1.04 (1.01-1.07)	0.009*	1.67 (1.01-1.36)	0.04*	-	-	-	-
Ambulatory Systolic BP, 5mmHg	118 (7.91)	124 (9.65)	1.09 (1.03-1.15)	0.002*	-	-	1.51 (1.14-1.98)	0.004*	-	-
Maximal Systolic CPET BP, 5mmHg	205 (25.69)	224 (20.77)	1.041 (1.02-1.06)	0*	-	-	-	-	1.21 (1.09-1.36)	0.001*

Table 5.6 Relationship of presence of peri-coronary adipose tissue attenuation and blood pressure parameters by uni- and multivariate linear regression adjusting for age, sporting discipline and years of endurance training.

	PCAT							
	Unadjusted		Adjusted Model 1 (Resting Systolic 'Office' BP)		Adjusted Model 2 (Ambulatory Systolic BP)		Adjusted Model 3 (Maximal Systolic BP CPET)	
	B (95% CI)	P value	B (95% CI)	P value	B (95% CI)	P value	B (95% CI)	P value
Resting Systolic 'Office' BP, 5mmHg	0.09 (0.001-0.19)	0.048*	0.53 (0.05-1.01)	0.03*	-	-	-	-
Ambulatory Systolic BP, 5mmHg	0.03 (-0.10-0.15)	0.69	-	-	0.15 (-0.48-0.77)	0.64	-	-
Maximal Systolic CPET BP, 5mmHg	-0.005 (-0.06-0.05)	0.87	-	-	-	-	0.009 (-0.29-0.31)	0.95

Table 5.7 Relationship of presence of plaque vulnerability markers and blood pressure parameters by uni- and multivariate multinomial regression adjusting for age, sporting discipline and years of endurance training.

	Plaque Morphology			Unadjusted				Adjusted Model 1 (Resting Systolic 'Office' BP)				Adjusted Model 2 (Ambulatory Systolic BP)				Adjusted Model 3 (Maximal Systolic BP CPET)			
	None	Calcified	Partially and non-calcified	Calcified		Partially and non-calcified		Calcified		Partially and non-calcified		Calcified		Partially and non-calcified		Calcified		Partially and non-calcified	
				RRR (95% CI)	P value	RRR (95% CI)	P value	RRR (95% CI)	P value	RRR (95% CI)	P value	RRR (95% CI)	P value	RRR (95% CI)	P value	RRR (95% CI)	P value	RRR (95% CI)	P value
Resting Systolic 'Office' BP, 5mmHg	127 (14.68)	118 (8.12)	137 (17.24)	1.05 (0.94-1.67)	0.41	1.20 (1.04-1.37)	0.01*	0.99 (0.88-1.11)	0.82	1.34 (0.98-1.32)	0.09	-	-	-	-	-	-	-	-
Ambulatory Systolic BP, 5mmHg	118 (8.00)	129 (13.20)	124 (8.95)	1.05 (0.90-1.23)	0.52	1.50 (1.17-1.93)	0.001*	-	-	-	-	1.06 (0.91-1.24)	0.48	1.51 (1.16-1.97)	0.02*	-	-	-	-
Maximal Systolic CPET BP, 5mmHg	203 (22.43)	207 (22.59)	222 (20.76)	1.04 (0.97-1.12)	0.27	1.2 (1.09-1.33)	<0.001*	-	-	-	-	-	-	-	-	1.04 (0.96-1.12)	0.34	1.20 (1.08-1.34)	<0.001*

B indicates beta coefficient; CI, 95% confidence interval; OR, odds ratio; RRR, relative risk ratio.

OR's, RRR's and B's are calculated based on a 5mmHg increase in each respective BP.

*P<0.05

1.4.1 Resting Systolic 'Office' Blood Pressure

Resting 'office' systolic BP was predictive for a CAC score ≥ 100 AU on univariate analysis, however, this did not hold up once adjusted for age, years of endurance training and sporting discipline (table 5.2). A high-normal 'office' BP (130-135/85-90 mmHg) was also significantly associated with a CAC score ≥ 100 AU compared to normal 'office' BP ($p=0.08$, $OR_{unadjusted}= 4.05$ (95% confidence interval (CI) 1.44-11.36) and remained so even after adjustment for age, years of endurance and sporting discipline ($p=0.03$, $OR_{adjusted}= 3.51$ (95% CI 1.12-11.03)). Furthermore, athletes with an abnormal 'office' BP i.e. high-normal or above ($\geq 130/85$) demonstrated a significant relationship with a CAC score ≥ 100 AU ($p=0.08$, $OR_{adjusted}= 3.97$ (95% CI(1.43-10.99))), and a borderline significance for the presence of plaque vulnerability markers ($p=0.07$) and a stenosis $>50\%$ ($p=0.08$) (table 5.8). Multiple regression showed a 5mmHg increase in resting 'office' systolic BP to be predictive for a stenosis greater than 50% ($OR_{adjusted}=1.40$, 95% CI 1.12-1.75) (table 5.3) and TCFA ($OR_{adjusted}=1.67$, 95% CI 1.01-1.36) (table 5.5). Univariate analysis also demonstrated an increase in resting systolic 'office' BP to be predictive for plaque vulnerability markers (table 5.4) and partially calcified and non-calcified morphology plaque (table 5.7); however, this was not maintained on multivariate adjustment. Finally, an increase in resting 'office' systolic BP predicted for the presence of an increasing PCAT, that would pertain to less coronary inflammation (table 5.6).

Table 5.8 Unadjusted Logistic Regression for Abnormal ‘office’ Blood Pressure and Coronary Artery Disease Risk Markers.

	Abnormal Blood Pressure ($\geq 130/85$)			
	Unadjusted Model			
	BP $\geq 135/80$ mmHg	BP $< 135/80$ mmHg	OR (95% CI)	P value
CAC Score ≥ 100 , n (%)	27 (24.3)	6 (6.5)	4.61 (1.81-11.73)	0.001*
Stenosis $\geq 50\%$, n (%)	9 (8.2)	2 (2.2)	4.01 (0.84-19.05)	0.08
Plaque Vulnerability Markers, n (%)	21 (9.1)	9 (9.8)	2.18 (0.94-5.02)	0.07
TCFA, n (%)	16 (14.5)	7 (7.6)	2.07 (0.81-5.27)	0.18
PCAT, Median (IQR)	-73.73 (-81.91--67.62)	-71.87 (-78.18— 65.21)	1.02 (0.99-1.05)	0.12
Plaque Morphology				
Calcified	34 (39.6)	26 (28.3)	-	0.43
Partially Calcified and non-calcified	19 (16.5)	9 (9.8)	-	0.10

BP, Blood pressure; CAC, Coronary Artery Calcium; IQR, interquartile range; OR, Odds ratio; TCFA, Thin-capped fibroatheroma

1.4.2 Ambulatory and Maximal Systolic Exercise BP

Ambulatory systolic BP and maximal exercise systolic BP were not significantly predictive for a CAC score ≥ 100 AU (table 5.2). A 5mmHg increase in both systolic ambulatory and maximal exercise BP, were predictive for a stenosis $>50\%$ in a major vessel, including when adjusted for age, years of endurance exercise and sporting discipline ($OR_{adjusted}=1.79$, 95% CI 1.20-2.66 and $OR_{adjusted}=1.28$, 95% CI 1.09-1.51), respectively (table 5.3). Neither resting, ambulatory or exercise systolic BP were predictive for the presence of calcified plaque compared to no plaque. Both ambulatory ($p<0.001$) and maximal exercise BP ($p=0.04$) were predictive for the presence of partially calcified and non-calcified compared to none; for a

5mmHg increase in ambulatory and exercise BP an athlete was 1.7 and 1.1 times more likely to have partially calcified and non-calcified than none, respectively (table 5.7). Ambulatory systolic BP and maximal exercise systolic BP were also predictive for the presence of plaque vulnerability markers including TCFA, with a 5mmHg increase in either BP parameter corresponding to a 1.34 and 1.14, and 1.51 and 1.21 greater likelihood of an athlete demonstrating plaque vulnerability markers and TCFA, respectively, ($OR_{adjusted}=1.34$, 95% CI 1.06-1.71; $OR_{adjusted}=1.14$, 95% CI(1.04-1.25)) and ($OR_{adjusted}=1.51$, 95% CI 1.14-1.98; $OR_{adjusted}=1.21$, 95% CI 1.09-1.36) (table 5.4 and 5.5).

It is also worthy of note that three of the 4 athletes who underwent coronary intervention demonstrated an abnormal ABPM and a maximum exercise blood pressure >220mmHg.

In summary, amongst this cohort, ABPM was the strongest predictor for a stenosis greater than 50% ($p=0.004$; ($OR_{adjusted}=1.79$, 95% CI 1.20-2.66) plaque vulnerability markers ($p=0.016$; $OR_{adjusted}=1.34$, 95% CI 1.06-1.71) and partially calcified and non-calcified ($p=0.02$; $RRR_{adjusted}=1.51$, 95% CI 1.16-1.97).

1.5 Discussion

1.5.1 Coronary Artery Calcium

Hypertension is accepted to be the major preventable cause for CAD worldwide²⁶⁰ and CAC is a surrogate prognostic marker for atherosclerotic volume and a strong risk predictor for coronary events in the general population. Furthermore, systolic BP is predictive for the presence of CAC³¹². Despite these facts, no significant association was demonstrable

between resting 'office', ambulatory or maximal exercise systolic BP and a CAC score ≥ 100 AU in athletes, after adjusting for age, sporting discipline and years of endurance training. The data suggests that although BP is predictive for other more direct markers of risk, it is not such a powerful predictor of risk for CAC in the master athlete cohort. This upholds the argument that CAC in the endurance athlete may occur in part because of an alternative mechanism that relates to the physiological changes associated with chronic endurance exercise, rather than being largely related to CVS risk factors including BP and may therefore not be such a useful surrogate marker of risk for coronary events in this cohort.

1.5.2 Direct Markers of Coronary Risk

Direct markers of coronary risk including plaque morphology and plaque vulnerability markers are known to be associated with increased coronary events in the general population^{152,153}. Calcified plaques are considered to be more stable i.e. less prone to rupture and associated with lower MACE amongst the general population, compared to partially calcified morphology plaques that are more unstable and rupture prone and consequently pose a risk of acute coronary syndrome.^{313,314} Although in previous data athletes have demonstrated predominantly calcified lesions compared to controls, who have predominantly partially calcified morphology plaques,^{6,7} master endurance athletes do exhibit a notable prevalence of partially calcified and non-calcified lesions (14%). This data demonstrates that ambulatory and maximal exercise systolic BP were predictive for partially calcified or non-calcified coronary plaque compared to no plaque ($p=0.02$; RRR (relative risk ratio)_{adjusted}=1.51, 95% CI 1.16-1.17 and $p<0.001$; RRR_{adjusted}=1.20, 95% CI 1.08-1.34) for a 5mmHg increase in blood pressure) but not for calcified plaque or a CAC score ≥ 100 AU. Resting systolic 'office' BP was not predictive for calcified plaque and predictive for partially

calcified or non-calcified plaque only prior to adjustment for age, years of endurance and sporting discipline. As described, ambulatory and maximal exercise systolic BP were also predictive for plaque vulnerability markers and TCFA. The data suggests that the greatest relationship of BP parameters and CAD lies in the more direct markers of CAD risk of plaque morphology and plaque vulnerability markers.

1.5.3 Coronary Stenosis

Amongst the athletes in this cohort, an increase in all 3 BP parameters i.e., resting 'office' systolic, ambulatory systolic and maximum exercise systolic were found to be predictive for the presence of a coronary artery stenosis >50%, consistent with what one would expect and suggesting a well-established relationship between BP and degree of stenosis. Although there is evidence to suggest an association between the degree of coronary stenosis and risk of MACE in a high-risk asymptomatic individual,³¹⁵ equally, the relevance of such a stenosis in a chest pain free low-risk athlete, is uncertain. There are several important differences to consider between a master endurance athlete and member of the general population when interpreting the finding of coronary stenosis. Firstly, athletes may have an increased ischaemic threshold given that they develop an extensive network of collaterals. However, equally, endurance exercise imposes huge myocardial oxygen demands that routinely far exceed the demands of a typical general population subject. Furthermore, athletes undergo large shifts in electrolytes as well as surges of adrenaline that might reduce the arrhythmia threshold in the context of an ischemic substrate. The advent of CT FFR may afford a non-invasive method of evaluating these lesions under stress to quantify their functional significance; however, it remains that the physiological differences between athletes and non-athletes described, and the non-athletic population from which the

current conventional FFR cut-offs are derived, may mean these values require further validation in athletes.

1.5.4 Peri-Coronary Adipose Tissue Attenuation

PCAT is a novel imaging biomarker of coronary inflammation. Large scale studies have demonstrated that it is associated with high-risk plaque features, CAC and independently predicts MI and MACE. PCAT volume has been associated with severity of stenosis and plaque presence independent of CVS risk factors.^{268,316}^{156,268,316} This study demonstrated that for a 5mmHg increase in resting 'office' systolic BP the PCAT increased significantly ($OR_{adjusted} = 0.53$; 95% CI 0.05-1.01), consistent with less, rather than more inflammation as one might expect. However, a PCAT ≥ -68.2 HU was associated with the presence of a CAC score ≥ 100 AU ($p=0.04$; $OR=1.94$, 95% CI 0.90-4.18). This data is consistent with the finding in non-athletes that a positive PCAT is associated with the presence of CAC and affects CAD independent of CVS risk factors including hypertension.¹⁵⁶

1.5.5 Clinical Relevance

This thesis provides novel findings to demonstrate that ambulatory and exercise systolic BP are predictive for several CT measures of CAD risk. This data demonstrates ambulatory BP to be the stronger BP parameter overall to predict markers of CAD in this cohort, in particular coronary stenosis, plaque vulnerability markers and partially calcified or non-calcified, all of which are known to be associated with increased MACE in the general population.^{152,153,315} The data found the BP profile of an athlete less useful in predicting the presence of CAC, although a high-normal BP was predictive for CAC score ≥ 100 AU. Based on this data,

recommendations for the CVS evaluation of master athletes should advise a low threshold for physicians to prescribe a non-invasive maximal exercise testing and/or ABPM (which is currently the gold standard of hypertension diagnosis), for assessing athletes with resting hypertension and even high-normal BP, as a formal part of their BP evaluation and risk stratification, to increase the efficacy of current screening practice in this cohort. These investigations are both widely available, economical and non-invasive.

Secondly, the data demonstrated a weaker association of CAC and BP compared with more direct CCTA markers, in this cohort. CCTA has also been shown to have greater prognostic power than CAC score in the general population with CAC score missing prognostically important hypertensive patients with non-calcified plaque.³¹⁷ Furthermore, hypertension has been linked to both intimal and medial calcification which cannot be differentiated by CAC scoring. Intimal calcification is associated with risk of plaque rupture while medial calcification is not, highlighting a significant limitation of this technique. Consideration should be given to amending guidance to recommend CCTA in addition to CAC scoring in these individuals where screening is indicated until further longitudinal data from large studies is available; given the greater predictive power of CCTA in the risk stratification of this cohort. This modification in radiological approach is easily justified in terms of radiation exposure, given the rapid advancement in CT technology that is continuously affording lower CCTA radiation doses and new techniques such as FFR and stress CT, meaning CCTA can offer both structural and functional evaluation. There are however some financial implications give the necessity for the presence of a doctor and need for a venflon for contrast injection.

Some of the differences observed between the relationships of resting 'office' systolic blood pressure and systolic ABPM to coronary artery disease parameters is possibly explained by the observation made in chapter 3 that almost half of those who met the criteria for resting 'office' hypertension also met the criteria for the white coat hypertension i.e., having a normal ABPM. This suggests that a proportion of the group had an alternative pathophysiology resulting in a hypertensive measurement i.e., reflex sympathetic activation, as opposed to true hypertensive physiology, thus diluting the data within this group and consequently impacting the relationships explored.

It was hypothesised that increasing BP parameters would predict the presence of CAD. Although this was the case to some degree there was an important dichotomy identified with those risk markers unrelated to coronary calcium shown to be associated with BP, but measures of coronary calcium were not. As discussed in chapter 5, this may suggest that the pathophysiology driving calcium-associated CAD versus non-calcified markers may differ with the former more pathological and therefore carrying adverse risk and the latter representing a more benign or even protective mechanism in some athletes. This finding sheds more light upon the question of the role of BP in CAD amongst male master endurance athletes than was expected and as such informs physicians of the importance of thoroughly investigating blood pressure when quantifying an athlete's risk during the preparticipation evaluation process.

1.5.6 Limitations

Limitations of this study relating to this chapter include the lack of matched controls; therefore, it was not possible to easily compare this novel data to non-athletes. However, the objective was to examine the relationship of CAD risk markers with BP parameters, a relationship which is well described in the literature in the non-athlete.

1.6 Conclusion

This study has revealed several novel findings in relation to CAD and BP in male master endurance athletes. Firstly, undiagnosed, untreated, hypertension is prevalent, and in the master athlete population is mostly low-grade, yet has an important relationship to the presence of high-risk CAD. Secondly, high-risk CCTA markers (stenosis greater than 50%, partially calcified or non-calcified, plaque vulnerability markers and TCFA), several of which have not previously been described in athletes, are also prevalent amongst these athletes. This finding contrasts with the on-going uncertainty surrounding the significance of the CAC score in terms of risk of coronary events, in this cohort. Finally, this study demonstrates a significant relationship between high-risk CCTA markers and an abnormal BP profile. These findings call for increased awareness amongst healthcare professionals of the prevalence of low-grade hypertension amongst this cohort and the necessity to consider male master endurance athletes in the same way as non-athletes with respect of risk stratification for CAD. Given the predictive power of the BP profile for high-risk CT clinical features, and the low cost of non-invasive exercise testing and ABPM, recommendations^{318–320} for CVS evaluation of master athletes should consider adopting a low threshold to investigate for hypertension in the middle-aged endurance athlete, even in those with a high-normal BP.

There is a need for large prospective studies evaluating MACE in relation to BP parameters amongst this cohort, to further substantiate the findings from this data.

6 Myocardial Fibrosis and its Relationship to Coronary Artery Disease, Blood Pressure and Exercise Dose.

6.1 Hypotheses

- BP and exercise dose are important determinants of MF in the male master endurance athlete.
- There is a significant relationship between the presence of CAD and ischaemic pattern MF in the male master endurance athlete.

6.2 Background

The master endurance athlete has a greater prevalence of myocardial fibrosis (11-17%) compared to the general population.^{6,8,9,176,177,179} This is identified primarily as late gadolinium enhancement (LGE) on cardiovascular MRI and results from the accumulation or delayed washout of gadolinium contrast secondary to increased extracellular space.¹⁷⁹ MF is associated with arrhythmia risk and SCD in the general population¹⁸¹. In one study of athletes, non-sustained VT was identified amongst 3 master athletes with ischaemic pattern MF and accompanying LAD stenosis greater than 50%.⁶ The presence of VAs accompanied by mid-wall or sub-epicardial MF in a striae pattern have also been demonstrated to increase the risk of malignant arrhythmic events,¹⁸⁵ making this an important issue warranting further exploration.

6.2.1 Patterns of Late Gadolinium Enhancement.

Given the heterogenous pattern of LGE in athletes, its investigation must evaluate all LGE patterns together as well as the numerous patterns, such as insertion point, ischaemic and

non-ischaemic LGE, separately. The identification of a small amount of LGE that does not fit with any established typical pattern i.e., typical patterns such as those associated with myocarditis and infiltrative or hypertrophic cardiomyopathy for example, is thought to be benign amongst the general population.¹⁷⁸ Given the acute physiological and metabolic shifts associated with endurance exercise, that may reduce arrhythmia threshold, it is not possible to assume that the same applies to the endurance athlete. In fact, one study demonstrated that small areas of LGE with largely a non-ischemic pattern, was associated with the presence of exercise induced VAs.³²¹ A large proportion of pathological LGE detected amongst athletes is in the inferolateral and septal mid wall; most suggestive of a myocarditis pattern in this is context¹⁷⁹

Hinge point LGE, most often detected inferiorly at the RV insertion point, is the most prevalent pattern of enhancement seen in the master endurance athlete cohort at between 20-37%,^{179,322} compared to 10% amongst the general population,³²³ and has been correlated with number of years of endurance training, hours per week and number of events complete^{179,322} Its prognosis amongst endurance athletes remains unknown however amongst the general population it is considered benign.³²³ It is hypothesised that prolonged periods of high pressure and volume endured during intense exercise causes high wall stress, affecting the thin-walled RV more than left,¹⁸⁶ that results in microinjuries that culminate in small areas as insertion LGE consistent with myocardial fibrosis. The same findings are seen in pulmonary arterial hypertension and pulmonary regurgitation where the RV is subject to similar conditions.^{324–326}

6.2.2 Determinants of Pathological Late Gadolinium Enhancement

The pattern and distribution of pathological LGE consistent with MF amongst athletes differs from the general population, suggesting there are exercise-specific determinants that are currently unidentified. Data exists demonstrating an association between the number of endurance events completed and years of training, and the presence of LGE consistent with MF suggesting exercise dose may be one such determinant.^{8,9,176,180} Only one study to date has considered an association between LGE consistent with MF and BP amongst athletes. It demonstrated that peak exercise systolic BP was predictive for the presence of non-ischaemic fibrosis amongst 30 male triathletes aged 45 ± 10 years.⁹ Given the known correlation of exercise load and exercise systolic BP³²⁷, as seen on exercise testing, it is possible that such a finding overlaps with the aforementioned relationship to exercise dose.

The predictability of other BP parameters such as resting and ambulatory BP, for presence of different LGE patterns, has yet to be evaluated.

6.2.3 Late Gadolinium Enhancement and Coronary Artery Disease

There is limited data evaluating the relationship between LGE and CAD amongst athletes; however, one notable prior study of 108 male marathon runners over 50 years of age established that CAC percentile, as well as number of marathons completed, were predictive for the presence of pathological LGE consistent with MF,¹⁵⁸ with 12 athletes exhibiting LGE, 58% of whom had an ischaemic pattern and the remainder a non-ischaemic pattern of LGE. They also established that LGE when present in the context of CAC was predictive for MACE, suggesting some association exists between CAD and LGE consistent with MF in the master endurance athlete.¹⁸⁰

6.2.4 Extra Cellular Volume and T1 Mapping

There is limited data evaluating the alternative techniques for the identification of diffuse MF including ECV and T1 mapping amongst master endurance athletes. It is known that an increase in both native T1 and ECV correlate with increasing diffuse MF. One multicentre general population study defined normal values for T1 and ECV as 950 ± 21 msec and $25 \pm 4\%$ ³²⁸. However, there is no consensus about the normal range for ECV and T1 amongst athletes, with data suggesting both an increase and decrease in both, with T1 ranging from 943-1268 ms and ECV 20-26%, amongst those studies to date.¹⁷⁹ Some of this discrepancy may be related to differences between scanners, contrast agents and T1 sequences between studies; however, ECV largely corrects for these factors. McDiarmid *et al* revealed ECV to be relatively reduced in athletes compared to sedentary controls at a younger age (31.7 ± 7.7 years).³²⁹ This finding did not hold true in a study of athletes of an older age (54 ± 5 years), who exhibited a significantly increased ECV, although remaining within the normal range.³³⁰ McDiarmid *et al* detailed that this finding represented a relative reduction in ECV secondary to a physiological increase in cellular mass, which was supported by the finding of an inverse relationship between VO_2 max, a surrogate marker of fitness, and ECV.³²⁹

Tahir *et al* demonstrated a higher ECV in the myocardium of athletes with non-ischaemic MF, measured remotely to the area with LGE, suggesting that in some cases the fibrosis is more diffuse and prevalent than what can be detected by LGE, and ECV may be a more sensitive marker.⁹

Amongst patients with heart failure raised ECV and T1 values are associated with increase mortality and cardiac events.³³¹ The clinical significance of raised ECV and T1 amongst endurance athletes remains unknown.

