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Insights into the incidence and causes of cardiac death in the young: a multifaceted approach.

Dr Raghav Tilak Bhatia

Cardiovascular Clinical Academic Group

St. George's, University of London

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

December 2023

Professional training is not just training in medicine but also in life and how to prepare yourself for what lies ahead.

Dr Deepak Bhatia (*Papa*)

A constant source of inspiration in my journey.

Declaration

The work described within this thesis was carried out within the Clinical and Molecular Sciences Institute at St George's, University of London, under the kind supervision of Professor Michael Papadakis, Professor Sanjay Sharma, Dr Gherardo Finnochiaro and Professor Aneil Malhotra. Unless otherwise acknowledged, this work was carried out by the author. This thesis has not been submitted, in either whole or part, for the purpose of obtaining any other degree.

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Dr Raghav Tilak Bhatia

November 2023

Abstract

Background: Understanding the incidence and causes of young sudden cardiac death (YSCD) is crucial to guide preventative strategies.

Aims: The aims of this thesis are to: 1. report on the incidence of cardiac and sudden cardiac death (SCD) in individuals under the age of 35 years in England and Wales, and identify any temporal trends in mortality over two decades. 2. Investigate the role and implications of the expert cardiac autopsy in the setting of SCD, specifically in the context of gender, age, circumstances of death and distinguishing between similar disease entities. 3. Following a novel pandemic, from a cardiac screening perspective, investigate the prevalence and diagnostic significance of de-novo electrocardiogram (ECG) changes post COVID-19 infection in elite soccer players.

Methods: Large scale population level data from the Office for National Statistics (ONS) and the Cardiac Risk in the Young Centre for Cardiac Pathology (CRY-CCP) was analysed. This correlated to mortality in individuals aged 0-34 years, between 2001 to 2021. Descriptive statistics and Poisson log-linear models were created to assess trend shifts over time. All autopsy evaluations and histological analyses were conducted by expert cardiac pathologists in accordance with established protocols. Furthermore, a multicentre observational study was performed between March 2020 and May 2022 where 511 consecutive soccer players, from the English, Dutch and Brazilian Football Associations with COVID-19 infection were evaluated.

Results: The incidence of cardiac and YSCD in England and Wales is 1.68 per 100,000 individuals per annum. The most prevalent conditions were ischaemic heart disease (28.4%), cardiomyopathies (25.9%) and sudden arrhythmic death syndrome (SADS) (21.8%). An overall downward trend in cardiac mortality over 21-years was observed, whilst the incidence of SADS demonstrated an 8.5% increment annually ($p<0.001$) up until 2010. Deaths attributed to cardiomyopathies and SADS peak during the 10-to-19 and 20-to-29-year age group.

Data from the CRY-CCP revealed: similar increments in SADS deaths over the study period. SCD occurs less frequently in female athletes and SADS is more frequent than male counterparts. Macro and microscopic evaluation of hearts demonstrated that mitral valve abnormalities were over four-fold more common in individuals with hypertrophic cardiomyopathy (HCM) and may be used as supportive criteria to differentiate from idiopathic left ventricular hypertrophy (ILVH). In young individuals with HCM, SCD was the first manifestation of the condition in 79% of cases and a high age-related variability in terms of the circumstances of death was observed. Individuals aged 10 to 15 years appear to be the most vulnerable in terms of exercise related SCD. Data from the CRY-CCP revealed that myocarditis is a rare cause of SCD in non-hospitalised individuals, however almost 20% reported prodromal cardiac symptoms prior to death.