This thesis aims to evaluate the relationship between patterns of MF as defined by LGE and ECV, and CAD risk markers (CAC score, degree of stenosis, plaque morphology, plaque vulnerability markers and PCAT), BP profile (rest, ambulatory and peak exercise) and exercise dose (years of endurance exercise, average MET-hours per week and lifetime MET-hours), amongst a cohort of ostensibly healthy male master endurance athletes.

6.3 Methods

6.3.1 Participants

Participants underwent cardiovascular MRI scanning at St Bartholomew's Hospital, London under the supervision of Professor James Moon. Scans took place over a series of weekend days between January and September 2019. The MRI protocol used is described in the methods **section 2.6.9**

6.3.2 Coronary Artery Evaluation using CAC scoring and CCTA

Please refer to **Chapter 2, Section 2.6.8**

6.3.3 Exercise Dose

Please refer to **Chapter 2, Section 2.6.11**

6.3.4 Blood Pressure Evaluation

Please refer to **Chapter 2, Section 2.6.7**

6.3.5 Reporting

Off-line analysis was undertaken using Circle CVi 42 software (Calgary, Canada) at the end of all data collection. Semi-automated epi- and endocardial contours were drawn using this software. Left and right atrial end-diastolic and end-systolic volumes were derived by manual tracing of endocardial atrial contours. Every effort was made to avoid confounders, with blood partial voluming being a particular concern. ECV was calculated using the mean segmental pixel values, with the mid anteroseptal region of interest used for analysis.

Images were reported blindly using Circle CVi 42 Software.

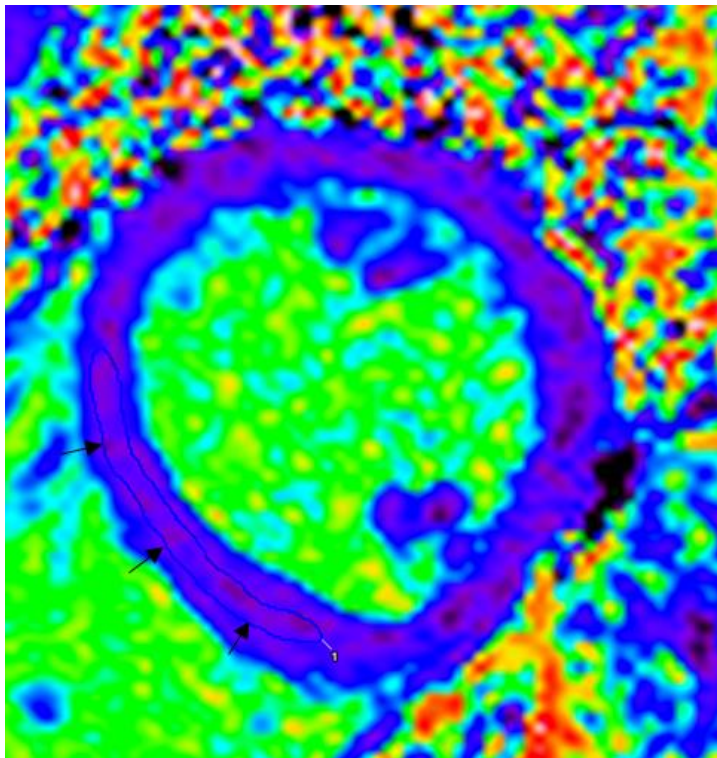


Figure 6.1 Image demonstrating measurement of ECV using a sample from the interventricular septum at the level of the papillary apparatus.

LGE patterns consistent with MF were classified as ischaemic and non-ischaemic. Ischaemic was sub-divided into subendocardial and transmural and described according to the coronary territory. Non-ischaemic LGE was further classified into insertion point, mid myocardial and subepicardial. For the purposes of this thesis, pathological LGE is defined as any ischaemic or non-ischaemic pattern of LGE, excluding insertion or hinge point LGE.

6.4 Results

Table 6.1 Basic Descriptive of all athletes who underwent CMR, grouped by pattern of LGE

Variable		No LGE	RV Insertion point LGE	Non-Ischaemic LGE	Ischaemic LGE
Age (years)		51.85 (6.81)	50.13 (7.36)	55 (6.77)	57.75 (3.5)
Height (cm)		178 (174-182)	179 (172.38-183.5)	181 (176-185)	174 (167.75-182.5)
Weight (kg)		74 (71.3-80.5)	76 (72.5-82)	74 (71-86)	76 (67.65-76)
Ethnicity	Caucasian	115 (92.7)	37 (97.4)	15 (100)	4 (100)
Sport Type	Multi-Endurance	73 (58.9)	25 (65.8)	8 (53.3)	4 (100)
	Run	32 (25.8)	8 (21.2)	3 (20)	0 (0)
	Cycle	19 (15.3)	5 (13.2)	4 (26.7)	0 (0)
Hours Per Week (hours)		9.5 (7-11.5)	8.8 (6.7-11.1)	9.25 (7.5-14)	11.63 (9.3-14.5)
Years Endurance (years)		15 (9-30)	13 (6.8-29.3)	34 (15-39)	25 (17.8-37.5)
Average MET Hours Per Week		97.65 (74.5-137.4)	83.86 (64.8-113.43)	127.25 (80.2-149.25)	100.85 (91.53-108.92)
Lifetime MET Years		1.93 (0.89-4.44)	1.24 (0.65-2.69)	4.27 (2.34-6.74)	2.51 (2.15-2.93)
VO ₂ Max Percentage Predicted (%)		153 (19)	156 (16)	157 (28)	172 (20)
Max HR (%)		96.98 (7.10)	96.32 (5.98)	96.4 (5.8)	96.5 (15.29)
Resting 'Office' Systolic (mmHg)		130 (15)	125 (15)	129 (13)	146 (21)
Resting 'Office' Diastolic (mmHg)		80 (8)	80 (9)	78 (8)	85 (3)
Hypertension Classification	None	49 (39.5)	21 (55.3)	8 (53.3)	1 (25)
	High Normal	41 (33.1)	9 (23.7)	3 (20)	1 (25)
	Hypertension	34 (27.4)	8 (21.1)	4 (26.7)	2 (50)
Average Ambulatory Systolic (mmHg)		119 (8)	118 (8)	120 (6)	112 (14)
Average Ambulatory Diastolic (mmHg)		76 (6)	76 (6)	79 (5)	80 (6)
Diurnal Mean Systolic (mmHg)		123 (9)	122 (9)	124 (7)	123 (14)
Diurnal Mean Diastolic (mmHg)		80 (7)	79 (7)	82 (5)	82 (6)
Nocturnal Mean Systolic (mmHg)		106 (9)	106 (10)	108 (9)	113 (3)
Nocturnal Mean Diastolic (mmHg)		66 (7)	66 (8)	68 (6)	73 (10)

Ambulatory Hypertension		53 (43.4)	11 (29.7)	4 (26.7)	2 (50)
Masked Hypertension		24 (19.7)	4 (10.8)	2 (13.3)	2 (50)
Max Exercise BP Diastolic (mmHg)		205 (23)	207 (21)	208 (22)	232 (21)
Max Exercise BP Systolic (mmHg)		79 (8)	76 (10)	78 (10)	79 (14)
Hypertensive Response to Exercise (%)		37 (29.8)	16 (42.1)	7 (42.1)	3 (75)
Dietary Inflammatory Index Score		-2.7 (-3.8—1.25)	-2.3 (-3.67—1.35)	-3.1 (-3.8—0.2)	-3.3 (-3.3—3.3)
Total Cholesterol (mmol/l)		5.1 (0.8)	5.1 (1.1)	5.2 (0.9)	4.8 (0.4)
LDL Cholesterol (mmol/l)		2.7 (0.8)	2.7 (0.8)	2.9 (0.9)	2.6 (0.5)
HDL Cholesterol (mmol/l)		1.8 (0.4)	1.8 (0.4)	1.8 (0.3)	2.6 (1.4)
Glucose (mmol/l)		4.9 (0.8)	4.7 (0.8)	5.5 (1.07)	5.1 (0.68)
Coronary Artery Calcium Score (AU)		0 (0-32.5)	0 (0)	7.9 (0-42)	13.5 (0-50.2)
Coronary Artery Centile		0 (0-71.25)	0 (0)	45 (0-79)	22 (0-57.5)
Coronary Artery Calcium Score ≥100 AU		19 (15.6)	8 (21.2)	3 (20)	0 (0)
Predominant Plaque Morphology	None	69 (55.6)	23 (60.5)	5 (33.3)	2 (50)
	Calcified	39 (31.5)	6 (15.8)	7 (46.7)	1 (25)
	Non-calcified	2 (2.4)	0 (0)	0 (0)	0 (0)
	Partially Calcified	11 (8.9)	9 (23.7)	3 (20)	1 (25)
Number of vessels with coronary artery disease	0	69 (57)	23 (60.5)	5 (33.3)	1 (25)
	1	31 (25.6)	9 (23.7)	6 (40)	3 (75)
	2	16 (13.2)	1 (2.6)	4 (26.7)	0 (0)
	3	5 (4.1)	5 (13.2)	0 (0)	0 (0)
Total no. all plaques		0 (0-2.5)	0 (0)	3 (0-4)	2 (0.5-2.75)
Stenosis >50%		6 (4.8)	3 (7.9)	0 (0)	1 (25)
Diseased LAD		36 (38)	15 (39.5)	10 (66.7)	3 (75)
Plaque Vulnerability Markers		16 (12.9)	9 (23.7)	3 (20)	2 (50)
TCFA		11 (8.9)	6 (15.8)	3 (20)	2 (50)
Peri-coronary adipose tissue attenuation		-72.6 (-82.7—67.3)	-72.8 (-78.3—64.9)	-72.1 (-77—67.6)	-67.74 (-85.3—61.9)
Ejection Fraction (%)		65 (6)	64 (5)	66 (8)	59 (12)
Maximal Wall Thickness (mm)		9.6 (1.3)	9.7 (1.3)	9.5 (1.4)	10.9 (1.2)
ECV		23.7 (1.7)	24.3 (1.9)	24.4 (1.3)	25.7 (2.5)

AU, Agatston Units; BP, Blood pressure; HR, Heart rate; HDL, high density lipoprotein; LAD, Left anterior descending artery; LDL, Low density lipoprotein, LGE, Late Gadolinium Enhancement; TCFA, thin-capped fibro atheroma; RV, Right Ventricle

6.4.1.1 Patterns of Myocardial Fibrosis

Thirty two percent of athletes had evidence of LGE of any pattern or distribution on cardiac MRI, 23% of whom has RV insertion point (inferior hinge point) and 11% pathological LGE consistent with MF i.e., non-insertion point subendocardial, subepicardial or mid wall LGE. Four athletes (2.2%) had evidence of MF in an ischaemic pattern and 15 (8.3%) exhibited non-ischaemic i.e., 13 mid-wall and 2 subepicardial MF. The distribution of non-ischaemic MF was limited to the basal to mid lateral (n=12), inferior walls (n=2), and basal septal walls (n=1) and 2 of these athletes exhibited accompanying LV systolic dysfunction.

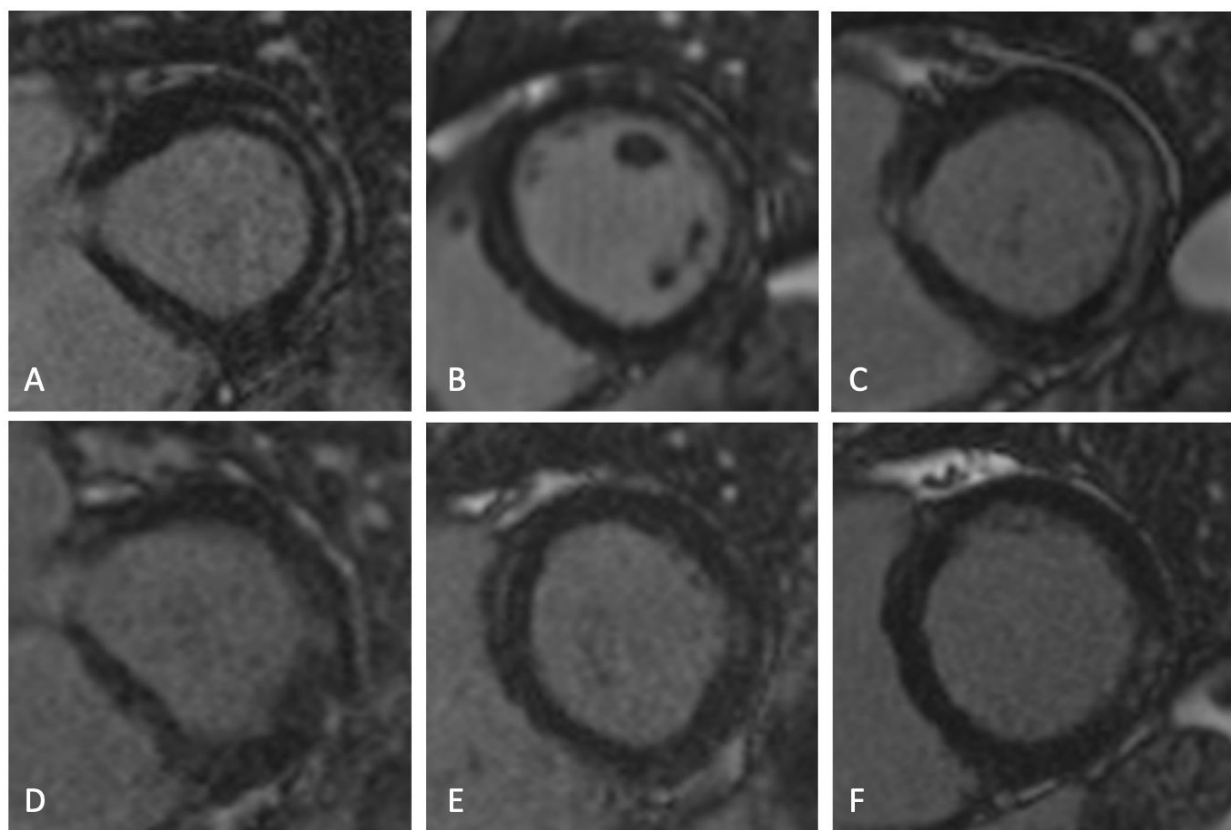


Figure 6.2 Short Axis LGE Images Depicting Non-Ischaemic Patterns of MF.

Panels A-C showing athletes with halo-shaped enhancement in the lateral wall and panels D-F showing more focal patches of mid-wall fibrosis in the lateral wall.

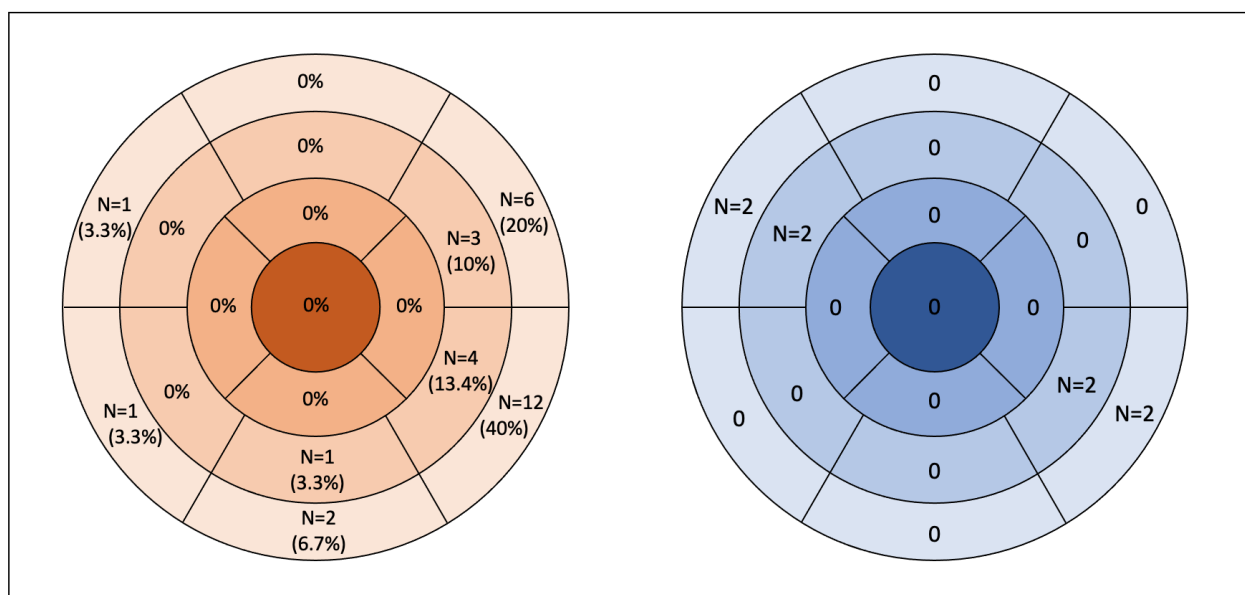


Figure 6.3 Distribution of non-ischaemic (orange) and ischaemic (blue) Patterns of MF

According to the 17-segment Model. More than 80% of non-ischaemic MF is distributed in the basal to mid lateral wall.

The mean T1 value was 992.85 msec (SD 24.71) and ECV 23.92% (SD 1.74). Athletes with no LGE had a lower mean ECV of 23.7%, compared to those with RV LGE, non-ischaemic and ischaemic pattern LGE, where the mean was 24.3%, 24.4% and 25.7%, respectively. Analysis of the relationship of ECV with the presence of LGE demonstrated that all types of LGE including RV insertion, non-ischaemic and ischaemic LGE, both separately and together were predictive for a greater ECV; however, only the association between RV insertion LGE ($p=0.015$) was upheld with adjustment for years of endurance training.

6.5 Pathological Myocardial Fibrosis and Exercise Dose

Athletes who participated in a greater number of years of endurance exercise were more likely to have evidence of any type of pathological LGE in an unadjusted regression model

($p=0.012$, $OR_{unadjusted}=1.04$, CI 1.01-1.08); however, this did not remain significant after adjustment for age ($p=0.15$). The presence of a non-ischaemic pathological pattern of LGE was also significantly associated with the number of years of endurance exercise including when adjusted for age ($p=0.03$, $OR_{adjusted}=1.04$, CI 1.01-1.08). Neither of 'pathological LGE' or 'non-ischaemic LGE' groupings were associated with MET hours per week or lifetime MET years. Ischaemic pattern LGE alone was not associated with any exercise dose measures. Number of years of endurance exercise was also significantly predictive for the presence of a greater ECV, independent of age ($p=0.018$), with every 1-year increase in number of years participating in endurance exercise increasing the value of the ECV by 0.028%.

There was a borderline association between lifetime MET years and RV insertion point LGE ($p=0.07$) but other exercise dose markers including years of endurance exercise and hours per week and VO_2 max were not significantly associated with this LGE pattern.

6.6 Blood Pressure Profile and MRI findings

A higher resting systolic 'office' BP was significantly associated with an ischaemic pattern of LGE ($p=0.03$, $OR_{unadjusted}=1.07$, CI 1.01-1.13), but did not remain significant after correction for age. However, a higher maximum exercise systolic BP was significantly associated with the presence of ischaemic pattern LGE including following correction for age ($p=0.03$, $OR_{adjusted}=1.05$, CI 1.01-1.11). Ambulatory BP measures were not associated with any patterns of LGE. There was no association identified with any BP parameters and the presence of non-ischaemic LGE or RV hinge point LGE. An increase in ambulatory BP was negatively associated with ECV, even after correction for years of endurance exercise

($p=0.03$, $B_{\text{adjusted}}=-0.59$ CI $-1.11—0.07$). All other measures of BP were negatively, but not significantly, associated with increasing ECV.

6.7 Coronary Artery Disease and MRI Markers of Fibrosis

Four athletes (A-D) had a subendocardial pattern of LGE consistent with an ischaemic origin suggestive of prior MI. All 4 were multi-endurance athletes and above the mean age. All demographics and outcome measures for these athletes are provided in table 6.2

Table 6.2 Demographics and findings of the 4 Athletes with Ischemic Pattern Myocardial Fibrosis

	Athlete A	Athlete B	Athlete C	Athlete D	Entire Cohort N=214
Age, y	62	59	56	54	51.36 (7.06)
Years Endurance Exercise, y	40	30	17	20	15 (8.75-30)
Sporting Discipline	Multi-endurance	Multi-endurance	Multi-endurance	Multi-endurance	-
VO ₂ Max percentage predicted, %	172	186	186	144	154.24 (19.34)
Ejection Fraction MRI, %	50	49	67	72	64.85 (6.12)
Resting Systolic 'Office' BP, mmHg	138	142	128	176	128.79 (14.84)
Resting Diastolic BP, mmHg	88	86	80	86	79.37 (8.49)
Ambulatory Systolic BP, mmHg	117	122	109	142	118.69 (8.3)
Ambulatory Diastolic BP, mmHg	78	78	75	89	76.3 (6.30)
Ambulatory Hypertension	Yes	No	No	Yes	11.5%
Masked Hypertension	Yes	No	No	Yes	6.8%
Hypertensive Response to exercise	No	Yes	Yes	Yes	35%
Total cholesterol, mmol/l	4.5	5.3	4.3	4.9	5.10 (0.83)
LDL, mmol/l	2.4	3.1	2.0	2.7	2.72 (0.78)
HDL, mmol/l	1.8	4.7	2	1.91	1.80 (0.41)
Glucose, mmol/l	5.4	4.7	4.4	5.9	4.93 (0.81)
Framingham Risk Score, %	5.8	7.2	2.9	5.8	3.9 (2.64)
Coronary Artery Calcium Score	27	58	0	0	0 (0-37)
Plaque Morphology	Calcified	Calcified	None	Non-calcified	-
Stenosis >50%	No	No	No	Yes	5.4%
LAD Disease	Yes	Yes	No	Yes	40.1%
PCAT RCA, Hu*	-89.8	-71.8	-63.7	-61.3	77 (38.5)
Plaque Vulnerability Markers	None	Yes	None	None	13.3%
TCFA	None	Yes	None	Yes	-

LAD, left anterior descending; Hu, Hounsfield Units; PCAT, peri-coronary adipose tissue attenuation; RCA right coronary artery.

*Cut-off for abnormal PCAT is less than -68.2 Hu.

Data given in column labelled 'entire cohort' is presented as mean (standard deviation) and median (interquartile range) for continuous data and as a percentage for categorical data.

Athlete A and B had subendocardial LGE in the lateral wall, one with calcified plaque and one with a tiny amount of calcium, both in the LAD territory (third diagonal and mid LAD), respectively. Athlete A had a CAC score of 27 AU and athlete B had a CAC score of 58 AU. Athlete B had evidence of plaque vulnerability markers, specifically spotty calcification and positive remodelling as seen in the CCTA image in figure 6.4. Athletes C and D demonstrated LGE in the antero-septum, both with zero CAC scores. Athlete C has no evidence of CAD and athlete D had evidence of non-calcified coronary plaque with a stenosis of greater than 75% in the proximal LAD. All athletes demonstrated an abnormal BP profile with abnormal resting, ambulatory and/or exercise hypertension.



Figure 6.4 CT Image of Athlete B Demonstrating Spotty Calcification and Positive Remodelling.

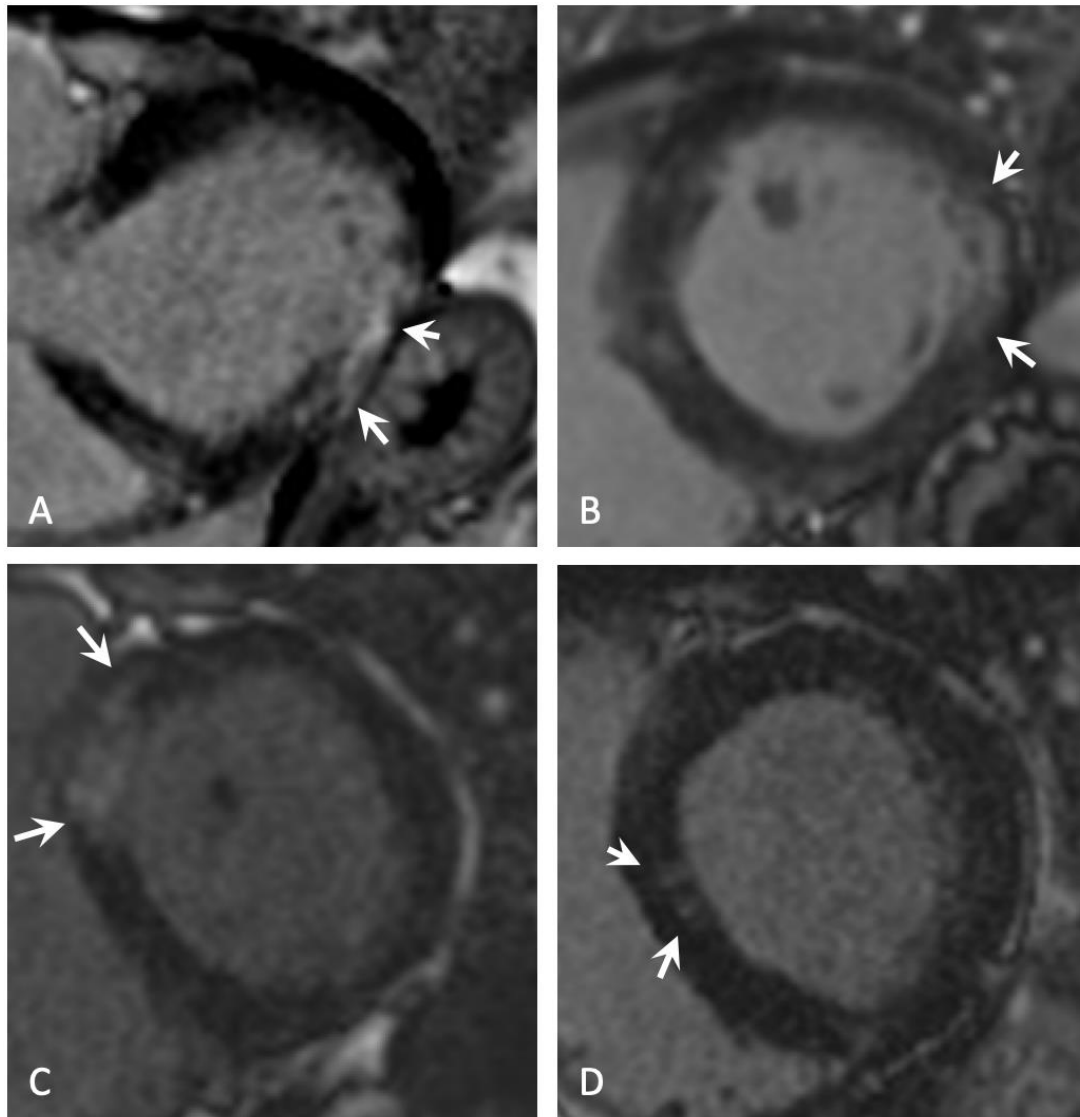


Figure 6.5 Short Axis Images of Athletes with Subendocardial LGE Consistent with Ischaemic Myocardial Fibrosis.

Athlete A and B exhibit subendocardial fibrosis in the lateral wall consistent with infarction in the territory of the first diagonal branch of the LAD or obtuse marginal branch of circumflex. Athletes C and D exhibit anteroseptal ischaemic fibrosis consistent with infarction in the proximal LAD territory.

No CT coronary markers of disease were found to be significantly associated with the presence of ischaemic LGE.

It is also noteworthy that the presence of a diseased LAD was significantly predictive for the presence of non-ischaemic pattern LGE ($p=0.049$, $OR_{unadjusted}=1.05$ CI 1.00-8.1); however, this was not upheld when adjustment was made for age or years of endurance exercise.

6.8 Discussion

6.8.1 Distribution of Patterns of Myocardial Fibrosis

The prevalence of RV insertion point LGE consistent with MF in this cohort (23%), is comparable to prior studies whose prevalence lies between 20-37%.^{179,322} Only one other study of 102 male veteran marathon runners has described the prevalence of both ischaemic and non-ischaemic LGE within its cohort and demonstrated a prevalence of 4.9% and 6.9%,¹⁵⁸ respectively, which is comparable to this cohort with 2.2% and 8.3% respectively. Other studies have singularly reported either insertion point, ischaemic or non-ischaemic MF.¹⁷⁹ Consistency between this data and existing similar studies suggest this data is a reliable reflection of the prevalence of MF patterns amongst the male master endurance athlete cohort.

General population data from the MESA study of 1084 asymptomatic adults aged 68 ± 9 years found a prevalence of ischaemic MF of 2.3% and non-ischaemic fibrosis 3.9%.³³²

Although the prevalence of ischaemic MF is similar between athletes in this study and the non-athletes in the MESA data, the MESA cohort were considerably older and therefore one would normally expect a higher prevalence of MF in the MESA cohort, if there was no

difference between groups. This therefore suggests that athletes have a higher prevalence of silent ischaemic MF than the general population, which can be explained by embolic events occurring secondary to the acute prothrombotic state associated with endurance events,^{10,176,333,334} or demand ischaemia from otherwise subclinical stenosis in the context of ischaemic pre-conditioning. This may explain the findings in athlete C who demonstrated subendocardial MF but had no evidence of coronary plaque or prior plaque rupture. Conversely, despite the older age of the MESA cohort, athletes in this thesis had a higher prevalence of non-ischaemic MF compared to the general population in the MESA study, with the majority of scar seen in the inferolateral wall, the site typical for myocarditis³³⁵ and consistent with existing data.^{9,329} It has been hypothesised that exercising whilst in the acute stages of cold or flu reduces immunity in the immediate post event period and increases the risk of developing myocarditis.³³⁶ When questioned, 72% of participants in this study declared having previously continued endurance exercise despite a cold or flu illness. Non-ischaemic MF, which is a sequelae of myocarditis is considered benign in the general population¹⁷⁸ however, long-term studies would be necessary to ascertain the risk to an endurance athlete who is exposed to a lowered arrhythmia threshold during and after extreme exercise. Finally, it cannot be excluded that the development of non-ischaemic MF is a direct effect of years of exposure to the chronic haemodynamic and volume stresses of endurance exercise.

Athletes with no evidence of LGE had a lower mean ECV (23.7%) than those with LGE. This value also lies at the lower end of the spectrum in comparison to other data from athletes (20-26%)¹⁷⁹ and the general population ($26 \pm 4\%$),³²⁸ consistent with the hypothesis made

by McDiarmid *et al* of a physiological increase in cellular mass with age, resulting in a relative reduction in ECV.³²⁹

The previous finding by Tahir *et al*⁹ of an increased ECV in non-ischaemic MF was not upheld by this data once correction was made for exercise dose in terms of years of endurance exercise; however, it is worth noting that both studies had small numbers with this LGE pattern (n=9 and n=15) respectively. Larger studies are warranted to substantiate this finding further.

6.8.2 Exercise dose

Although the relationship between 'pathological LGE' and exercise dose, measured in years of endurance exercise, was only significant in the unadjusted model, it appears that this positive finding derives from the non-ischaemic group, which maintained a significant relationship following age adjustment, but was diluted by the lack of relationship of ischaemic MF and exercise dose. This finding supports a hypothesis that the greater the number of years of endurance exercise the greater the likelihood that an athlete will have exposed themselves to the stresses of exercise whilst experiencing acute cold or flu symptoms, thus increasing the risk of developing acute myocarditis, or that such patterns of MF arise directly as a result of exercise itself. The association of increasing exercise dose and the presence of MF is consistent with findings from 2 previous studies. In the first study of 12 veteran athletes >50 years of age, there was a significant association between presence of LGE (all patterns) and years of training and number of marathons and ultra-endurance events; however, numbers were notably small.⁸ The latter study of 83 triathletes aged 43 ± 1 years found that those athletes with LGE had completed greater cumulative distances of

swimming and cycling and more ironman events.⁹ This thesis adds to the existing literature, identifying that this association arises from the non-ischaemic pattern specifically, which has not been previously described.

Despite both the existing and this study's data showing an association of CAC and exercise dose,⁷ but absence of an association with any other CAD risk markers, there was no association found between years of exercise and the presence of ischaemic MF in this cohort. Given that the study was sufficiently powered for this outcome, this would suggest that CAC alone is a poor predictor of high-risk disease.

Prior studies suggest RV insertion point fibrosis is associated with lifetime exercise load and intensity.³²² Analysis of the association of RV insertion point LGE consistent with fibrosis to all exercise dose parameters revealed only a borderline significant relationship between lifetime MET years and RV insertion point MF ($p=0.067$) with no association with other dose parameters and RV insertion MF. Possible explanations for the discrepancy in findings in this study and the study by Demenech-Xiemenos *et al*, is the difference in exercise load, with athletes in the other study training more than 12 hours per week for at least 5 years, and being older aged, suggesting that they were subject to higher lifetime doses of exercise than this cohort. It is also possible that insufficient numbers, in particular the dose parameters of lifetime MET years and MET hours per week, that have 49 values missing values, explains this finding.

The positive association of years of endurance exercise and increasing ECV following adjustment for age is consistent with prior findings.⁹ Tahir *et al* also found a relationship

between LGE, greater cumulative distance and ECV amongst a cohort of 83 asymptomatic triathletes. Given ECV is not known to increase with age in the general population^{328,337} and that age and years of endurance exercise are significantly correlated in this cohort ($r=0.50$, $p<0.01$), this finding is likely to be determined by the effect of years of endurance exercise as opposed to age and represents a true association between years of exercise and ECV. The presence of RV insertion LGE was also predictive for the presence of an increasing ECV, regardless of years of endurance exercise ($p=0.015$), suggesting that detectable RV insertion point fibrosis is not only isolated to the area of LGE but represents a diffuse pattern of MF, as seen in pulmonary hypertension patients.³³⁸ One possibility that pulls together both such findings, is that repetitive prolonged myocardial high demand and wall stress, especially with inadequate recovery, as demonstrated by the 50% of athletes in this cohort exercising at least 6 days per week, may cause microscopic injuries that culminate in fibrosis detectable as ECV, not only isolated to the RV insertion point but throughout the ventricular myocardium.

6.8.3 Blood Pressure

Although no association was identified between pathological LGE and BP, the data did show that an increasing resting 'office' systolic and maximal exercise systolic BP to be predictive for the presence of ischaemic pattern LGE ($p=0.03$, $OR_{unadjusted}=1.07$ CI 1.006-1.128 and $p=0.03$, $OR_{adjusted}=1.05$ CI 1.006-1.109), respectively, and likely to represent the role of BP as a significant risk factor for high-risk CAD amongst male master endurance athletes. BP evaluation identified all 4 athletes with ischaemic LGE as having an abnormal BP profile and therefore being potentially at risk. Athlete A demonstrated a high-normal resting BP and ambulatory hypertension, athlete B resting hypertension and HRE, athlete C HRE and

athlete D a hypertensive resting BP, ambulatory hypertension and HRE. These findings support the argument in favour of using resting, ambulatory, and exercise BP evaluation as part of screening to identify at-risk athletes and the importance of identifying and managing it appropriately when present amongst this cohort.

Existing data studying triathletes training more than 10 hours a week, from Tahir al, demonstrated a significant relationship between the presence of non-ischaemic MF and a higher peak systolic exercise BP (mean = 213 ± 24 mmHg),⁹ which was not found in this study. It is noteworthy to mention that the study did not correct for age and therefore it is possible given the increase of BP with age, which although attenuated by exercise is not negated, could account for this effect.

The data revealed a significant negative correlation between ECV and ambulatory hypertension ($p=0.027$), and negative, but not significant relationship to all other BP parameters also, suggesting BP is not a driver of diffuse fibrosis in the master endurance athlete.

6.8.4 Coronary Artery Disease

There was no significant association found between CAC measures and the group 'any pattern of LGE' and specifically no association was found between CAC score and ischemic LGE pattern either. No athlete with ischemic LGE had a CAC score ≥ 100 AU. As such, conventional CT CAC scoring for risk stratification would not have detected these athletes. Conversely, a CCTA would have identified athlete B and C as at high-risk, warranting further management, likely in the form of being offered statin therapy. Therefore, CAC score alone

would have labelled these individuals as low risk but the addition of CCTA changed the management in 2 athletes.

This data could suggest that CAC score is a poor predictor of CAD at high-risk of infarction. However, caution should be exercised in this interpretation as the numbers may be too small to draw such a conclusion. The small numbers could also explain the discrepancy of this finding as compared to the study by Möhlenkamp *et al* showing CAC centile to be predictive for pathological LGE (both ischaemic and non-ischaemic together). However, the Möhlenkamp cohort (n=108), was smaller than this one and pathological LGE was identified in the same proportion of athletes (11%)¹⁵⁸ making this explanation less likely. Although there was no relationship found between CAC or any other CCTA markers of coronary risk and LGE, there were some associations found between BP parameters and the presence of LGE; BP having been demonstrated to be highly predictive for CAD both in the general population and amongst this cohort.

Ischaemic LGE was also significantly associated with MWT ($p=0.04$). This may represent hypertensive LVH and is consistent with the finding of a significant association of resting systolic 'office' BP with MWT, and the abnormal BP profile present amongst all 4 athletes in this group.

An abnormal PCAT score suggestive of coronary artery inflammation amongst the general population¹⁵⁶, was the only CCTA finding in athlete C and therefore may offer an alternative explanation for this athlete's ischaemic fibrotic lesion. Athlete D also had an abnormal PCAT;

however, this was in addition to a significant stenosis, non-calcified morphology plaque and TCFA.

Athlete A demonstrated only a small amount of calcium in the LAD (CAC score =27 AU); this could represent a previously high-risk lesion that has calcified because of the postulated calcification effects of exercise.

The data revealed distinct differences in CMR findings between those athletes with ischaemic versus non-ischaemic MF, as such the hypothesis is accepted in some contexts; however, the data found no relationship between CAD risk markers and MF and specifically no relationship to ischaemic MF. There was however an association between BP parameters and MF, with abnormal raised BP being a lot more prevalent than CAD risk markers, and ischaemic MF, supporting the importance and clinical implications of the BP findings amongst male master endurance athletes. Secondly, exercise dose in terms of years of endurance exercise was a significant predictor for non-ischemic MF and increased ECV, representative of diffuse fibrosis, suggesting there is a dose-response relationship that is worthy of further exploration.

6.8.5 Limitations

The most pertinent limitation of this data is the sample size. Despite 214 athletes entering the study only 181 attended for their CMR scan, resulting in loss of statistical power of the data, which may have resulted in some important associations failing to reach statistical significance. This is particularly pertinent to the relationship of LGE patterns to MET-hours

per week and lifetime MET-hours as these groups contained only 164 athletes due to the collection of this exercise dose data later in the study and resultant poor response rate.

The heterogeneity in reporting of ECV is well known and explained by variation in scanners, contrast and native T1 sequences, as such it is recommended that values should be interpreted in comparison to a healthy control group; however, this is not possible in this data as no controls were included. Therefore, inference of the ECV findings relative to the general population is limited but this still allows for identification of associations of ECV with important explanatory variables.

6.8.6 Conclusion

Exploration of the relationships of CAD, exercise dose and BP profile to the presence and patterns of MF amongst male master endurance athletes revealed an increased prevalence of both ischaemic and non-ischaemic MF but no association of either pattern to CAD markers. Exercise dose is an important determinant of non-ischaemic MF and blood pressure is an important predictor of ischaemic MF. Long-term studies of the outcomes of both ischaemic and non-ischaemic MF to determine the risk of such findings amongst this cohort are warranted

7 Inflammation, Diet and Coronary Artery Disease

1.1 Hypothesis

A pro-inflammatory diet as defined by a raised dietary inflammatory index (DII) is predictive for the presence of coronary artery disease amongst male master endurance athletes.

1.2 Introduction

1.2.1 Inflammation and Coronary Artery Disease

The role of chronic and acute inflammation in the development of atherosclerosis by means of tissue injury, oxidative stress, angiogenesis and fibrotic remodelling of the extracellular matrix in the general population is well established,^{164,339} such that the latest ESC guidelines for the prevention of CAD recognise highly sensitive CRP as a marker of CVS risk^{340,341}.

Routine measurement is not recommended however as there is contradictory data relating to its additive benefit over conventional risk stratification to justify the additional cost of its use³⁴¹. In support of the pro-atherogenic nature of inflammation are studies of the novel coronary anti-inflammatory drugs Evolocumab and Canakinumab, that have demonstrated their success in reducing CVS events.^{342,343} Statins and aspirin also have potent anti-inflammatory properties that promote stabilisation of coronary plaque and portend MACE benefit^{171,340,344,345}, independent of their mechanisms of actions first described i.e. lipid lowering and anti-platelet respectively. As discussed in chapter 1, a study of participants in the race across the USA revealed an increase in non-calcified plaque volumes and CRP amongst those athletes with pre-existing coronary plaque, supporting the concept that acute

exercise-induced inflammation plays an important role in high-risk coronary artery plaque amongst endurance athletes.⁵⁸

1.2.2 Diet and Coronary Inflammation

As discussed in chapter 1, the performance enhancing focus to the dietary approach amongst endurance athletes predominantly advocates a high-carbohydrate diet with more refined carbohydrates (high glycaemic index), particularly during endurance events as it allows energy to be rapidly gleaned. Some studies suggest such foods are pro-inflammatory^{346,347} and therefore promote the development of CAD. Furthermore, the PURE study demonstrated increased CVS events associated with a carbohydrate-rich diet.³⁴⁸

1.2.3 The Dietary Inflammatory Index

The evaluation of dietary habits is notoriously difficult and controversial and as such related research attracts scepticism. Accepting this controversy, the use of the validated DII aims to provide valuable insights into the interaction of dietary inflammation and coronary atherosclerosis. The DII is a validated tool used to quantify levels of dietary inflammation, developed by the University of South Carolina. The score was developed using almost 2000 research articles that assessed the role of dietary constituents on specific inflammatory markers such as CRP, IL-1 β , IL-4, IL-6, IL-10, and tumour necrosis factor.³⁴⁹ The DII has been validated in a study of 600 individuals followed with intensive dietary and physical activity monitoring for one year and shown to be predictive for highly sensitive CRP,³⁵⁰ in addition to several other dietary markers of inflammation. Data from the Whitehall study in addition to a meta-analysis of 14 studies exploring DII in association with CVD and MACE risk, demonstrated that a pro-inflammatory diet, as defined by a high DII score >0, correlated

with an increase in all cause and CVS disease mortality.^{351,352} Thus, there is substantial evidence that the DII score is a good predictor of CVS disease but is yet to be applied in an athletic cohort. Figure 7.1 provides an algorithmic explanation of the method by which the DII is derived.

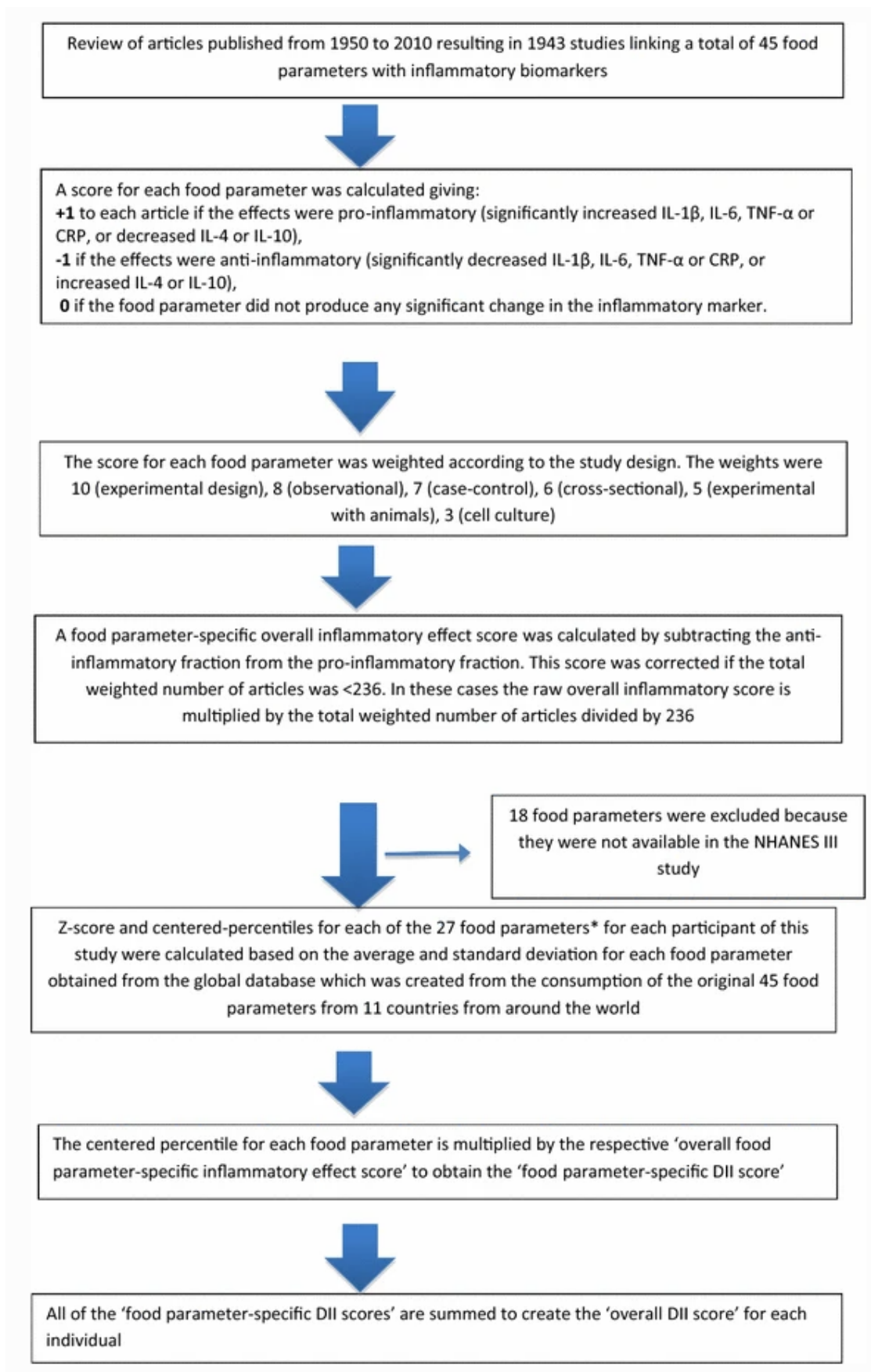


Figure 7.1 Sequence of Steps in Creating DII for a study.³⁵³

This chapter will evaluate of the role of dietary inflammation in the development of CAD amongst male master endurance athletes.

1.3 Methods

Athletes completed an online dietary evaluation to derive the DII as described in chapter 2, Section 2.6.10.

1.4 Results

One hundred and seventeen athletes (55% of the cohort) completed the dietary questionnaire following the end of all 3 days of testing. The median DII was -2.60 (-3.80—1.50), with the scale for DII ranging from +5 to -5. The maximum DII score for any athlete was +1.8 and only 8% had a pro-inflammatory DII score i.e., >0, suggesting that the majority the cohort reported an anti-inflammatory diet.

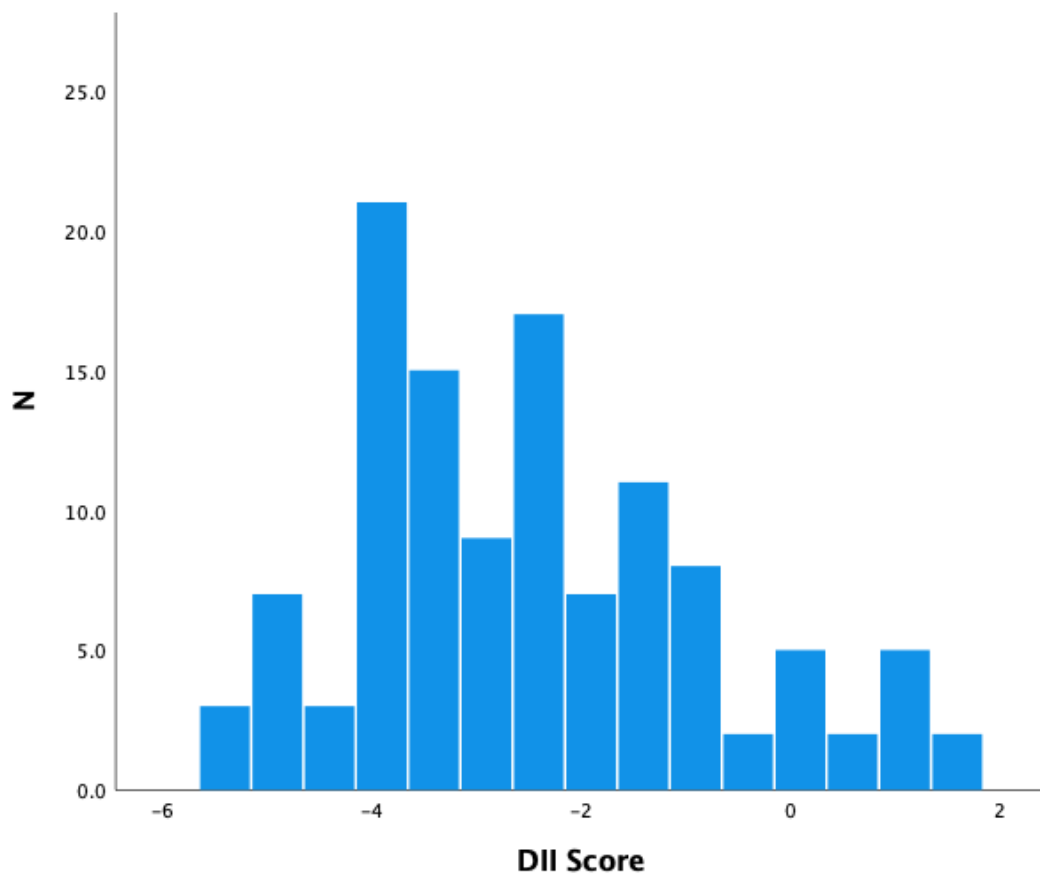


Figure 7.2 Bar chart demonstrating distribution of DII data with majority lying in the anti-inflammatory range.

Preliminary analysis of DII using correlation, Mann-Witney U and T-testing did not demonstrate any statistically significant associations between DII and any of the baseline characteristics or outcomes under investigation. Therefore, this variable was not considered significant in the development of CAD markers and therefore not included in multiple regression modelling. All outcome variables evaluated for this association and the respective p values are given in figure 7.3.

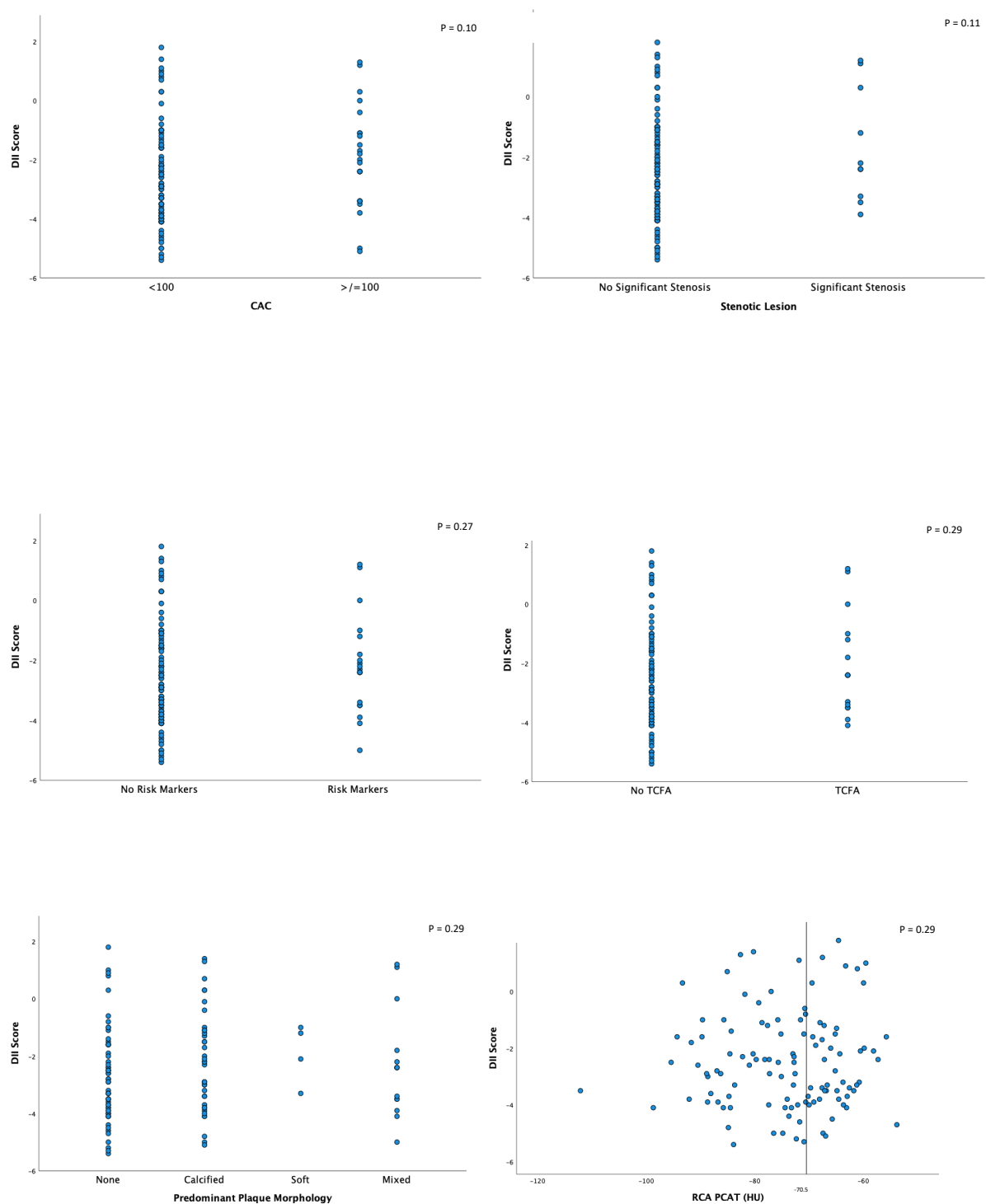


Figure 7.3 Dot and Scatter Plots of DII and CAD outcomes

1.5 Discussion

This is the first study examining the potential deleterious effects of diet, in particular a pro-inflammatory diet, on the coronary arteries of athletes. Accepting the limitations of dietary tools in achieving reliable research outcomes, the numbers in this cohort were likely too small to achieve adequately statistical power and therefore meaningful findings. Prior data demonstrating the ability of DII to predict CAD and MACE in the general population arose from a meta-analysis including thousands of participants.³⁵¹

It was particularly notable that there was no relationship identified between PCAT, which is a marker of coronary inflammation, and the DII, which would have been most likely to show a significant association amongst the CAD risk markers. The lack of association between the risk scores i.e., FRS and HeartScore®, is also notable given the known association between DII score and hs-CRP³⁵⁰ and that the predictability of hs-CRP and the risk scores for CAD risk are comparable.³⁴¹

There is a growing acknowledgement of the impact of nutritional intake on inflammation and the consequent development of chronic diseases, including CAD and therefore this research question is worthy of exploration. The advent of technologies and precision medicine is likely to bring greater access for athletes to record diet, similar to those available for recording training and exercise sessions such as Strava, which will make data downloadable in a format that can be databased and used for research. The comprehensive evaluation of nutrition requires not only measures in terms of type and amount of food, but also quality and temperature, pattern and timing of consumption, mode of preparation, and environment in which it is consumed. Large scale studies evaluating the dietary patterns of

an endurance athlete and the relationship to CAD are called for to delineate the gravity of potential harm resulting from a performance-driven diet as well as to establish the optimal diet to achieve both high performance and prevent CAD.

1.5.1 Limitations

It is possible that the absence of significant expected findings and therefore the rejection of the hypothesis is related to the low response rate of the questionnaire i.e., just over half of the cohort. The point at which this data was collected i.e., following closure of testing days 1-3 is likely to explain the poor uptake. This was due to limitations of funding and consequent delayed set up of this aspect of the research. Ideally, this questionnaire would have been administered at the point of recruitment into the study at which time athletes would have been motivated to have their cardiac testing and therefore motivated to complete the questionnaire as a step to achieve this. In addition, there is likely to have been significant reporter bias amongst those completing the questionnaire making it unlikely that this sample is representative of the study population.

Another possible explanation for the absence of significant findings is the inherent flaw in collecting dietary data using a questionnaire given that it offers data only from one cross-sectional time point, whereas the development of atherosclerosis is determined by lifetime dietary exposure. It is extremely likely that all individuals will have variations in their diet both over the short (e.g., seasonally) and long term. However, the DII is a validated tool which as discussed in the introduction, has been demonstrated in the general population to predict CAD and MACE.³⁵¹

Other biases worthy of discussion that may have affected the data included the social desirability of the athletes, i.e., bias in their reporting of diet amongst some athletes towards a healthier one, due to a desire to be perceived as eating a healthy diet, to receive social approval and avoid criticism.

1.6 Conclusions

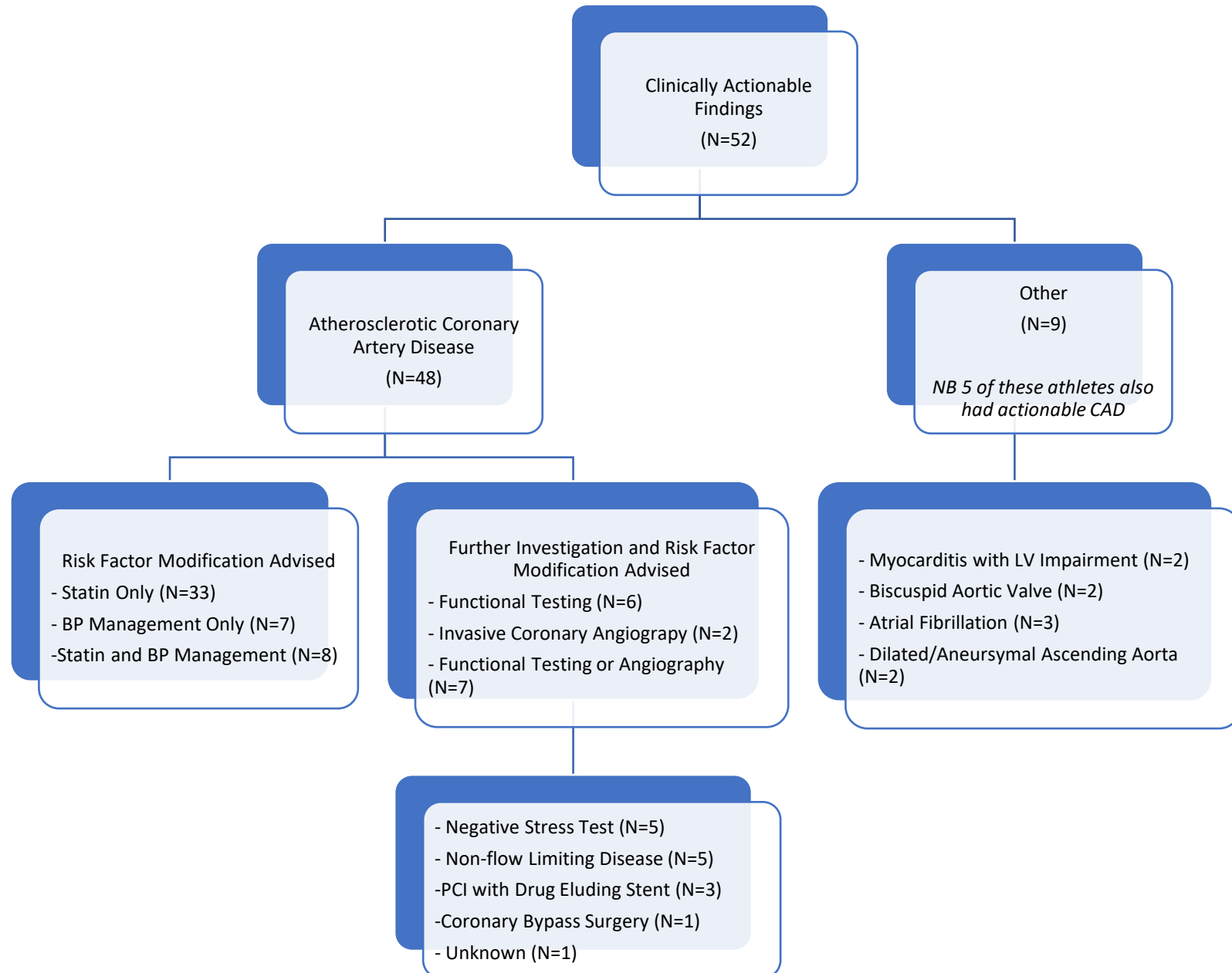
Data analysis failed to bring any evidence to support the hypothesis in relation to dietary inflammation and CAD. Reasons for this have been discussed extensively and largely relate to insufficient statistical power and the biases and difficulties inherent in achieving meaningful data in the evaluation of an individual's lifelong dietary habits. Although this data did not identify any important relationships to allow meaningful conclusions to be drawn, it opens a dialogue and invites new perspective surrounding performance-related nutrition and its potential deleterious contribution to CVS disease amongst endurance athletes. It also highlights the need to consider diet when undertaking preparticipation evaluation and addressing any abnormalities detected. It is hoped that in highlighting this issue, there will be a greater awareness and a continued exploration of this novel question in future research.

8 Actionable Clinical Findings

8.1 Cardiac Findings Requiring Clinical Action

In addition to those requiring further management for BP, a total of 52 athletes, had cardiac findings warranting further investigation and/or management and follow-up. These findings and subsequent outcomes, where known, are summarised in the flow diagram in figure 8.1 below. The majority (47/52) of these athletes consisted of those who had findings of atherosclerotic CAD that were either significant enough to warrant further intervention or was associated with significant and previously unidentified risk factors of hypertension and/or hypercholesterolaemia which required further management. Three athletes required percutaneous coronary intervention (PCI) to the LAD or its branches, all received drug-eluting stents, and 2 underwent FFR guided PCI. One athlete with partially calcified morphology disease with a blocked LAD, severe disease in the first diagonal and first and second obtuse marginal branches and evidence of prior infarction on cardiovascular MRI, was deemed to warrant coronary artery bypass surgery. Three of the 4 athletes above who underwent coronary intervention demonstrated an abnormal blood pressure profile. All 3 athletes in the study who either during or subsequently developed AF had evidence of non-calcified morphology coronary atherosclerosis. Two athletes demonstrated impaired and dilated bi-ventricular function with inferolateral wall MF warranting onward referral for investigation and follow-up. Two athletes had a dilated ascending aorta in the absence of any CAD, one measuring 46mm. One athlete has a LBBB and aneurysmal appearance to the LV despite normal coronary arteries. Finally, seven of these athletes were advised to cease competitive or intense exercise either until further investigation or indefinitely.

Figure 8.1 Flow Diagram of Clinically Actionable Findings from Coronary CCTA



8.2 Extra Cardiac CT Findings

A total of 101 athletes (50%) of the 203 who underwent CCTA has extra-cardiac findings reported, some with multiple abnormalities, of whom 39 required further investigation. The commonest findings were lung abnormalities including pulmonary nodules, enlarged lymph nodes, bronchial thickening, scarring, atelectasis and ground glass opacification. Three athletes had either filling defects or bronchial collaterals requiring CTPA with one confirmed to have pulmonary embolic disease. Twenty-seven athletes required further CT chest either immediately or within months for monitoring purposes, 24 of whom were to exclude a lung malignancy diagnosis. Seven other athletes required further investigation to exclude malignancy involving the oesophagus (n=3 requiring oesophageal duodenoscopy), thymus, liver, kidney and rib. No athletes reported back any malignant diagnosis; however, they were not contacted directly to confirm the outcome.

8.2.1.1 Discussion

Overall, a quarter of all athletes had abnormal CCTA findings warranting further investigation and management, although the majority were recommended statin therapy alone. Although it is impossible to say that these findings could result in adverse outcomes, amongst those with significant CAD, the risk of this is likely to be high. Similarly, a large number of athletes with asymptomatic extra-cardiac findings required additional testing, with numerous requiring exclusion of malignancy. It is important to recognise the financial and psychological burden these findings purport. Long-term prospective studies evaluating the clinical outcomes and financial implications of pre-participation evaluation, in contrast to the cost implications without it, will be instructive in determining if this approach is plausible.

The finding of significant CAD amongst all 3 athletes who developed AF is of interest and further research is warranted to explore this relationship and the possibility of a unifying inflammatory process, amongst this cohort, who are regularly exposed to high CVS demands.

9 Discussion

Ostensibly healthy male master endurance athletes have an increased prevalence of high coronary artery calcium scores and atherosclerotic plaques^{6,7} and prevalent myocardial fibrosis, the prognostic significance of which is unknown. The known prognostic consequences of these findings in the general population and the knowledge that the male master endurance athlete cohort is at greatest risk of ischaemia related SCD during exercise, makes this an important clinical concern, demanding greater exploration and understanding. Seemingly free of conventional modifiable CVS risk factors, the characteristics that identify those athletes at risk of CAD and MF have been until now, largely unknown. One study suggested that lifetime exercise dose measured in lifetime-MET-hours was a predictor for higher CAC scores and more atherosclerotic plaques,⁷ although these athletes were not free of known CVS risk. It has been hypothesised that the common pattern of non-ischaemic MF in athletes may be a sequelae of myocarditis, with athletes exposing themselves to greater risk of this by exercising whilst suffering viral illness. One approach to further our understanding of these issues is to explore the prevalence of potential contributory factors in order that they can be both modified and accounted for where appropriate. In addition, a novel exploration of the nature of relationships between these contributory factors and known markers of CAD and MF, affords a more detailed and comprehensive picture. This thesis has extensively explored the role of exercise dose, sporting discipline, BP parameters and diet in the development of CAD and MF amongst the male master endurance athlete. The relationship of sporting discipline, BP and diet, have not been previously evaluated in this context. In particular, the thorough evaluation of BP using resting 'office', ambulatory and exercise BP values is novel. Finally, the quantification

of coronary risk markers including TCFA and PCAT on CCTA, and ECV in the case of CMR is yet to be described in athletes.

The key novel findings of this thesis that contribute to the field of knowledge of the male master endurance athlete are:

1. Undiagnosed low-grade hypertension and high-normal BP is common amongst the male master endurance athlete cohort.
2. Blood pressure, in particular ambulatory BP, is an important determinant of non-calcified CAD risk markers. BP was not identified to predict calcified CAD despite this being the primary outcome, for which the study was powered.
3. A greater number of years of endurance exercise participation is predictive for calcified CAD but not non-calcified risk markers.
4. Cyclists are more likely to develop non-calcified coronary risk markers but not calcified disease.
5. A greater number of years of endurance exercise is predictive for non-ischaemic MF and greater ECV.
6. BP is a significant predictor of ischaemic MF, but CAC is not.

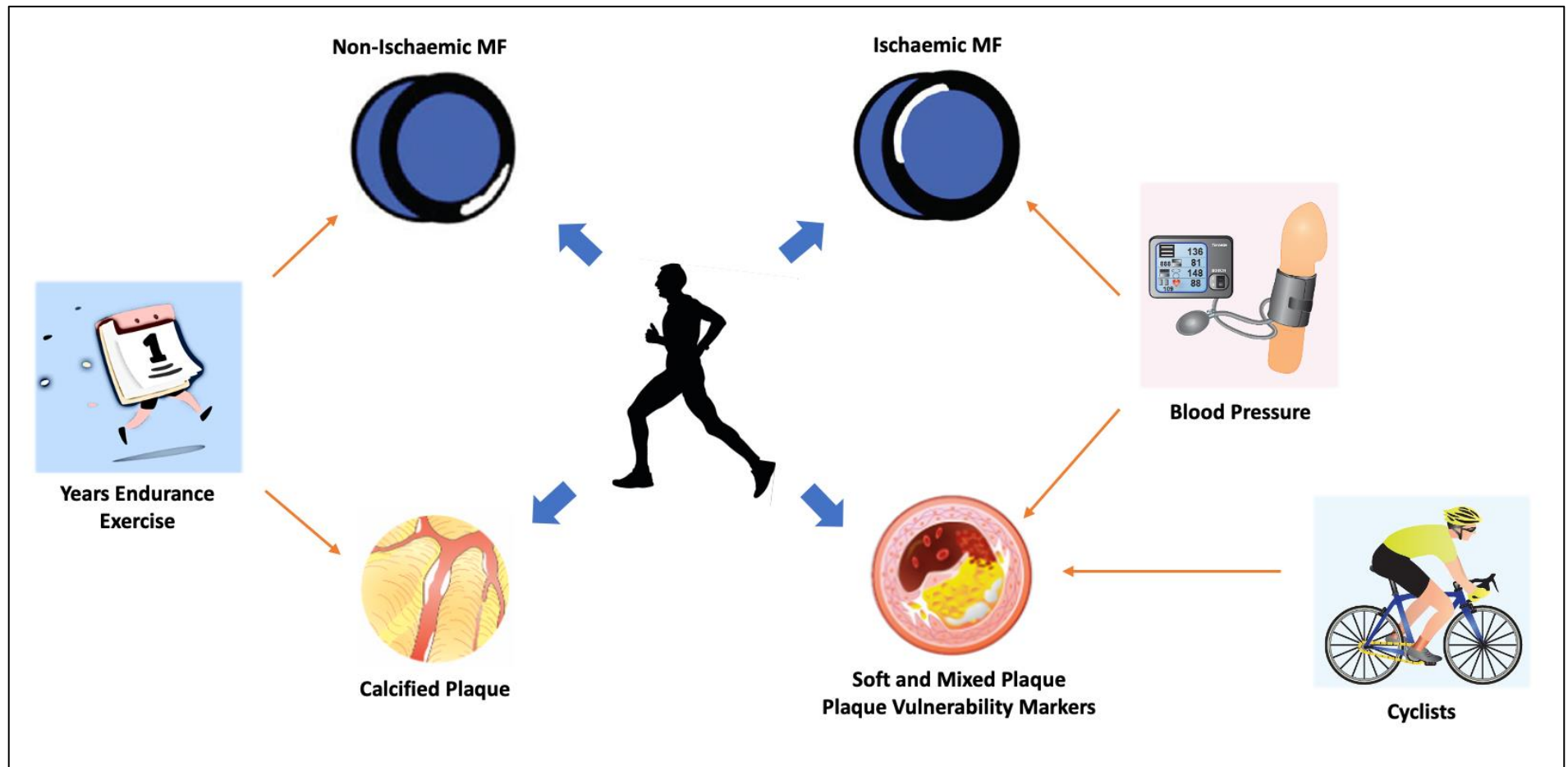


Figure 9.1 Summary Image of Key Novel Findings.

Examining these findings with respect to the hypotheses there are some clear differences that are worthy of discussion.

9.1 Study Strengths

The key strengths of this study are that it was carefully designed, with the support of a medical statistician from the outset, to ensure adequate power for the primary outcome measure. Secondly, there was a rigorous screening process for recruitment to ensure athletes were truly free of CVS symptoms, previous cardiac problems and other medical conditions or pharmacology that could have created confounding.

Furthermore, the evaluation of multiple BP parameters amongst this cohort provided a comprehensive and broad picture of the athlete's BP profile, allowing patterns in BP abnormalities amongst endurance athletes to be revealed for the first time.

The study cohort being made up of 40–65 year-old male master recreational endurance athletes with a seemingly low CVS risk and absence of symptoms, makes up a major proportion of endurance athletes and are in particular those at greatest risk of SCD during exercise. In fact, 50% of athletes who suffer an exercise related acute coronary event have no prior symptoms or history of CAD.³⁵⁴ This low-risk group makes up a considerable proportion of those athletes in which evidence-based preparticipation guidance is scant. Overall, this data is extremely helpful with wide clinical applicability.

9.2 Study Limitations

It is important to consider the limitations of this data to appropriately adopt the findings in clinical practice. These are addressed herein. It is equally important to acknowledge that several findings in this thesis are novel, as such the possibility of random chance or signal noise cannot be excluded. Further research of these important findings will help to strengthen their reliability.

The observational nature of the study design has its inherent limitations, in that data accrued from one off examination is cross-sectional in nature and secondly, it is only possible to describe associations as opposed to attributing causation. As such the explanatory variables investigated can only be described in terms of predictability rather than being able to attribute their presence directly to the development of the patterns of CAD and MF detected. Long term prospective studies with at least 10-years of follow-up would be needed to ascribe causation between these variables and predict event rates and this data is collected with the intention of long-term follow-up in mind.

The recruitment of athletes was on an all-comers basis, with exclusions for those outside of the criteria. In an ideal world, to maximally reduce bias, a sample of eligible athletes would need to be randomly selected from a large UK population; however, this was not feasible and therefore the inherent biases accepted.

The study design did not include a lower limit for lifelong endurance exposure which was intended to capture a broad spectrum of exercise doses; however, this also meant there were some athletes who had only been participating in endurance exercise for a short

period e.g., only 1 year, whereas others had been engaged in exercise lifelong. It is possible that the late starting endurance athlete may have a different risk profile to those athletes who have been exercising lifelong, with abnormal findings being less attributable to exercise and more related to other lifestyle choices. The data does not account for these differences, and it may be difficult to distinguish these athletes as they are on a spectrum as opposed to belonging to 2 distinct groups.

The variety of doses and sporting disciplines of the athlete may have diluted some findings because of the differences between sporting disciplines earlier discussed, that make it challenging to accurately compare and quantify exercise doses between sports. However, the more variables are controlled, the smaller the population to which the results are applicable.

Athletes were not all recruited at once, as such biases could have been introduced amongst those recruited, for example, participants may have been advised to be tested by friends or team-mates who had already participated in the study testing and been found to have an abnormality. Equally some individuals may or may not have chosen to participate due to concerns regarding what might be uncovered.

Athletes were more likely to live or work near the centre for testing although there were some athletes who travelled from Northern England and Wales. The mere fact that they were willing to travel and cover the expense of coming such a distance may have had its inherent biases due to their motivation being likely to differ from those living close by in some cases. It also affected their capacity to find a convenient time to attend for day 2 and

3 tests which was reflected in such athletes making up a significant proportion of those lost to follow-up. Indeed, one athlete travelled from the Isle of Man and it transpired on arrival that he had previously seen a cardiologist for an episode of collapse and been discharged without any further action; however, on attending for the study it was clear that the syncope was likely of a cardiac nature and echocardiography and subsequent testing revealed a significant cardiomyopathy with episodes of VT, requiring a comprehensive management plan, in addition to immediate cessation of competitive endurance sport. As such he was excluded from the study. It is likely that this athlete was interested to attend a centre of excellence for the master endurance athlete to be re-evaluated although this was not declared or made clear on his pre-participation questionnaire, which did seek to make a thorough investigation of prior cardiac symptoms. A further geographical factor of note is that by undertaking the study in London, a large proportion of participants came from the local area with a reflective membership to the higher social classes observed and the overall lower CVS risk associated with this,³⁵⁵ that may not be representative of the UK population as a whole³⁵⁶.

Due to the large numbers of athletes being studied and limited capacity, data collection was undertaken throughout the year. Seasonal differences amongst data collection may have had an impact upon athletic adaptation findings, in particular the right heart data, given that it is very sensitive to volume loading but also level of coronary inflammation and consequent CAD, levels of VO_2 , reporting of exercise participation and dose parameters and weight, which may have subsequently impacted BP findings.

There may also have been biases amongst athletes recruited in terms of reasons for participation. Some expressed an interest in contributing to research and understanding about the subject for their own interest or career e.g. as a sports coach or doctor; some were concerned for their health and clearly considered it an 'MOT'; in some cases having known someone who had had an adverse event was the motivating factor; some possibly had noticed subtle symptoms or changes in their exercise capacity that they did not share but wished to have checked out and many had mixed motivations.

The absence of control participants in this study limits the ability to compare the findings e.g., prevalence of hypertension and coronary markers to the general population directly; however, given the extensive research already performed in the general population in this area, there are abundant sources of quality research permitting some level of comparison to be made. The decision not to include controls was considered and deliberate with justification being that the primary aim of the research was to explore the prevalence of CAD amongst a range of exercise dose exposures and therefore controls were deemed as not required.

There may be other contributory factors that have an important role in the pathogenesis of CAD amongst male master endurance athletes that are outside the scope of this thesis and therefore have not been considered. One such factor could be the use of performance enhancing drugs including anabolic steroids, that are associated with an adverse lipid profile, increased risk of hypertension, increased thrombotic risk and MI and erythropoietin, that is also associated with increased thrombotic risk and hypertension.³⁵⁷ Other factors that are potentially relevant include genetics, psychological stress, alcohol consumption,

PTH and magnesium. Other training related factors such as inadequate recovery may also impact upon the stability and risk of coronary lesions.

Despite random glucose being within the normal range in all athletes, there was a relationship between glucose and the presence of CAD abnormalities and the presence of pathological LGE, which may suggest that this is a relevant factor. Further studies should include a fasting glucose to more confidently exclude impaired fasting glucose. In addition, further research looking at an athlete's diet and glucose to ascertain whether athletes who consume a diet rich in refined carbohydrates make an important contribution to prevalent CAD in this cohort.

During the initial study design the measurement of biomarkers, in particular hs-CRP, to quantify inflammation, were considered. During this process an in-person discussion took place with Professor Peter Libby, leading global expert in the field of the relationship between inflammation and CAD. It was concluded that given the rise in hs-CRP associated with endurance exercise, accurate and meaningful quantification would not be possible without stopping all extreme exertion for at least 2 weeks prior to measurement. This was not deemed feasible to impose upon the study cohort and was therefore not pursued and the evaluation of the DII was employed as an alternative.

9.3 Clinical Implications

Overall, the findings from this thesis make a significant contribution to understanding how to quantify cardiac risk and detect potentially high-risk CAD, as part of the preparticipation evaluation of the male master athlete. It is crucial that those physicians involved in the pre-

participation evaluation of athletes are conscious of the factors influencing the risk of CAD amongst the master endurance athlete cohort.

The following can be recommended:

- Master endurance athletes including those who are asymptomatic and seemingly low-risk with a high or high-normal resting 'office' BP should be comprehensively evaluated for hypertension with ABPM or home monitoring according to the ESH guidelines and when a diagnosis of hypertension is established treated should be as per current recommendations.¹⁶
- Master athletes should have an annual screening resting blood pressure check.
- Master endurance athletes diagnosed with hypertension should be considered at significantly greater risk of unstable CAD and therefore managed and monitored aggressively.
- Master endurance cyclists should be considered at greater risk of unstable CAD and therefore the threshold for evaluation for CAD lower.
- Those athletes who have been endurance exercising for longer can be expected to have more CAC on CAC scoring which should not be assumed to be prognostically significant in the same way it is in the general population.
- CCTA evaluation should include plaque vulnerability markers, partially calcified and non-calcified morphology plaque and possibly PCAT and when identified, athletes should be considered at high risk and managed with statin therapy and monitored.

The current ESC recommendations for pre-participation CVS evaluation of asymptomatic athletes over the age of 35 years,¹⁶ summarised in figure 9.2, state that athletes who are at

high or very high risk i.e. HeartScore® $\geq 5\%$, 'planning to undertake high-intensity exercise as well as selected individuals planning to undertake moderate-intensity exercise should undergo a physical examination, 12-lead ECG, and exercise stress test 'to identify prognostically important CAD' and 'an abnormal exercise test should be further investigated according to current ESC guidance for chronic coronary syndromes'.²⁵¹ If we apply these guidelines¹⁶ to this cohort, 71.4% of athletes have a moderate risk i.e. HeartScore® $\leq 5\%$, 27.7% high ($5 < 10\%$) and 1% very-high risk ($\geq 10\%$), and all athletes would be considered to be exercising to high or very high intensity (see definitions according to ESC in appendix 20). Of note, it was impossible for athletes in this cohort to be low risk i.e., less than 1%, due to all participants being at least 40 years of age and male. Therefore, almost a third would undergo exercise tolerance testing (unless ECG is poor quality in which case functional testing is indicated instead). All athletes underwent exercise tolerance testing and 4 athletes having an inconclusive test that would necessitate further functional imaging according to the ESC guidelines, and only one athlete in the cohort had evidence of significant ischaemia on exercise ECG secondary to a LMS and LAD aneurysm; however, his HeartScore® was only 1.5% and therefore would not have undergone exercise testing under current guidelines. Exercise tolerance testing in the general population is known to have poor sensitivity and specificity i.e., 57% and 62%, respectively.³⁵⁸ To illustrate the point, for comparison, CCTA has a sensitivity and specificity of 97 and 78% respectively. In fact, SCOT-heart data demonstrated that the addition of CCTA plus the standard of care (which was usually an exercise tolerance test) in routine diagnostic testing significantly reduced the 5-year risk of acute MI (HR = 0.59, 95% CI 0.42-0.84, $p=0.004$), compared to use of ETT alone.¹⁵⁴ The 2020 guideline for the diagnosis and management of chronic coronary syndromes does acknowledge the poor sensitivity and specificity of exercise testing in mild-moderate

obstructive CAD, that accounts for up to 50% of acute coronary syndromes.²⁵¹ In this study exercise testing failed to identify any of the athletes with severe obstructive CAD suggesting a very poor sensitivity and specificity amongst this cohort, possibly worse than the general population due to the test being an insufficient effort to induce ischaemia as a result of advanced ischemic pre-conditioning. As such, the limitations of this diagnostic tool should be emphasised clearly in the guidance. If all athletes with a HeartScore® >5%, underwent CCTA directly instead of exercise testing, 4 would have been referred for invasive coronary angiography based on the criteria of either '3 vessel disease with proximal stenosis' or 'LMS or proximal LAD disease', which subsequently would have identified 2 of the 3 athletes known to have undergone PCI. The third would have been missed due to a low HeartScore® (3%) as would have the athlete with a blocked LAD requiring bypass surgery (HeartScore® also 3%).

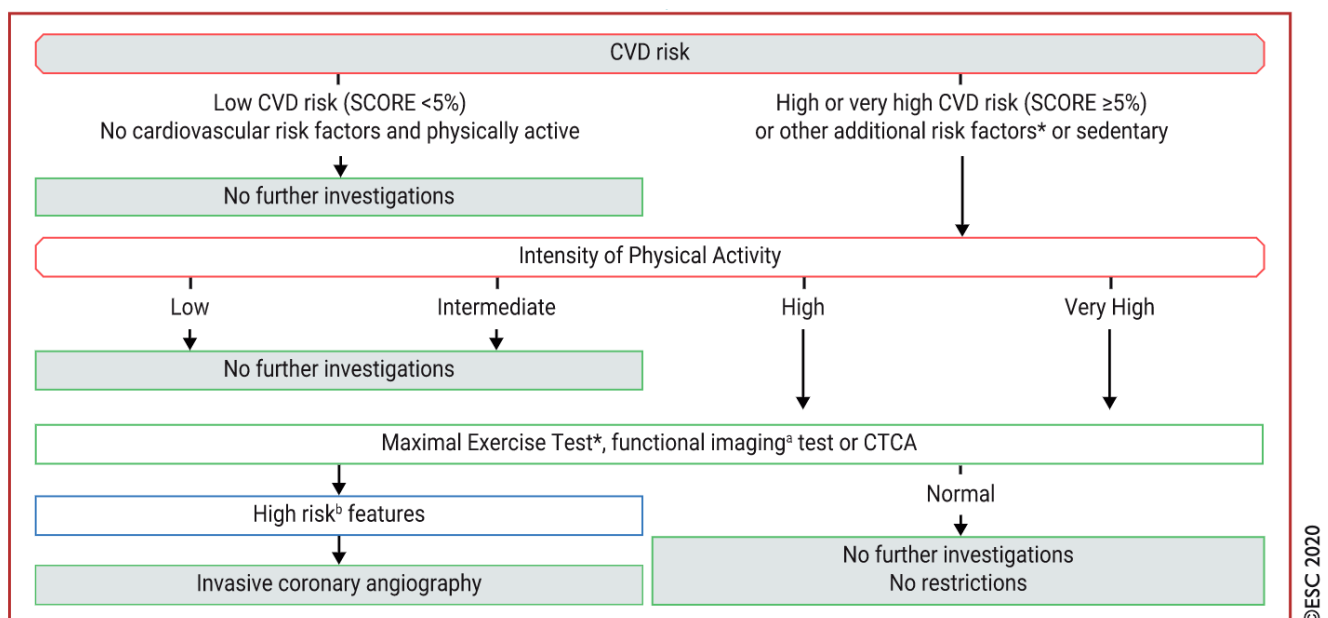


Figure 9.2 Algorithm from the ESC recommendations for pre-participation CVS evaluation of asymptomatic athletes over the age of 35 years.¹⁶

CVD, Cardiovascular Disease; CCTA, CT Coronary Angiogram.

*'Consider functional test or CCTA if exercise stress test is equivocal or the ECG is uninterpretable'

^aList of functional imaging options given below. ^bSingle-photon emission computed tomography: area of ischaemia $\geq 10\%$ of the left ventricular myocardium; stress echocardiography: ≥ 3 of 16 segments with stress-induced hypokinesia or akinesia; stress cardiovascular magnetic resonance: ≥ 2 of 16 segments with stress perfusion defects or $\geq$ dobutamine-induced dysfunctional segments; coronary computed tomography angiography (CCTA): three-vessel disease with proximal stenoses; left main disease; proximal left anterior descending disease.'

This thesis would argue that the diagnostic test of choice for those athletes with a high or very-high HeartScore® exercising at high or very-high intensity should be CCTA for numerous reasons. Firstly, CCTA has the highest sensitivity and specificity for the diagnosis of CAD over all functional imaging tests as illustrated in figure 9.3.

Test	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	Prevalence
Exercise Electrocardiography	Overall*	67%	46%	41%	72%	NR	NR	NR
	Suspected CAD	62%	68%	57%	72%	1.94	0.56	41%
Stress Echocardiography	Overall†	84–87%	72–77%	85–89%	69–73%	3.08–3.65	0.18–0.21	66–68%
	Suspected CAD	88%	89%	93%	80%	8.35	0.13	64%
Single Photon Emission Computed Tomography	Overall	83–85%	77–85%	79–85%	79–85%	3.56–5.13	0.18–0.22	50%
	Suspected CAD	83–84%	79–85%	72–85%	84%	3.88–5.01	0.19–0.21	41% [‡]
Positron Emission Tomography	Overall	82–90%	86–88%	93–96%	53–84%	5.57–5.88	0.11–0.21	63–80%
	Suspected CAD	90–91%	82–91%	94%	75–84%	4.97–8.89	0.11	75% [‡]
Stress Magnetic Resonance Imaging	Overall	83%	86%	94%	68%	5.93	0.20	71%
	Suspected CAD	81%	87%	93%	70%	6.39	0.21	67%
Coronary Artery Calcium Scoring	Suspected CAD	98–99%	35–40%	65–68%	93–95%	1.51	0.04	55–56%
Coronary Computed Tomography Angiography (Low radiation dose) [§]	Suspected CAD	100%	89%	93%	99%	9.2	0.00	58%
Coronary Computed Tomography Angiography (Radiation dose not specified)	Suspected CAD	98.2%	81.6%	90.5%	99.0%	NR	NR	59.9% (28–85%)

Figure 9.3 Summary of Diagnostic Accuracy of Non-invasive Tests Compared to Invasive

Coronary Angiography by Skelly *et al.*³⁵⁹

CAD, Coronary Artery Disease; LR -, Negative Likelihood Ratio; NPV, Negative Predictive Value; NR, Not Reported; LR+, Positive Likelihood ratio; PPV, Positive Predictive Value.

*'Values for diagnostic test measures are taken from or derived from systematic reviews.'

†'Values reported are for combined groups of patients with known CAD and patients with suspected (but not confirmed) CAD'.

‡'Mean prevalence only available or calculable for one of the two included reviews.'

§'All included studies used prospective electrocardiography gating for CT; uses much lower radiation doses than other techniques.'

Secondly, CCTA can identify multiple markers of modifiable high-risk disease and highlight those with obstructive disease that warrant further functional imaging. Based on this thesis it is recommended that CCTA findings of plaque morphology, plaque vulnerability markers and possibly PCAT can be adopted in addition to location and stenosis of plaques, to identify high-risk disease, particularly given that both plaque vulnerability markers and PCAT predict high risk of MACE.^{156,316} The current guidance states the following: 'identification of atherosclerotic CAD should prompt aggressive management of risk factors and preventive medical treatment.'¹⁶ which essentially leaves all management in the hands of the physician. Offering a list of high-risk CAD CCTA features would facilitate the physician in applying this recommendation, giving specific merit to the factors unique to the master endurance athlete. If we apply the recommendation of including CT markers of non-calcified plaque and plaque vulnerability markers to this cohort, 40 athletes had one of these 2 markers and 15 athletes had evidence of both and therefore would have been identified as high-risk and recommended statin therapy. With the addition of PCAT the number increases to 100 athletes.

Finally, CT FFR is now recommended by the National Institute of Clinical Excellence (NICE) for clinical use in those individuals being evaluated by CCTA, for recent onset stable chest pain and will soon be a widely clinically applicable tool, which in addition to CT perfusion will transform CCTA into a functional as well as structural imaging modality. At this point the additional step of further functional imaging can be replaced by a single test that demands no additional scanning or radiation and will prevent the need for invasive coronary angiography with its inherent risks and costs or streamline invasive coronary interventions where intervention is necessary. It does however carry increased costs with the scan costing £700 and the expertise in interpretation also drawing additional costs.³⁶⁰ Nevertheless, the use of CT-FFR is likely to revolutionise the evaluation of high-risk asymptomatic CAD with data showing that CT-FFR is non-inferior to invasive coronary angiography plus FFR for decision making and identifying targets for revascularisation.³⁶¹ However, this technique will require validation specifically amongst athletes prior to being applied given the physiological differences in coronary haemodynamics between athletes and non-athletes. A study that retrospectively examined 52 endurance athletes and 48 sedentary controls who had undergone CCTA including CT FFR gave half of the participants from both groups GTN. FFR was found to be higher in athletes compared to controls and athletes given GTN had a higher volume/mass ratio than athletes without, whereas there was no difference between the controls, suggesting that athletes have not only a higher FFR but also a greater vasodilatory capacity than non-athletes.³⁶²

It is important to highlight the potential drawbacks of CCTA. Particularly applicable in this context is the increased prevalence of extensive CAC, which can result in non-diagnostic

imaging; however, this can be overcome with the addition of CT perfusion imaging, although this is not currently a widely available modality. The second major drawback is the inherent exposure to ionizing radiation; however, the technology is advancing at such a rate the doses now are at much more acceptable rates. In addition, the athlete population receive doses at the lower end of the spectrum due to being lean and having a stable and slow heart rate, with data showing that individuals with these parameters can receive average doses as low as 0.29 mSv^{2, 363} which is equivalent to approximately 14 chest x-rays.

The current ESC guidelines¹⁶ for the evaluation of blood pressure in athletes recommend all athletes undergo a resting BP to risk stratify them using SCORE2 version of the HeartScore®. If a systolic BP ≥ 140 mmHg is detected then the advice is to reduce salt and alcohol intake, weight loss if appropriate, smoking cessation and advise a 'balanced diet', followed by pharmacological therapy if systolic BP remains above 140mmHg despite this. No advice is offered for the management of isolated diastolic hypertension. Applying this guidance to this cohort would have failed to identify hypertension amongst 56 athletes who had masked hypertension i.e., normal resting BP but meeting the criteria for a diagnosis of hypertension on ABPM. Secondly, based on the novel findings from this thesis and given the risk of a white coat hypertension associated with resting BP evaluation that is more prevalent amongst athletes, it is recommended that further guidance should be added to these guidelines, advising ABPM or home measurements prior to commencing pharmacological therapy, given the increased burden of pharmaceutical side-effects amongst athletes. The guidance also recommends monitoring with ABPM for those with a 'borderline BP'; however, this is undefined and therefore at the discretion of the physician, with no advice given for those with a high-normal resting 'office' BP. This thesis found high-

normal BP to be a significant predictor for CAD in this cohort and therefore this guidance to evaluate ABPM or home measurements, should be included for these athletes also. Finally, the guideline recommends that those athletes with an exaggerated response to exercise i.e., maximum ≥ 220 mmHg systolic, but normal resting BP, should undergo a transthoracic echocardiogram and ECG; however, no recommendation is given for monitoring. Based on this thesis, ABPM monitoring would be recommended to investigate a HRE further and for on-going monitoring. To assist with the application of this guidance, the following algorithm (figure 9.4) is proposed for the management of the athletes BP.

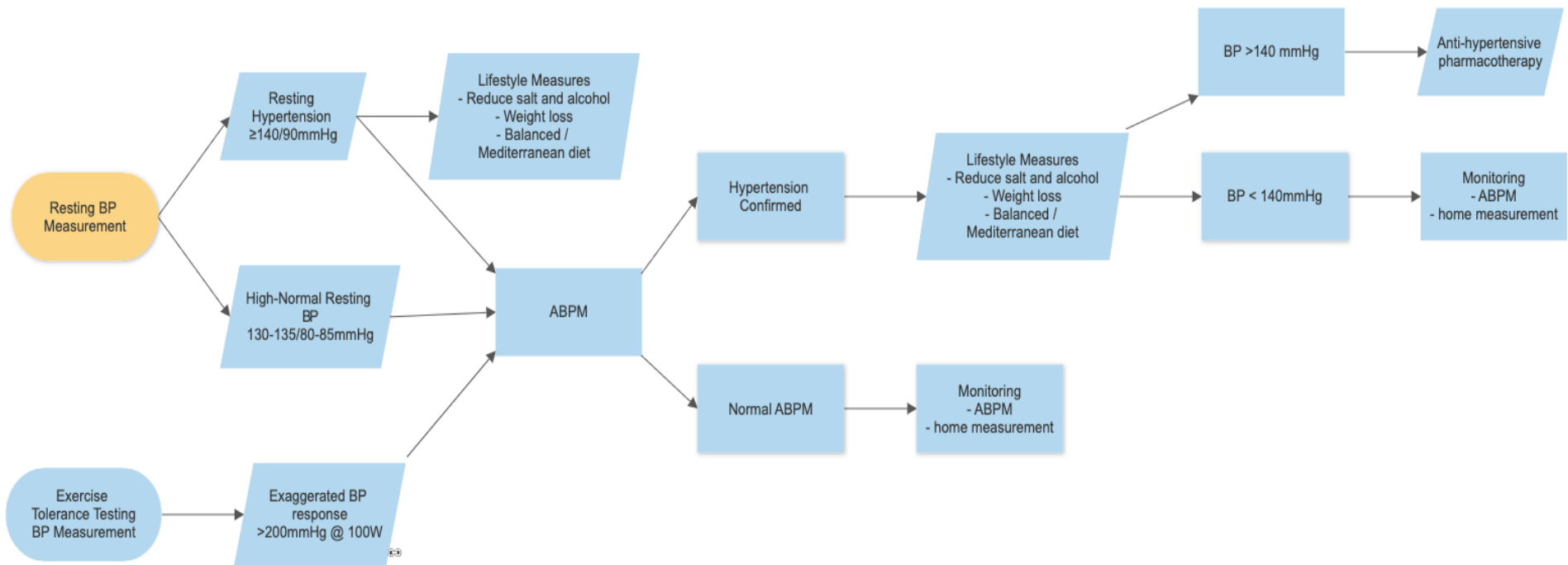


Figure 9.4 Proposed algorithm for ESC guidelines for the evaluation and management of BP in athletes.

ABPM, ambulatory blood pressure monitoring; BP, Blood pressure.

Assuming that the 4 athletes with an ischaemic pattern of LGE MF can be considered high-risk (all 4 had a HeartScore® $\geq 5\%$), hypertension would have only been identified in 2 of them according to the current BP guidelines i.e. based on resting 'office' BP, and therefore risk would not have been modified by clinical pre-participation evaluation. However, if the recommendations from this study were applied, all 4 athletes would have been diagnosed with an abnormal BP profile and risks managed accordingly.

Applying these recommendations to this cohort demonstrates the clear additional benefit of these amendments to risk stratification and management.

9.4 Future Research

This thesis has addressed some of the outstanding questions about the cardiovascular effects of endurance exercise; however, there remains large scope for further research, with some further questions arising because of this work. Longitudinal data relating to outcomes of the abnormal findings amongst endurance athletes is what is needed most. The group at St George's University have now collected approximately 800 master endurance athletes through 3 observational studies, with the intention to contribute to this long-term data. Such studies should seek to understand how the CAD found progresses, as this is a major determinant of future MI risk even when accounting for plaque severity.³⁶⁴ Particular areas warranting further research include the long-term MACE and mortality outcomes of athletes with raised troponins post exercise, ventricular arrhythmias, the various patterns of CAD including calcified and non-calcified disease, significant stenoses, vulnerability markers, PCAT and both non-ischaemic MF, that is a presumed sequelae of myocarditis, and ischaemic MF. The relationship of exercise dose and non-ischaemic fibrosis also warrants

further exploration. Finally, further research examining the differences between the protective effects of oestrogens in females and deleterious effects of testosterone, including examining differences between pre- and post-menopausal women, with respect to CAD and MF, would be instrumental in explaining which aspects of this picture relate directly to exercise itself. Furthermore, large studies of the individual sporting disciplines would help in further delineating the differences in CAD and MF between these groups. Finally, the examination of the diet of endurance athletes in terms of its potentially harmful impact, merits further study.

9.5 Overall Conclusion

As the number of individuals participating in evermore extreme endurance exercise, of all ages, but in particular of an older age continues to grow, so does the need for an evidence-base upon which to develop guidance for pre-participation risk evaluation and management. The data from this thesis offers a positive and clinically translatable contribution to this knowledge and understanding.

This research contributes to the growing scientific picture revealing that despite the huge benefits of moderate intensity exercise, even the most ostensibly healthy athletes are far from immune from developing both hypertension and high-risk CAD. This is highly relevant in the context that high intensity exercise poses an increased risk of SCD from ventricular arrhythmias arising from coronary plaque rupture, demand ischaemia or pre-existing myocardial fibrosis, and merits sharing with the wider sports cardiology community, be that physicians, researchers, coaches, athletes or other.

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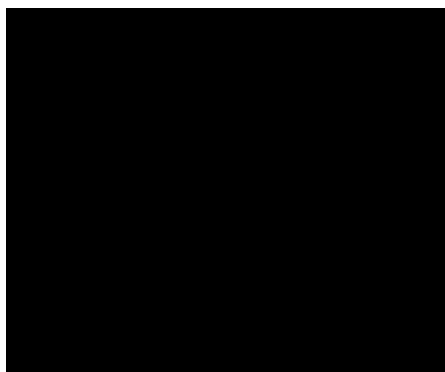
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11 Appendices

Appendix 1 Official Advertisement



Are you A Male Master Endurance Athlete?



Beginner? Intermediate? Pro? 40-65 years of age?

Do you regularly run, swim and/or cycle or participate in other endurance sports?

Would you like to volunteer for tests on your heart?

The Centre for Inherited Cardiovascular Conditions and Sports Cardiology at St George's Hospital, in South London, is currently researching the cardiac effects of long-term endurance exercise in older athletes.

We are enrolling healthy male volunteers with no history of heart disease, high blood pressure, high cholesterol, smoking, kidney disease or diabetes. The study involves 3 hospital visits each lasting up to 2 hours. Two at St Georges Hospital and 1 at the Bart's Heart Centre (Central London). Each volunteer will be offered an electrocardiogram, echocardiogram, cardiopulmonary exercise test (VO2 test), cardiac MRI, cardiac CT, blood test and a 24-hour heart and blood pressure monitor.

If you are interested, please complete the eligibility questionnaire at the following link:

www.sgul.ac.uk/master_athletes_study

If you are eligible, we will then provide you with the participant's information sheet. If you would like this information prior to completing the eligibility assessment, please email: **Dr Gemma Parry-Williams@:**
masterathletesstudy@sgul.ac.uk

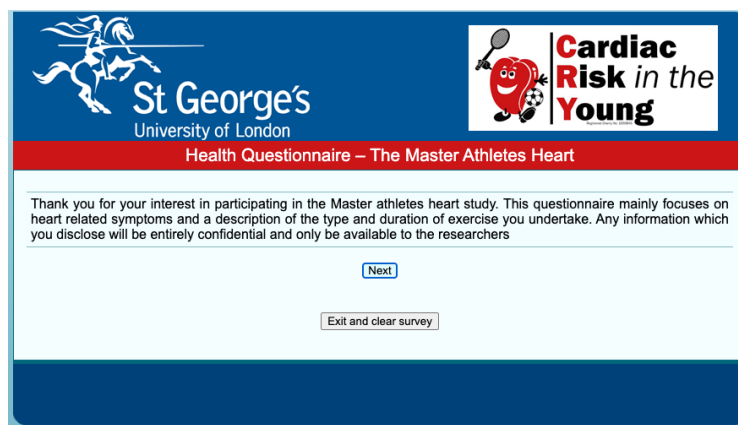


Participant Advert/Version 8 (12/04/2018) Veteran Athlete's Heart Study

IRAS ID- 132679

REC ref – 13/SW/0163

Appendix 2 Online Screening Questionnaire



The screenshot shows a web-based questionnaire interface. At the top, there is a blue header bar. On the left side of the header is the St George's University of London logo, which includes a white horse emblem and the text "St George's University of London". On the right side of the header is the "Cardiac Risk in the Young" logo, featuring a red heart character with a stethoscope and the text "Cardiac Risk in the Young". Below the header is a red horizontal bar with the text "Health Questionnaire – The Master Athletes Heart" in white. The main content area has a light blue background and contains a paragraph of text: "Thank you for your interest in participating in the Master athletes heart study. This questionnaire mainly focuses on heart related symptoms and a description of the type and duration of exercise you undertake. Any information which you disclose will be entirely confidential and only be available to the researchers". Below this text are two buttons: a blue "Next" button and a grey "Exit and clear survey" button.

St George's
University of London

Cardiac Risk in the Young

Health Questionnaire – The Master Athletes Heart

Thank you for your interest in participating in the Master athletes heart study. This questionnaire mainly focuses on heart related symptoms and a description of the type and duration of exercise you undertake. Any information which you disclose will be entirely confidential and only be available to the researchers

Next

Exit and clear survey

Health Questionnaire – The Master Athletes Heart

* Name

* Gender

☐ Female ☐ Male

* Date of birth

* Age

* Phone number

* Email addresses

* Height (cms)

* Weight (kgs)

* Which of these ethnic groups describes you best? (Please tick one box)

- ☐ British
- ☐ Irish
- ☐ Other
- ☐ White & Black Caribbean
- ☐ White & Black African
- ☐ White & Asian
- ☐ Other Mixed
- ☐ Indian
- ☐ Pakistani
- ☐ Bangladeshi
- ☐ Other Asian
- ☐ Black Caribbean
- ☐ Black African
- ☐ Other Black
- ☐ Chinese
- ☐ Other Ethnic Group

Next

Exit and clear survey

* Do you suffer from any of the following conditions?

- ☐ Angina
- ☐ Diabetes
- ☐ Ischaemic heart disease
- ☐ High blood pressure
- ☐ High Cholesterol
- ☐ Kidney disease
- ☐ Any other medical conditions (heart related or other), please specify

Please tick if you have had any of the following symptoms, and provide details

- ☐ Chest pain
- ☐ Breathlessness
- ☐ Dizziness
- ☐ Palpitations
- ☐ Blackouts

* Are you currently taking any medicines?

☐ Yes ☐ No

Please list names?

* Do you suffer from any allergies, in particular allergies to IV contrast used in x rays?

- ☐ No
- ☐ Yes
- ☐ If so which ones?

* Do you currently smoke?

☐ Yes ☐ No

If yes, how many per day and for how many years?

* Have you previously smoked?

☐ Yes ☐ No

If so, when did you stop? How many per day? How many years?

* Is there any family history of heart related problems?

☐ Yes ☐ No

If so what?

* Have you ever exercised whilst suffering from a cold/flu?

☐ Yes ☐ No

* **Are you currently training in endurance sports?**

☐ Yes ☐ No

* If so, what sport(s)? (Please list all)

* In the time you have been endurance training, on average how many hours of endurance training do you do per week? (If more than 1 sport please list for each sport)

* How many days per week? (If more than 1 sport please list for each sport)

* What distances (e.g. miles) would you cover on an average week?

*

Concerning your exercise history:

How many years have you been exercising for?

* How many years have you been training for and/or participating in endurance events?

* Have you had any breaks of >12 weeks during this time? Please detail reasons.

☐ No

☐ Yes

☐ Please detail reasons.

* Do you have any limitations in your ability to exercise? Please detail

☐ No

☐ Yes

☐ Please detail

* Have you taken part in any sporting competitions?

☐ Yes ☐ No

If yes, please give details below:

	Types of competition	How many?	Over how many years?	What is your personal best?	At what age?
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					

Submit

Exit and clear survey

Appendix 3 Sample Day 1 Appointment Confirmation and Instructions Email



Gemma Parry-Williams
Re: Master athletes heart study
To: [REDACTED]

17 January 2019 at 17:21

Thank you [REDACTED]

I can confirm that you are booked in for the study on 11/02/2019 at 18:00.

On the day of the study please present yourself at the Youde Room (please knock the door and await to be attended) which is found in the Cardiac Investigations unit. This is located in the Atkinson Morley wing of St George's Hospital, Blackshaw Road, Tooting, SW17 0QT.

As you enter the Atkinson Morley entrance continue past the Peabody's cafe, through the double-doors and past the lifts and turn right. The cardiac investigations unit is on your left. Continue straight into the unit and the Youde room is along the corridor on your left (sign post on the door). If you have an early morning or weekend appointment and the department is closed when you arrive, please take a seat outside the cardiac investigations unit and I will come to collect you.

Please arrive in your sports gear ready for the exercise test. You may wish to wear padded shorts for the bike if you have them, as some people have found the seat uncomfortable.

You are welcome to shower after your tests, we have one available. Please bring your own towel etc.

Finally, if you do need to cancel your appointment I would be extremely grateful if you could let me know as early as possible. The slots are precious and limited so I would like to ensure maximal usage of the time and funding by filling any gaps that may appear. Thank you for your consideration.

Look forward to meeting you.

Thanks and best wishes,

Gemma

Dr Gemma Parry-Williams
Clinical Research Fellow to Professor Sanjay Sharma
St George's University, London

Appendix 4 Sample Day 2 (CT) Appointment Confirmation and Instructions Email



Gemma Parry-Williams

Master athletes heart study Day 2 CT scan

To: [REDACTED]

19 January 2019 at 10:11



Dear [REDACTED]

Thank you for booking your CT scan!

I can confirm that you are booked in for the study on 10/02/2019 at 10:15.

On the day of the study please present yourself in the scanning department which is found in the Lanesborough Wing of St George's Hospital, Blackshaw Road, Tooting, SW17 0QT. Enter via the main entrance of the hospital, if you are coming from the tube it will be the first entrance you meet on entering the hospital grounds (which is on your right as you walk down the hospital perimeter road). There are several shops including a Marks and Spencers in the entrance hall. Pass through the entrance hall and head for the large wooden double doors. You will see the security desk on the left hand side. Go through the doors and passed the toilets on your right and you will arrive immediately at a T-junction, turn right and enter Lanesbrough wing. Continue down the corridor for approximately 50m and you will see a sign projecting from the wall labelled 'scanning department' with a list of sub-departments that will include 'CT scanning'. There may not be anyone at reception. If not please wait and we will attend to you shortly. Please note there is a direct entrance to Lanesbrough wing at the back of the hospital, however it is not so accessible neither from the Blackshaw Road (where parking is recommended and free on Sundays) or the tube.

I attach a scan checklist form. If possible please could you print and complete it prior to your attendance to allow things to run smoothly on the day. If not you will be able to complete one on your arrival.

Finally, if you do need to cancel your appointment I would be extremely grateful if you could let me know as early as possible. The CT scans are charged whether the slots are filled or not, therefore if a cancellation is made last minute and cannot be filled the money will be lost and supplies are short so it may mean this crucial part of the scan will only be done in a limited number of athletes weakening the results. Thank you for your consideration. You can do this by email or text or call 07447 927376.

Look forward to seeing you again.

Thanks and best wishes,

Gemma

Dr Gemma Parry-Williams

Clinical Research Fellow to Professor Sanjay Sharma

St George's University, London

Appendix 5 Sample Day 3 (MRI) Appointment Confirmation and Instructions Email

☆ GP Gemma Parry-Williams
Master athletes heart study Day 3 MRI scan
To: [REDACTED] 30 January 2019 at 22:49

Dear [REDACTED]
Thank you for booking your Cardiac MRI scan!

I can confirm that you are booked in for the study on 07/04/2019 at 16:15.

On the day of the study please present yourself in the 'Cardiac Imaging' department at the ST BARTHOLOMEWS ('Bart's') Cardiac Centre which is found in the King George V Building, 2nd floor, EC1A 7BE. Please see attached maps for directions and travel recommendations. Parking is very tricky and costly and we would advise against it.

The nearest underground or rail stations are: St Paul's, Farringdon, Blackfriars, City Thameslink, Barbican. **Please check TFL for tube closures.**

There is no restriction on diet, caffeine, or water intake prior to the scan.

Jewellery and other accessories should be left at home, if possible, or removed prior to the MRI scan. These include jewellery, watches, credit cards and hearing aids, pins, hairpins, metal zippers and similar metallic items, removable dental work, pens, pocket knives and eyeglasses and body piercings. Please bring £1 coin for lockers to keep valuables safe if needed.

You will be asked to wear a gown and/or scrubs trousers.

I attach an MRI safety checklist form. If possible please could you print and complete it prior to your attendance to allow things to run smoothly on the day.

The scan usually lasts for about an hour. Please aim to attend 5-10 minutes early.

Finally, if you do need to cancel your appointment I would be extremely grateful if you could let me know as early as possible. The MRI scans are charged whether the slots are filled or not, therefore if a cancellation is made last minute and cannot be filled the money will be lost and supplies are short so it may mean this crucial part of the scan will only be done in a limited number of athletes weakening the results. Thank you for your consideration. You can do this by email or text or call 07447 927376.

Thanks and best wishes,
Gemma

Dr Gemma Parry-Williams
Clinical Research Fellow to Professor Sanjay Sharma
St George's University, London

Appendix 6 CT Safety Questionnaire

V2 January 2018. Author: Lead CT Radiographer

CT Cardiac questionnaire

AFFIX PATIENT LABEL HERE

CT scans **sometimes** require the injection of contrast (dye) into a vein. As a precaution please answer the following safety questions. Please **circle** your answer and add further information in the space provided.

1. Have you had a CT before and if so when?	YES / NO	
2. Did you have x-ray contrast (dye) injected?	YES / NO	
3. If so did you have any reaction/problems?	YES / NO Details	
4. Are you allergic to anything?	YES / NO	If yes, to what are you allergic to?
5. Do you have any of the following conditions?	Asthma YES / NO If yes, is your asthma well controlled? YES/NO If yes, have you ever been hospitalised with asthma? YES/NO Thyroid problems YES / NO	
6. Do you have any of the following conditions?	Diabetes (type 1 or 2) YES / NO If yes, do you take Metformin/Glucophage YES/NO Kidney problems YES / NO High blood pressure YES / NO Heart failure YES / NO	
7. Do you have either of the following conditions?	Angina YES/NO Heart Block YES/NO	Heart Valve disease YES / NO Heart Surgery YES / NO
8. How much do you weigh?		10. Have you had beta-blockers medication before? YES / NO
9. Have you had caffeine or nicotine in the last 8 hours?	YES/NO	11. Do you take Viagra or Verapamil (Sildenafil) YES / NO

I give consent for the performance of the CT Cardiac exam including the injection of IV contrast and the administration of Beta-blockers if required

X Patient signature: Date:

Radiographer Use Only

If you consider the patient to be at increased risk of a contrast reaction or renal function is under question, then check with a radiologist & record outcome		Initial Heart Rate on inspiration:	
Give B-Block YES / NO Give GTN YES / NO		Heart Rate after Beta-blockers (on inspiration):	
If no, why?:		Heart Rate after IV contrast / during scan (on inspiration):	
(record prescription details on Cardiac prescription chart)		Heart rhythm: Regular / Irregular	
		S.I.W.C.T: Sequence used: FLASH / AD / CIRC	
If patient under 70 years of age <u>and</u> has answered NO to questions 7. No renal function check required			
Renal function:		Cannulated by:	No. of attempts:
Date:	Cr:	eGFR:	
Give IV contrast YES / NO		Omnipaque has been administered under PGD SGUH/RAD/08	
Radiographer Initials / Signature		Contrast Label – Document contrast details on Soliton	

Appendix 7 MRI Safety Questionnaire

Barts and The London
NHS Trust

MRI safety questionnaire: to be completed by ANYONE entering the MAGNET ROOM

MRI scanning uses strong magnetic fields. For your own safety and the safety of others, it is very important that you do not go near the magnet with any metal in or on your body or clothing. You will be asked to remove any loose metallic objects and will be asked to change in to a hospital gown. All personal belongings will be placed in a secure locker. For your own safety, you will be offered ear protection and maybe monitored on CCTV while in the department. Please answer the following questions carefully, circling **YES** or **NO** as appropriate, and ask if anything is not clear or want more information. All information is held in the strictest confidence.

Name:			
MRN:	DOB:	WEIGHT:	Height:

Do you have a heart pacemaker or ICD? These may stop working near the magnet	YES	NO
Could you be pregnant or breastfeeding? If so please inform the department	YES	NO

1.	Are you claustrophobic?	YES	NO
2.	Do you have a waist circumference more than 44"?	YES	NO
3.	Do you have any implants, wires, or other foreign bodies in your body? <i>For example replacement joints, drug pumps, shunts, shrapnel, contraceptive coil</i>	YES	NO
4.	Have you had any surgery on your head, brain, eyes, or heart?	YES	NO
5.	Have you had any surgery in the past 2 months?	YES	NO
6.	Have you ever had any metal particles in your eyes? <i>For example, from welding or metal work</i>	YES	NO
7.	Have you had blackouts, epilepsy or fits in the past 2 months?	YES	NO
8.	Do you have any tattoos or trans-dermal patches (skin patches)?	YES	NO
9.	Do you wear hearing aids?	YES	NO
10.	Have you experienced any problems with previous medical scanning?	YES	NO
11.	Do you consent to an injection of contrast agent (dye) if required?	YES	NO
12.	Do you have any kidney problems?	YES	NO

I have read, understood and answered all questions

Signature: _____ Date: _____

Print Name: _____

Form completed by: Patient ☐ Relative ☐ Doctor ☐ Radiographer ☐

Checked by (MRI Authorised Person):

Date:

Appendix 8 Participant Information Sheet



PARTICIPANT INFORMATION FOR **ATHLETIC VOLUNTEERS**

Research Study: The Veteran Athlete's Heart

IRAS ID: 132679

REC ref: 13/SW/0163

What is the purpose of the research?

The benefits of moderate exercise are well known. Individuals who exercise regularly live longer and are healthier compared to their sedentary counterparts. However elite athletes perform way beyond the recommended levels of exercise, often undertaking several hours of training per day and participating in physically gruelling events such as marathons and triathlons. There is growing controversy in the scientific community about the health implications of such high intensity exercise especially over many years. Our research team is studying effects of long term high endurance exercise on the heart in order to establish whether there are any detrimental effects.

Who is eligible to take part?

We are interested in healthy male athletic volunteers, who are 40-65 years of age, the so called "master athletes". Eligible participants need to be actively endurance training, and have participated in competitions e.g. marathons, ultra-marathons, cyclo sportive, triathlons etc.

Are there any factors which would exclude eligibility?

Since we are interested in healthy athletes, the following factors will exclude eligibility to the study:

- ☐ Actively smoking or having smoked in the past
- ☐ A past medical history of coronary heart disease or other significant heart disease
- ☐ A diagnosis of diabetes mellitus or impaired fasting glucose
- ☐ A diagnosis of high blood pressure
- ☐ A diagnosis of chronic kidney disease
- ☐ Contraindications to an MRI scan of the heart e.g. a pacemaker implant, a metal implant, an allergy to the contrast used or kidney problems
- ☐ Contraindications to a CT scan of the coronary arteries e.g. an allergy to the contrast used or kidney problems
- ☐ Not wanting your general practitioner to be informed if an abnormality is found
- ☐ Inability to exercise on a bicycle

What would the study entail?

Having expressed an interest in the study you will be asked to complete the online health questionnaire. The questionnaire mainly focuses on heart related symptoms and a description of the type and duration of exercise you undertake. Any information which you disclose will be entirely confidential and only be available to the researchers.

You have now been provided with this information sheet (including the sample consent form). You will be asked to sign a consent form on attending for testing and have the opportunity to discuss any queries. Prior to signing the consent form, we would encourage you to read through this information sheet in detail.

The next step will be to book the appointments for your tests using the online booking system.

You will be asked to book three hospital visits, each lasting less than 2 hours. All participants must undergo Day 1 of tests before proceeding to further testing. If you are found to have a raised cholesterol profile following blood tests on day 1 you will not be eligible to continue with the remainder of the tests i.e. CT scan and MRI. Details of the tests are given below.

Day 1: This will begin with obtaining your full consent. You will then undergo the following tests: Electrocardiogram, Echocardiogram, Cardio-pulmonary exercise test (CPET), 24-hour blood pressure and heart rhythm monitors and blood tests. These tests will take place at St Georges Hospital, Tooting, South London.

Cardiac MRI: This will take place at the Bart's Heart Centre, Central London

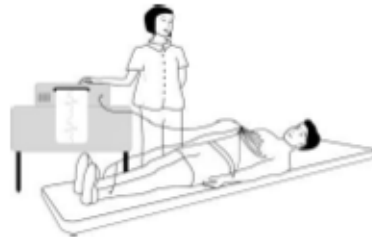
CT scan: This will take at St Georges Hospital, Tooting, South London.

Maps and directions will be sent to you for each of these venues. We appreciate that things would have been easier if they were in one place but each of these centres offers a dedicated expertise in each form of investigation. This will guarantee accurate and excellent data quality.

The final part of the study involves an annual to bi-annual follow-up phone call or email to ascertain whether you have experienced any cardiac issues since participation in the study.

The Tests

- **Electrocardiogram (ECG):** This is an electrical tracing of your heart. It is performed by placing wires around your heart in order to record electrical tracings transmitted by your heart. This gives an idea of the electrical structure and function of your heart. It is neither painful nor uncomfortable and involves no radiation. However, you will be asked to undress from the waist upwards. This will be in a private room or cubicle.



Electrocardiogram (ECG)

- **Echocardiogram (ECHO):** This is an ultrasound scan of your heart, similar to that performed on pregnant women. The test provides important information on the structure, shape, size and function of your heart. Like the ECG, it is neither painful nor uncomfortable and involves no radiation.



Echocardiogram (Echo)

- **Blood test:** This will be done by a trained clinician and performed under sterile settings. The purpose of the blood tests is to test for raised cholesterol and raised sugar levels anaemia (as it may affect some of our results) and to check your kidney function to ensure it is safe for you to have a heart MRI and CT scan. We will ask for your consent to store the blood samples anonymously. This is so that we can do genetic tests at a later date if we find any abnormalities on your tests. These genetic tests are limited to heart diseases and will not be used for any other medical or commercial purposes. Details of the tests are strictly confidential and can only be viewed by our research team.
- **Cardiopulmonary Exercise Testing (CPEX):** This is a useful tool for evaluating the fitness of your heart and lungs. The test will be performed by a trained clinical physiologist or clinician and on average takes 20-30 minutes. Sticky electrodes will be applied to your chest to monitor your heart rate and rhythm. Your breathing will also be assessed through a tube attached to the CPEX machine. You will then be asked to cycle whilst breathing through a facemask whilst still breathing in room air. The test is designed to test your fitness and so you will undergo a rigorous work-out. It will start off relatively easy but eventually the

resistance on the pedals increases gradually every few seconds. We will be monitoring you, your heart tracing and blood pressure during the entire duration of the test and so can terminate the test in the unlikely event of spotting a serious abnormality. The test is safe and there is no harm apart from the discomfort of rigorous exercise towards the end of the test. It is extremely uncommon to injure yourself or fall of the bike.



Cardiopulmonary Exercise Testing (CPEX)

- **24-hour heart rhythm monitor:** This is very similar to the ECG test except that you keep it on for a day. The machine records your heart beat over 24 hours, day and night, and during normal activities including sports. While you are having this test you must not have a bath or shower. Once the 24-hour period is complete, you can post the machine back or return it to our department. A paid envelope (addressed to the researcher) would be provided.



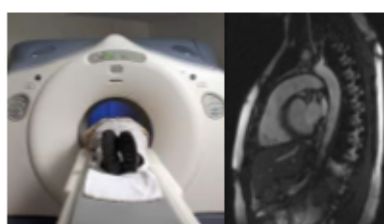
24-hour heart monitor

- **24-hour blood pressure monitor:** This is similar to a standard electronic blood pressure device. It will measure your blood pressure every 30 minutes over 24 hours. A cuff will fit around your preferred arm attached to a box. The cuff will inflate and gradually deflate in order to obtain a recording. You will need to avoid getting the device wet. You are asked not to exercise whilst wearing the device. Once the 24-hour period is complete, you can post the machine back or return it to our department. A pre-paid envelope (addressed to the researcher) will be provided.



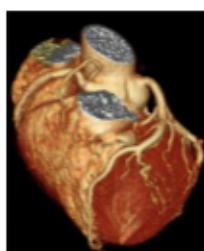
24-hour blood pressure monitor

- **Cardiac Magnetic Resonance Imaging (MRI) Scan:** Cardiac MRI uses magnets, and a computer to create detailed pictures of your heart. It is safe, useful and accurate and doesn't involve any radiation. During the 60-minute test, you lie in a short 'tunnel', which holds a large magnet that acquires images of your heart. The magnet can be fairly loud and so protective headphones are worn throughout which music of your choice can be played (you can bring your own music). We will remain in communication with you throughout the scan. Some people might feel uncomfortable lying in the MRI Tunnel and it is important that if you suffer from claustrophobia to not take part in the study. During the scan, an MRI contrast medication will be injected into a vein in your arm in order to give us better views of your heart. This medication is washed away by your kidneys within hours of having the test and rarely causes long term side effects. In exceptional cases (less than 1%) there is risk of allergy or kidney damage.



Cardiac MRI (CMR)

- **A Computerized Tomography (CT) coronary angiogram:** This is an imaging test to look at the arteries that supply the heart muscle with blood, demonstrating the presence/absence of coronary artery disease. It relies on an X-ray machine and a computer to create pictures of the heart and heart vessels. The time required for the scan is approximately 20mins. A cannula (a thin plastic tube, similar to a flexible needle) will be inserted into a vein in the arm which will later be used to inject X-ray dye during the scan so that your arteries become visible. This dye is washed away by your kidneys within hours of having the test and rarely causes long term side effects. In exceptional cases (less than 1%) there is risk of allergy or kidney damage. In addition, you will receive a spray of GTN (Glyceryl Trinitrate) under the tongue. The GTN works to increase the size of arteries so that they are better seen on the scan. It is a safe and commonly used medicine. Side effects are rare and temporary and include dizziness, or a mild headache.



CT Coronary Angiogram

Are there any risks to my health as a result of taking part?

Most of the tests are completely safe and are not detrimental to your health. The contrast agent used in the MRI scan and CT scan can, in rare circumstances, cause an allergic reaction or lead to kidney dysfunction (less than 1% risk). Allergies can be a mild itchy rash which is easily treated or in extremely rare cases (0.01%) an anaphylactic reaction which is a medical emergency requiring prompt treatment and hospitalisation. The CT coronary angiogram will expose you to a small amount of radiation. The radiation dose from the CT coronary angiogram on our CT scanner is very low as we employ all the dose reduction techniques available. The fact that athletes tend to have relatively low body mass index, allows us to lower the dose further. The total radiation dose is equivalent to that received by the average UK resident from natural sources over approximately 4 years. It corresponds to a lifetime risk of induced fatal cancer of approximately 1 in 2000 although this is age dependent. The natural lifetime risk of fatal cancer in the UK currently stands at approximately 1 in 3 to 1 in 4. Therefore, a risk of 1 in 2000 represents an increase of approximately 0.2% over the natural risk which is very small.

Who is organising the research?

The test is being carried out by the Centre for Inherited Cardiovascular Conditions and Sports Cardiology at St George's Hospital in Tooting, London. It is being funded by a charity called Cardiac risk in the Young (CRY) which raises awareness of sudden cardiac death in young adults and provides support for families (C-R-Y.org.uk). The research is being coordinated by Dr Gemma Parry-Williams (Cardiology Research Fellow for CRY) and Professor Sanjay Sharma (Professor of Inherited Cardiac Diseases and Sports Cardiology, Consultant Cardiologist and Medical director of the Virgin London Marathon)

Would I receive any compensation for taking part?

The research will provide a free and detailed evaluation of your heart. Some of these tests form part of the routine screening for serious heart conditions. Other tests are on the cutting edge of cardiology and are not ordinarily offered by a GP or a general cardiologist because of cost and other constraints. If all the tests are normal, then this will be an immense reassurance to you. If there is an abnormality, then we will inform you (in verbal and written form) and organise a referral to your GP.

Unfortunately, there will be no travel expenses provided for attending study appointments and there will be no financial incentive to take part.

What if things go wrong or you want to leave the study?

As mentioned above, the risk of adverse effects from the tests are very low. However, if something does go wrong then we will inform you, and treat the problem promptly. Where necessary, we will make the necessary referral to your GP or specialist for follow up/treatment of any side effect.

As a volunteer, you are entitled to leave the study at any time and withdraw your consent. If you're not happy about the conduct of the study or research team then you have the right to complain,

have your complaint investigated, and be given a full and prompt reply. Advice about how to complain and the complaints procedure can be obtained from the patient advice and Liaison service at St. George's hospital (contact details below). This organisation is independent of the research team. If you're not satisfied with the way the NHS has dealt with your complaint, then you can take your complaint to the independent Parliamentary and Health Service Ombudsman. You also have the right to claim for compensation if you've been harmed.

*Patient Advice and Liaison Service
St George's Hospital, Blackshaw Road, London, SW17 0QT
Email: pals@stgeorges.nhs.uk, Number: 020 8725 2453*

The study has been ethically approved by a research ethics committee (Committee South West - Central Bristol) which is part of the national research ethics service (NRES). The study is fully insured in the unlikely event of anything going wrong (NHS indemnity scheme and St Georges University of London Indemnity scheme).

What will you do with private information about me?

All the test results and information from your medical questionnaire and investigations will be kept confidential and only be seen by designated healthcare professionals of the research team. The blood samples, as mentioned above, will be stored with your consent

What happens if a serious heart abnormality is found?

We expect the majority of participants to have normal investigations or have subtle abnormalities which do not warrant any further medical attention. In a few cases, however, we might pick up an incidental serious abnormality which may require you to have specialist referral and/or treatment. If such an eventuality arises you will be immediately informed and a letter will be sent to your GP advising him or her to start treatment and/or make a referral to a cardiologist. It is important to note that being diagnosed with a heart condition may have implications on your lifestyle and may affect things such as obtaining various forms of insurance. However, picking up an abnormality early will clearly be advantageous in starting early treatment or lifestyle interventions.

Where can I obtain further information?

Further information about the study can be obtained by contacting the principal investigator,

*Dr Gemma Parry-Williams
Department of Cardiovascular Sciences, St George's University of London
Cranmer Terrace, London SW17 0RE
Number: [REDACTED] Email: [REDACTED]*

Appendix 9 Participant Consent Form



CONSENT FORM

Title: The Veteran Athletes Heart

IRAS ID: 132679

REC ref: 13/SW/0163

Name of Researcher: Dr Gemma Parry-Williams
Department of Cardiovascular Sciences,
St George's University of London

Participant Identification Number:

Please initial box

1. I confirm that I have read and understand the information sheet (Version 7, Date 19/10/2017) for the above study and have had the opportunity to consider the information, ask questions and have these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from St George's University of London (SGUL) and/or St George's University Hospitals NHS Foundation Trust (SGHT) or from the regulatory authorities. I give permission for these individuals to have access to my records. ☐
4. I understand that should a heart abnormality be identified, my GP will be informed so as to arrange further tests, treatment, and/or follow-up. I am aware that being diagnosed with a heart condition may have implications on my lifestyle and may affect me obtaining some forms of insurance. ☐
5. I give consent for blood samples to be taken, stored and analysed ☐
6. I accept that if I previously took part in one or more tests described in this study (in the last 2 years) then I give consent for the researchers to access these records for the purpose of avoiding duplication of investigations and unnecessary waste of resources. ☐
7. I agree to take part in the above study. ☐
8. I agree to contact being made with my GP and if necessary use of my NHS number to achieve this during the follow-up period, should I be uncontactable using the other forms of contact I have provided. ☐
9. I agree to the storage and use of my anonymised samples or of my anonymised data for the purposes of future research. ☐

Name Date Signature

Name of person taking consent Date Signature

Consent Form, Version 5-19/10/2017

Appendix 10 Ethical Approval Amendment 1



South West - Central Bristol Research Ethics Committee

Whitefriars
Level 3, Block B
Lewin's Mead
Bristol BS1 2NT
Email: nrescommittee.southwest-bristol@nhs.net

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

21 November 2017

Dr Sanjay Sharma
St. Georges, University Of London
Cranmer Terrace
London
SW17 0RE

Dear Dr Sharma

Study title:	The Veteran Athlete's Heart
REC reference:	13/SW/0163
Amendment number:	2
Amendment date:	06 November 2017
IRAS project ID:	132679

The above amendment was reviewed at the meeting of the Sub-Committee held on 17 November 2017 by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Appendix 11 Ethical Approval Amendment 2



South West - Central Bristol Research Ethics Committee

Whitefriars
Level 3, Block B
Lewin's Mead
Bristol BS1 2NT
Email: nrescommittee.southwest-bristol@nhs.net

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

08 May 2018

Dr Sanjay Sharma
St. Georges, University Of London
Cranmer Terrace
London
SW17 0RE

Dear Dr Sharma

Study title:	The Veteran Athlete's Heart
REC reference:	13/SW/0163
Amendment number:	3
Amendment date:	12 April 2016
IRAS project ID:	132679

The above amendment was reviewed at the meeting of the Sub-Committee held in 2018 by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Appendix 12 Instructions for Ambulatory Holter and ABPM

Instructions for monitoring devices

Please do not do any of the following whilst wearing these devices:

- ☐ Shower or get it wet
- ☐ Exercise vigorously (ideally no more than walking)
- ☐ Remove it
- ☐ Remove the batteries at any time as your data will be lost

Instructions for the heart rhythm monitor

- ☐ You do not need to touch any buttons on the device.
- ☐ Once the 24 hours has been completed remove the device
- ☐ You can dispose of the stickers
- ☐ You do not need to switch off the device once the 24 hours has been completed (it will continue recording until it reaches us).
- ☐ Please place the device in the bubble wrap provided (as shown) and return it to us in the pre-paid envelope provided along with the blood pressure monitor



Instructions for the blood pressure monitor

- ☐ You do not need to touch any buttons on the device.
- ☐ The device will go off at 30 minute intervals.
- ☐ There will be a warning beep when the device is about to go off and when the measurement is complete during the day only
- ☐ When the device beeps if possible you should cease activity and sit and rest with your arm relaxed in your lap in order to get an accurate measure.
- ☐ The device is not able to measure during vigorous movements.
- ☐ If the device fails to take a measurement the first time it will repeat it 5 minutes. This is likely to be due to either excessive movement or a kink in the tubing.
- ☐ If the tubing between the cuff and the device kinks or is crushed it will fail to take a measure.
- ☐ The measurement **will not** be visible on the screen for you to see.
- ☐ The only side-effect of this test is discomfort whilst the measurement is being taken and very rarely some individuals notice tiny bruises to the skin from the pressure of the cuff.
- ☐ Once the 24 hours has been completed remove the device and switch it off by pressing and holding the power button until the screen becomes blank.
- ☐ Remove the cuff and tubing from the device.
- ☐ Please place the device in the envelope provided (as shown), wrap the cuff and tubing around it and return it to us in the pre-paid envelope provided along with the heart rhythm monitor



If the device is causing you significant pain or injury then it may be removed. This will unfortunately invalidate this part of the study.

For any issues whilst wearing the device please contact myself on

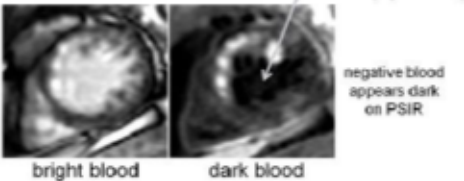
[REDACTED]

Please note these devices are extremely costly and we only have a very limited number to carry out everyone's tests for this research; therefore we are extremely grateful for you returning them to us as soon as possible and avoiding them coming to any harm.

Appendix 13 CMR Protocol

Project title: _____
Protocol Version X.X _____

Participant Study ID			
Age			
Wt (Kg)		Ht (cm)	
Gender (circle one)	M / F		
HR at start (bpm)		Dotarem Dose (0.1 mmol/Kg)	
1.5T Protocol	Notes	Copy protocol "Marathon" or "Athletes"	
1) Trufi_loc_multi_iPAT			
2) Trufi_loc_multi_iPAT@c	*Use to set cardiac shim box--automatically copies to all maps		
3) Transaxial Bright blood (trufi_tra_bright_blood)	☐ This does not have to be ECG-gated		
4) Transaxial dark blood-T2 weighted (haste_tra_db_2bh_iPAT)			
5) HepaFat GRE_3echos_3sl			
5) Single_shot_localizer_2ch (2ch pilot)			
6) Single_shot_localizer_SAX_5Slices			
7) Cines: 4CH (Vertical long axis) 2CH (Horizontal long axis) 3CH RV2CH			
8) LV SAX cine stack			
9) Native T1 mapping: pre_MOLLI 5s(3s)3s_256 1 x Mid SAX slice 1 x Long axis 4CH	☐ Copy image position ☐ Capture Cycle ☐ FOV = use smallest for the person- use the same FOV for the 3 SAX slices. ☐ Ensure to have identical FOV for pre and post contrast MOLLI.		
10) Native T2 mapping: T2map_trueFISP 1 x Mid SAX slice 1 x Long axis 4CH	☐ Copy image position of MOLLI. ☐ Same FOV size as Pre_contrast T1 map ☐ Capture Cycle -To access it (USER/Kellman/Cardiac Exam/T2 mapping)		
11) Fat water sequence (pre-contrast) BH_DB_FW_4e2i_GT 1 x Mid SAX slice	☐ Copy image position of MOLLI. ☐ Same FOV size as Pre_contrast T1 map ☐ Capture Cycle		
Inject the full dose of gadolinium (Dotarem)	(0.1 mmol/Kg)	Time: _____	
12) Contrast injection end – SAX Mid	☐ Time point		
13) LVOT cine			
14) AoV cine			
15) TI scout	Run it once on LV SAX Mid slice.		
16) 4,2,3Ch PSIR			
17) Full SAX stack			
After 15 minutes of injection			
18) Post contrast T1 mapping: ECV post_MOLLI_MOCO_4s(1s)3s(1s)2s 1 x Mid SAX slice 1 x Long axis 4CH	☐ copy image position ☐ Identical FOV size as Pre_contrast T1 map- check for synthetic ECV output ☐ Enter Haematocrit after the end of the scan (this will be done by the fellow)		
DB LGE sequence			
19) Dark Blood-LGE -Full LV SAX stack	Edit acquisition window if needed. Delta= -20 ms (standard) PSIR: Blood pool (black), myocardium (slightly grey) ☐ Measure blood pool T1 and myocardium T1 values from Mid SAX_MOLLI slice (anterior wall if normal).		

	☐ To enter data Sequence>> special ☐ T2 prep should be between 10-40 ms (unaltered) ☐ Enter T1 myo, T1 blood values ☐ Window level if necessary  T1 map  Δ=15 (myo > blood) negative blood appears dark on PSIR bright blood dark blood
Aorta planning and aortic flows	
20) Aorta_CandyCane_Pilot_iPAT	
21) Aortic arch / CandyCane cine	
22) Ascending_Aorta_flow_fb_150	
23) Abdominal_Aorta_flow_fb_150	

Appendix 14 Online Exercise Dose Questionnaire



Thank you once more for your contribution to the study to date. I would be extremely grateful if you would take a few minutes to complete this questionnaire as accurately as possible.

One of the key outcomes for the study is the amount of exposure you have had to endurance exercise through the years, i.e. Total Endurance Exercise Dose. This questionnaire aims to measure this.

• Full Name

• Date of birth

Format: mm-dd-yyyy

• Endurance exercising Q1

Years

How many years have you been intensively ENDURANCE exercising?
i.e. during how many years have you been swimming/cycling/running/rowing for an average of 6 or more hours per week?

• Endurance exercising Q2

Months

On average, how many months of the year do you participate in this level of intensive endurance exercise?

Physical Activities (METS): Bicycling

Please document your AVERAGE time spent cycling PER WEEK in hours and minutes

	Hours	Minutes
mountain, uphill, vigorous		
mountain, competitive, racing		
10-11.9 mph, leisure, slow, light effort		
12-13.9 mph, leisure, moderate effort		
14-15.9 mph, racing or leisure, fast, vigorous effort		
16-19 mph, racing/not drafting or > 19 mph drafting, very fast, racing general		
> 20 mph, racing, not drafting		
12 mph, seated, hands on brake hoods or bar drops		
stationary, 30-50 watts, very light to light effort		
stationary, 51-89 watts, light-to-moderate effort		
stationary, 90-100 watts, moderate to vigorous		
stationary, 101-160 watts, vigorous effort		
stationary, 161-200 watts, vigorous effort		
stationary, 201-270 watts, very vigorous effort		
stationary, RPM/Spin bike class		

Physical Activities (METS): Rowing**Please document your AVERAGE time spent rowing PER WEEK in hours and minutes**

	Hours	Minutes
rowing, stationary ergometer, general, vigorous	...	...
effort rowing, stationary, general, moderate effort	...	...
rowing, stationary, 100 watts, moderate effort	...	...
rowing, stationary, 150 watts, vigorous effort	...	...
rowing, stationary, 200 watts, very vigorous	...	...
rowing, 2.0-3.9 mph, light effort	...	...
rowing, 4.0-5.9 mph, moderate effort	...	...
rowing competition, >6 mph, vigorous effort	...	...

Physical Activities (METS): Running**Please document your AVERAGE time spent running PER WEEK in hours and minutes**

	Hours	Minutes
running, 4 mph (13 min/mile)	...	...
running, 5 mph (12 min/mile)	...	...
running, 5.2 mph (11.5 min/mile)	...	...
running, 6 mph (10 min/mile)	...	...
running, 6.7 mph (9 min/mile)	...	...
running, 7 mph (8.5 min/mile)	...	...
running, 7.5 mph (8 min/mile)	...	...
running, 8 mph (7.5 min/mile)	...	...
running, 8.6 mph (7 min/mile)	...	...
running, 9 mph (6.5 min/mile)	...	...
running, 10 mph (6 min/mile)	...	...
running, 11 mph (5.5 min/mile)	...	...
running, 12 mph (5 min/mile)	...	...
running, 13 mph (4.6 min/mile)	...	...
running, 14 mph (4.3 min/mile)	...	...
running, cross country	...	...
running, stairs, up	...	...

Physical Activities (METS): Swimming**Please document your AVERAGE time spent swimming PER WEEK in hours and minutes**

	Hours	Minutes
swimming laps, freestyle, fast, vigorous effort	...	...
swimming laps, freestyle, front crawl, slow, light or moderate	...	...
effort swimming, backstroke, general, training or competition	...	...
swimming, breaststroke, general, training or competition	...	...
swimming, butterfly, general	...	...
swimming, crawl, fast speed, ~75 yards/minute, vigorous effort	...	...
swimming, crawl, medium speed, ~50 yards/minute, vigorous	...	...
effort swimming, lake, ocean, river	...	...

Submit

Exit and clear survey

Appendix 15 Relevant Sections from 2011 Compendium of Physical Activities

2011 Compendium of Physical Activities

*Italicized codes and METs are estimated values

CODE	METS	MAJOR HEADING	SPECIFIC ACTIVITIES
01003	14.0	bicycling	bicycling, mountain, uphill, vigorous
01004	16.0	bicycling	bicycling, mountain, competitive, racing
01008	8.5	bicycling	bicycling, BMX
01009	8.5	bicycling	bicycling, mountain, general
01010	4.0	bicycling	bicycling, <10 mph, leisure, to work or for pleasure (Taylor Code 115)
01011	6.8	bicycling	bicycling, to/from work, self selected pace
01013	5.8	bicycling	bicycling, on dirt or farm road, moderate pace
01015	7.5	bicycling	bicycling, general
01018	3.5	bicycling	bicycling, leisure, 5.5 mph
01019	5.8	bicycling	bicycling, leisure, 9.4 mph
01020	6.8	bicycling	bicycling, 10-11.9 mph, leisure, slow, light effort
01030	8.0	bicycling	bicycling, 12-13.9 mph, leisure, moderate effort
01040	10.0	bicycling	bicycling, 14-15.9 mph, racing or leisure, fast, vigorous effort
01050	12.0	bicycling	bicycling, 16-19 mph, racing/not drafting or > 19 mph drafting, very fast, racing general
01060	15.8	bicycling	bicycling, > 20 mph, racing, not drafting
01065	8.5	bicycling	bicycling, 12 mph, seated, hands on brake hoods or bar drops, 80 rpm
01066	9.0	bicycling	bicycling, 12 mph, standing, hands on brake hoods, 60 rpm
01070	5.0	bicycling	unicycling
02001	2.3	conditioning exercise	activity promoting video game (e.g., Wii Fit), light effort (e.g., balance, yoga)
02003	3.8	conditioning exercise	activity promoting video game (e.g., Wii Fit), moderate effort (e.g., aerobic, resistance)
02005	7.2	conditioning exercise	activity promoting video/arcade game (e.g., Exergaming, Dance Dance Revolution), vigorous effort
02008	5.0	conditioning exercise	army type obstacle course exercise, boot camp training program
02010	7.0	conditioning exercise	bicycling, stationary, general
02011	3.5	conditioning exercise	bicycling, stationary, 30-50 watts, very light to light effort
02012	6.8	conditioning exercise	bicycling, stationary, 90-100 watts, moderate to vigorous effort
02013	8.8	conditioning exercise	bicycling, stationary, 101-160 watts, vigorous effort
02014	11.0	conditioning exercise	bicycling, stationary, 161-200 watts, vigorous effort
02015	14.0	conditioning exercise	bicycling, stationary, 201-270 watts, very vigorous effort
02017	4.8	conditioning exercise	bicycling, stationary, 51-89 watts, light-to-moderate effort
02019	8.5	conditioning exercise	bicycling, stationary, RPM/Spin bike class
02020	8.0	conditioning exercise	calisthenics (e.g., push ups, sit ups, pull-ups, jumping jacks), vigorous effort
02022	3.8	conditioning exercise	calisthenics (e.g., push ups, sit ups, pull-ups, lunges), moderate effort
02024	2.8	conditioning exercise	calisthenics (e.g., situps, abdominal crunches), light effort
02030	3.5	conditioning exercise	calisthenics, light or moderate effort, general (e.g., back exercises), going up & down from floor (Taylor Code 150)
02035	4.3	conditioning exercise	circuit training, moderate effort
02040	8.0	conditioning exercise	circuit training, including kettlebells, some aerobic movement with minimal rest, general, vigorous intensity
02045	3.5	conditioning exercise	Curves™ exercise routines in women
02048	5.0	conditioning exercise	Elliptical trainer, moderate effort
02050	6.0	conditioning exercise	resistance training (weight lifting, free weight, nautilus or universal), power lifting or body building, vigorous effort (Taylor Code 210)
02052	5.0	conditioning exercise	resistance (weight) training, squats , slow or explosive effort
02054	3.5	conditioning exercise	resistance (weight) training, multiple exercises, 8-15 repetitions at varied resistance
02060	5.5	conditioning exercise	health club exercise, general (Taylor Code 160)
02061	5.0	conditioning exercise	health club exercise classes, general, gym/weight training combined in one visit
02062	7.8	conditioning exercise	health club exercise, conditioning classes
02064	3.8	conditioning exercise	home exercise, general
02065	9.0	conditioning exercise	stair-treadmill ergometer, general
02068	12.3	conditioning exercise	rope skipping, general
02070	6.0	conditioning exercise	rowing, stationary ergometer, general, vigorous effort
02071	4.8	conditioning exercise	rowing, stationary, general, moderate effort

CODE	METS	MAJOR HEADING	SPECIFIC ACTIVITIES
11780	6.3	occupation	using heavy power tools such as pneumatic tools (e.g., jackhammers, drills)
11790	8.0	occupation	using heavy tools (not power) such as shovel, pick, tunnel bar, spade
11791	2.0	occupation	walking on job, less than 2.0 mph, very slow speed, in office or lab area
11792	3.5	occupation	walking on job, 3.0 mph, in office, moderate speed, not carrying anything
11793	4.3	occupation	walking on job, 3.5 mph, in office, brisk speed, not carrying anything
11795	3.5	occupation	walking on job, 2.5 mph, slow speed and carrying light objects less than 25 lbs
11796	3.0	occupation	walking, gathering things at work, ready to leave
11797	3.8	occupation	walking, 2.5 mph, slow speed, carrying heavy objects more than 25 lbs
11800	4.5	occupation	walking, 3.0 mph, moderately and carrying light objects less than 25 lbs
11805	3.5	occupation	walking, pushing a wheelchair
11810	4.8	occupation	walking, 3.5 mph, briskly and carrying objects less than 25 lbs
11820	5.0	occupation	walking or walk downstairs or standing, carrying objects about 25 to 49 lbs
11830	6.5	occupation	walking or walk downstairs or standing, carrying objects about 50 to 74 lbs
11840	7.5	occupation	walking or walk downstairs or standing, carrying objects about 75 to 99 lbs
11850	8.5	occupation	walking or walk downstairs or standing, carrying objects about 100 lbs or more
11870	3.0	occupation	working in scene shop, theater actor, backstage employee
12010	6.0	running	jog/walk combination (jogging component of less than 10 minutes) (Taylor Code 180)
12020	7.0	running	jogging, general
12025	8.0	running	jogging, in place
12027	4.5	running	jogging, on a mini-tramp
12029	6.0	running	Running, 4 mph (13 min/mile)
12030	8.3	running	running, 5 mph (12 min/mile)
12040	9.0	running	running, 5.2 mph (11.5 min/mile)
12050	9.8	running	running, 6 mph (10 min/mile)
12060	10.5	running	running, 6.7 mph (9 min/mile)
12070	11.0	running	running, 7 mph (8.5 min/mile)
12080	11.5	running	running, 7.5 mph (8 min/mile)
12090	11.8	running	running, 8 mph (7.5 min/mile)
12100	12.3	running	running, 8.6 mph (7 min/mile)
12110	12.8	running	running, 9 mph (6.5 min/mile)
12120	14.5	running	running, 10 mph (6 min/mile)
12130	16.0	running	running, 11 mph (5.5 min/mile)
12132	19.0	running	running, 12 mph (5 min/mile)
12134	19.8	running	running, 13 mph (4.6 min/mile)
12135	23.0	running	running, 14 mph (4.3 min/mile)
12140	9.0	running	running, cross country
12150	8.0	running	running, (Taylor code 200)
12170	15.0	running	running, stairs, up
12180	10.0	running	running, on a track, team practice
12190	8.0	running	running, training, pushing a wheelchair or baby carrier
12200	13.3	running	running, marathon
13000	2.3	self care	getting ready for bed, general, standing
13009	1.8	self care	sitting on toilet, eliminating while standing or squatting
13010	1.5	self care	bathing, sitting
13020	2.5	self care	dressing, undressing, standing or sitting
13030	1.5	self care	eating, sitting
13035	2.0	self care	talking and eating or eating only, standing
13036	1.5	self care	taking medication, sitting or standing
13040	2.0	self care	grooming, washing hands, shaving, brushing teeth, putting on make-up, sitting or standing
13045	2.5	self care	hairstyling, standing
13046	1.3	self care	having hair or nails done by someone else, sitting

CODE	METS	MAJOR HEADING	SPECIFIC ACTIVITIES
18130	4.5	water activities	sailing, in competition
18140	3.3	water activities	sailing, Sunfish/Laser/Hobby Cat, Keel boats, ocean sailing, yachting, leisure
18150	6.0	water activities	skiing, water or wakeboarding (Taylor Code 220)
18160	7.0	water activities	jet skiing, driving, in water
18180	15.8	water activities	skindiving, fast
18190	11.8	water activities	skindiving, moderate
18200	7.0	water activities	skindiving, scuba diving, general (Taylor Code 310)
18210	5.0	water activities	snorkeling (Taylor Code 310)
18220	3.0	water activities	surfing, body or board, general
18222	5.0	water activities	surfing, body or board, competitive
18225	6.0	water activities	paddle boarding, standing
18230	9.8	water activities	swimming laps, freestyle, fast, vigorous effort
18240	5.8	water activities	swimming laps, freestyle, front crawl, slow, light or moderate effort
18250	9.5	water activities	swimming, backstroke, general, training or competition
18255	4.8	water activities	swimming, backstroke, recreational
18260	10.3	water activities	swimming, breaststroke, general, training or competition
18265	5.3	water activities	swimming, breaststroke, recreational
18270	13.8	water activities	swimming, butterfly, general
18280	10.0	water activities	swimming, crawl, fast speed, ~75 yards/minute, vigorous effort
18290	8.3	water activities	swimming, crawl, medium speed, ~50 yards/minute, vigorous effort
18300	6.0	water activities	swimming, lake, ocean, river (Taylor Codes 280, 295)
18310	6.0	water activities	swimming, leisurely, not lap swimming, general
18320	7.0	water activities	swimming, sidestroke, general
18330	8.0	water activities	swimming, synchronized
18340	9.8	water activities	swimming, treading water, fast, vigorous effort
18350	3.5	water activities	swimming, treading water, moderate effort, general
18352	2.3	water activities	tubing, floating on a river, general
18355	5.5	water activities	water aerobics, water calisthenics
18360	10.0	water activities	water polo
18365	3.0	water activities	water volleyball
18366	9.8	water activities	water jogging
18367	2.5	water activities	water walking, light effort, slow pace
18368	4.5	water activities	water walking, moderate effort, moderate pace
18369	6.8	water activities	water walking, vigorous effort, brisk pace
18370	5.0	water activities	whitewater rafting, kayaking, or canoeing
18380	5.0	water activities	windsurfing, not pumping for speed
18385	11.0	water activities	windsurfing or kitesurfing, crossing trial
18390	13.5	water activities	windsurfing, competition, pumping for speed
19005	7.5	winter activities	dog sledding, mushing
19006	2.5	winter activities	dog sledding, passenger
19010	6.0	winter activities	moving ice house, set up/drill holes
19011	2.0	winter activities	ice fishing, sitting
19018	14.0	winter activities	skating, ice dancing
19020	5.5	winter activities	skating, ice, 9 mph or less
19030	7.0	winter activities	skating, ice, general (Taylor Code 360)
19040	9.0	winter activities	skating, ice, rapidly, more than 9 mph, not competitive
19050	13.3	winter activities	skating, speed, competitive
19060	7.0	winter activities	ski jumping, climb up carrying skis
19075	7.0	winter activities	skiing, general
19080	6.8	winter activities	skiing, cross country, 2.5 mph, slow or light effort, ski walking
19090	9.0	winter activities	skiing, cross country, 4.0-4.9 mph, moderate speed and effort, general

Appendix 16 Letter of support from British Triathlon



27th June 2018

To whom it may concern

Support for BHF Clinical Research Fellow Grant application for MD/PhD Research Project entitled 'The Master Athletes Heart Study'.

We are offering our support for the application by Dr Gemma Parry-Williams and Professor Sanjay Sharma for the above grant.

The British Triathlon Federation (BTF) with its partners, Triathlon England, Welsh Triathlon and Triathlon Scotland, has amongst its broad objectives the aim of improving the health and fitness of an aging population in the UK by encouraging participation in sport. Specifically, it supports the GB Age Group Team in its endeavours at National Championships and Qualifiers through to European and World Championships. It supports athletes through the entire age group range even up to the +80-year olds who successfully participate in the sport of triathlon at the highest levels. The GB Age Group Team is seen as one of the most successful teams in world-wide master's sport, consistently topping the medals table at championships.

The welfare of its Master Athletes is critical to the BTF. Whilst there are numerous studies on the cardiac effects of long term endurance exercise in the younger population (18-35 years old) there is very little research into these effects on older, +40 years old, athletes. The BTF is very keen to understand the impact of training for endurance sports on our older triathletes and to disseminate this information to our members.

The BTF, as a National Governing Body and a not for profit organisation, is unfortunately not in a position to offer financial support to the study. However, we are very keen to assist in identifying suitable athletes in our membership to volunteer and participate in the study. In addition, we would be happy to publicise the study and its results through our various social media and website channels to our members and the wider population.

BRITISH TRIATHLON

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Loughborough,
Leicestershire,
LE11 3WX

Tel: 01509 226161
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We wish Dr Parry-Williams and the team all the best with the research and will continue to encourage our members to get involved with this excellent work.

Yours faithfully



Andy Salmon, CEO

BRITISH TRIATHLON

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Appendix 17 Letter of support from British Master Athletes Federation

BRITISH MASTERS ATHLETICS FEDERATION

	President: Paul Dickenson	Affiliated to: World Masters Athletics
	Chairman: Arthur Kimber	European Masters Athletics
	Honorary Secretary: Bridget Cushen	
	Treasurer: David Oxland	
Website: bmaf.org.uk		

Dear Dr Parry-Williams

Letter of support for BHF Clinical Research Fellow Grant application for MD/PhD Research Project entitled 'Chronic Endurance Exercise in Male Master Athletes: The Relationship between Cumulative Exercise Dose and Coronary Artery Calcification and the Interplay with Blood Pressure Profile and Dietary Habits'.

I am writing in support of the application by Dr Gemma Parry-Williams and Professor Sanjay Sharma for the above grant.

The BMAF (British Masters Athletics Federation) recognises the importance of research in the area of Master athletes, fully understanding the impact that an athlete's death from heart disease has on the members of the BMAF.

This study that is being carried out under the supervision of Professor Sanjay Sharma, who is internationally reputed for his expertise in this area, provides an excellent opportunity for athletes to be screened and will advance the understanding of the impact of endurance training on the hearts of our athletes.

We wish Dr Parry-Williams and the team all the best with the research and will continue to encourage our members to get involved with this excellent work.

Yours sincerely
Arthur Kimber
Chairman, BMAF.

Appendix 18 Sample Result Letter Send to GP and Athlete

Email Address: stgh-tr.icc.clinic@nhs.net	
Consultants:	
Professor S. Sharma	Ext 1390
Dr M. Papadakis	Ext 1390
Prof E. Behr	Ext 4571
Dr Tome-Esteban	Ext 3576
Clinical Nurse Specialists:	
Amanda Potterton	Ext 5508
Molly MacAllister	Ext 5938
ICC Clinic Coordinator:	
Yasir Saleem	Ext 5526

Dear Doctor,

Re: *** , DOB **/**/******

Mr ***** was kind enough to participate in a study looking at the long-term effects of endurance exercise on the human heart (The Master Athlete's Heart Study). The study is an observational one involving routine cardiac investigations with addition of cardiopulmonary exercise test, CT coronary angiogram and a cardiac MRI. All athletes in the study engage in a minimum of 6hours of endurance training per week. Mr ***** denies having any symptoms and has no cardiovascular risk factors for coronary heart disease. Since his participation in the study he has developed atrial fibrillation and I understand he awaits an appointment at the Brompton to address this. Therefore, I provide a summary of his evaluation to date to assist with his care.

Mr *****'s routine ECG demonstrated a sinus bradycardia at 39bpm with a first-degree AV block at 261msecs. There was poor R wave progression in the anterior leads. No other ST, T wave or conduction abnormalities.

The transthoracic echocardiogram demonstrated normal LV systolic function, EF 69% by Simpson's. There was bi-atrial dilatation and the RV was at the upper end of normal. The valves were structurally normal.

Mr *****'s resting blood pressure measured 124/76mmHg and he demonstrated a normal blood pressure response to exercise. His cardiopulmonary exercise test revealed a super-normal VO₂ max (43.1ml/min/kg) with no inducible ischaemia. There were 2 ventricular ectopics seen at peak exercise and frequent atrial ectopics in recovery. His first-degree AV block resolved.

The 24-hour Holter monitor awaits interpretation.

His ambulatory blood pressure monitoring demonstrated a mean BP within normal limits at 109/74mmHg.

In terms of blood tests, his cholesterol was 5.9mmol/L, HDL 2.15 & LDL 3.3. His FBC, glucose and renal function were completely normal.

Mr ***** also went on to have a CT coronary calcium score and CT angiogram. The Agatston score was raised at 15.9. The angiogram suspected mixed morphology plaque resulting in less than 25% stenosis in the proximal RCA and minor calcified disease in the proximal LAD.

The cardiac MRI remains outstanding and he will be undertaken in the coming weeks

In summary, Mr ***** is an excellent master athlete who has been incidentally found to have some minor coronary artery disease. There have been some reports in the literature of master athletes having accelerated calcified atherosclerosis and myocardial scarring. In our experience, just over 40% of veteran male athletes have coronary artery calcium and 11% have a coronary artery calcium exceeding 300 Agatston units. The plaque morphology in these individuals suggests that the vast majority of the plaques are heavily calcified, as opposed to soft plaques or mixed morphology plaques which are observed in smokers and patients with hypercholesterolaemia or diabetes mellitus. It is unclear what the long-term significance of these calcified plaques is, but their stable nature is likely to mitigate the risk of acute plaque rupture and myocardial infarction which could explain why very few marathon runners sustain myocardial infarction. Data from a small cohort of male veteran athletes demonstrated that adverse events occurred in those with a coronary artery calcium score of >100. There is yet no universal consensus as how such master athletes should be managed. However, we would recommend consideration of statin therapy for the mixed morphology RCA lesion. Should he develop any symptoms, he should certainly stop and seek medical advice. We are more than happy to provide any information at your request.

I have contacted Mr ***** to inform him of the results and recommendations. We will remain in contact with Mr Wheatley and invite him to attend the cardiac MRI and repeat the ABPM in due course. We wish him the very best of luck and we are very grateful to him for participating in our study.

Yours sincerely



Dr Gemma Parry-Williams

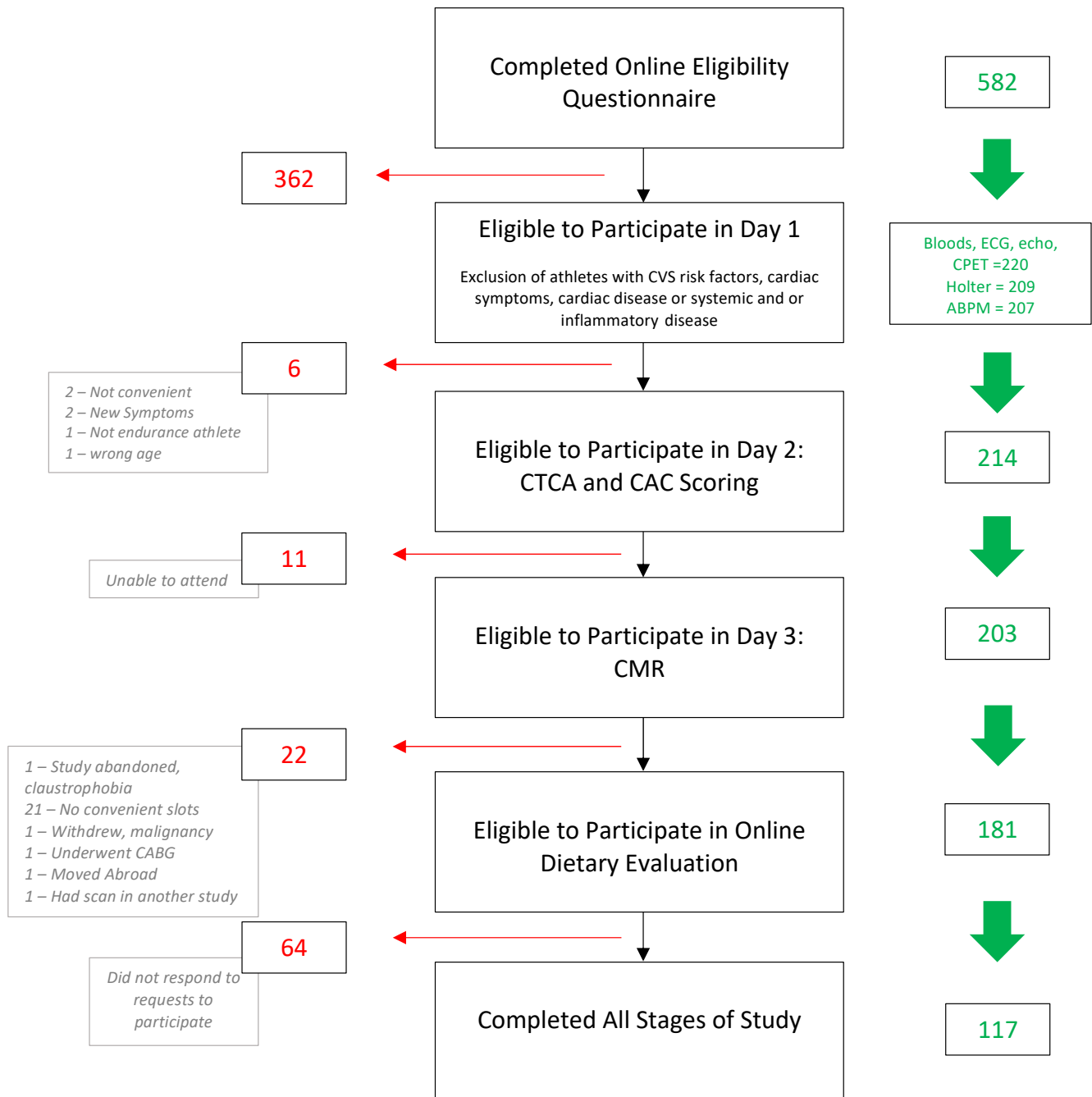
Study Principal Investigator

Cardiology Registrar and Clinical Research Fellow to Professor Sanjay Sharma

St George's University, London

CC: patient

Appendix 19 Flow Chart of Dropouts and Loss to Follow-Up



Appendix 20 Indices of exercise intensity for endurance sports from maximal exercise testing and training zones

Table 4 Indices of exercise intensity for endurance sports from maximal exercise testing and training zones

Intensity	VO_{2max} (%)	HR_{max} (%)	HRR (%)	RPE Scale	Training Zone
Low intensity, light exercise ^a	<40	<55	<40	10–11	Aerobic
Moderate intensity exercise ^a	40–69	55–74	40–69	12–13	Aerobic
High intensity ^a	70–85	75–90	70–85	14–16	Aerobic + lactate
Very high intense exercise ^a	>85	>90	>85	17–19	Aerobic + lactate + anaerobic

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HR_{max} = maximum heart rate; HRR = heart rate reserve; RPE = rate of perceived exertion; VO_{2max} = maximum oxygen consumption.

^aAdapted from refs ^{84,85} using training zones related to aerobic and anaerobic thresholds. Low-intensity exercise is below the aerobic threshold; moderate is above the aerobic threshold but not reaching the anaerobic zone; high intensity is close to the anaerobic zone; and very intense exercise is above the anaerobic threshold. The duration of exercise will also largely influence this division in intensity.

12 Permissions

Figure	Article Title	Source	Copyright Holder	Date	Permission	Reference
1.10	Perivascular Adipose Tissue and Coronary Atherosclerosis: from Biology to Imaging Phenotyping	Current Atherosclerosis Reports	Springer nature	29/6/2022	Yes	5338150230222
1.11	Prevalence of Subclinical Coronary Artery Disease in Masters Endurance Athletes With a Low Atherosclerotic Risk Profile	Circulation	Wolters Kluwer	29/6/2022	Yes	5338110684258
1.13	Medical gallery of Blausen Medical 2014	WikiJournal of Medicine			Not required	
1.16, 1.18, 4.1, 8.2	2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease: The Task Force on sports cardiology and exercise in patients with cardiovascular disease of the European Society of Cardiology (ESC)	European Heart Journal	Oxford university press	2/8/2022	Yes	5360680850139
1.17	Recommendations and Considerations Related to Preparticipation Screening for Cardiovascular Abnormalities in Competitive Athletes: 2007 Update	Circulation	Wolters Kluwer	29/6/2022	Yes	5338160099228
1.2	The Hallmarks of Aging	Cell	Elsevier	28/6/2022	Yes	5337710184567
1.3 and 1.4	The State of Ultra Running 2020.	https://runrepeat.com/state-of-ultra-running			Email	
1.6	Pheidippides Cardiomyopathy: A Review and Case Illustration	Clinical Cardiology	John Wiley and Sons	29/6/2022	Yes	5338140156873

3.3	Physiologic limits of left ventricular hypertrophy in elite junior athletes Relevance to differential diagnosis of athlete's heart and hypertrophic cardiomyopathy	Journal of the American College of Cardiology	Elsevier	29/6/2022	Yes	<u>5338160292641</u>
3.4	Effect of Sex and Sporting Discipline on LV Adaptation to Exercise	JACC: Cardiovascular Imaging	Elsevier	29/6/2022	Yes	<u>5338131459064</u>
4.1	Morphology of the "athlete's heart" assessed by echocardiography in 947 elite athletes representing 27 sports	The American Journal of Cardiology	Elsevier	29/6/2022	Yes	<u>5338160858948</u>
7.1	Inflammatory potential of diet and all-cause, cardiovascular, and cancer mortality in National Health and Nutrition Examination Survey III Study	European Journal of Nutrition	Springer nature	29/6/2022	Yes	<u>5338160961174</u>
8.3	Non-invasive Testing for Coronary Artery Disease	https://www.ncbi.nlm.nih.gov/books/NBK361148/pdf/Bookshelf_NBK361148.pdf	Agency for Healthcare Research and Quality		Not required	

Figure 1.3 and 1.4

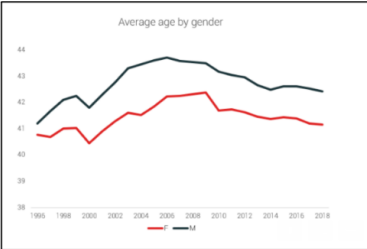
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 **Gemma Parry-Williams** <gparrywilliams@gmail.com>
to paul ▾

16:56 (17 minutes ago) ☆ ↩ ⋮

Dear Paul,
I am currently undertaking a PhD entitled 'Determinants of coronary artery disease in male master endurance athletes' and I would like to use the images below from your article <https://runrepeat.com/state-of-ultra-running>.
I am sincerely grateful in advance for you considering my request.
Sincerely yours,
Dr Gemma Parry-Williams
St George's University of London



Year	Male (M)	Female (F)
1996	41.5	40.5
1998	42.0	41.0
2000	41.5	40.5
2002	42.5	41.5
2004	43.5	42.0
2006	44.0	42.5
2008	43.5	42.5
2010	43.0	42.0
2012	42.5	41.5
2014	42.5	41.5
2016	42.5	41.5
2018	42.5	41.5

 **Jens Jakob Andersen** <jens@runrepeat.com>
to me, Paul ▾

17:01 (11 minutes ago) ☆ ↩ ⋮

Sure, go ahead



Figure 1.13

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Figure 8.3
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