Following evaluation of 511 soccer players with COVID-19 infection, 3% of athletes demonstrated de-novo ECG changes and 88% were diagnosed with cardiac inflammation. Athletes revealing de-novo ECG changes had a higher prevalence of cardiac symptoms (71% vs 12%, $p<0.0001$) and longer median symptom duration (5

days, IQR 3-10) compared with athletes without de-novo ECG changes (2 days, IQR 1-3, $p<0.001$). Most athletes exhibited cardiac symptoms, however, de-novo ECG changes contributed to a diagnosis of cardiac inflammation in 20% of athletes without cardiac symptoms. Following a median follow up of 270 days (IQR: 133-487 days), there were no adverse cardiac events among infected athletes in the entire cohort. All athletes identified with cardiac inflammation returned to play following conventional risk stratification tests and tailored exercise prescriptions without adverse events over a median follow up period of 479 days (IQR: 268-520 days).

Conclusions: Overall, my thesis provides novel insights into a decreasing trend in cardiac and SCD amongst young individuals in England and Wales. The incidence of SCD is likely underestimated and conceited efforts are required to ameliorate ambiguity in mortality coding with the aim of facilitating appropriate evaluation of surviving family members. The emphasis on expert cardiac histopathology assessment following SCD is crucial in elucidating the cause, distinguishing between similar disease entities, and providing insights for preventative strategies. Despite COVID-19 infection being a highly contagious disease, in the context of elite sport, most athletes experience a mild and self-limiting illness, with no adverse cardiac sequalae on follow-up. Novel insights from a cardiac screening and ECG perspective demonstrate a role for comparison of serial ECGs in the context of viral illness to facilitate tailored downstream investigations.

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Dedication

To my parents and brother, your boundless love and constant belief in my potential has shaped me into the person I am today.

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Publications during research tenure

1. **Bhatia RT et al**. “Exercise in the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) era: A Question and Answer session with the experts Endorsed by the section of Sports Cardiology & Exercise of the European Association of Preventive Cardiology (EAPC).” *European journal of preventive cardiology* vol. 27,12 (2020): 1242-1251.
2. **Bhatia RT et al**. “The Impact of COVID-19 on the Continuity of Cardiovascular Care.” *European heart journal* vol. 42,3 (2021): 215-217.
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6. **Finocchiaro G, Bhatia RT (*joint 1st authors*)**. Sudden Cardiac Death During Exercise in Young Individuals with Hypertrophic Cardiomyopathy et al. JACC Clinical Electrophysiology. In Press December 2022.
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20. **Bhatia RT et al**. “Coronary artery anomalies and the role of echocardiography in pre-participation screening of athletes: a practical guide.” Echo research and practice vol. 11,1 5. 22 Feb. 2024.
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22. British association of sports and exercise medicine (BASEM)– Sports Cardiology Edition of the Journal. **Bhatia RT**. 3 articles contributed. Published January 2021.

Key abstract presentations

1) Bhatia RT, Joo Yeo T, MacLachlan H, et al 2 Understanding cardiac and sudden death in young individuals: novel insights from the office for national statistics (ONS) in the United Kingdom Heart 2023;109:A3-A4. British Cardiovascular Society annual congress June 2023.

2) Bhatia RT, Al-Turaihi S, Quazi K, et al 201 Exploring the relationship between physical activity and covid-19 infection in a young, non-hospitalized cohort in the united kingdom Heart 2023;109:A236-A237. British Cardiovascular Society annual congress June 2023.

3) Bhatia RT, Malhotra A, MacLachlan H, et al 2 Prevalence and diagnostic significance of novel 12-lead ecg patterns following COVID-19 infection in elite soccer players Heart 2022;108:A2-A4. British Cardiovascular Society annual congress June 2022. Also presented at ESC Congress August 2022.

4) Bhatia RT, Westaby J, Behr E, et al 12 Sudden cardiac death during exercise in young individuals with hypertrophic cardiomyopathy Heart 2022;108:A10-A11. British Cardiovascular Society annual congress June 2022. Also presented at ESC Congress August 2022.

5) Bhatia RT, Khoury S, Westaby J, et al 1 Mitral valve abnormalities in decedents of sudden cardiac death due to hypertrophic cardiomyopathy and idiopathic left ventricular hypertrophy Heart 2022;108:A1-A2. British

Cardiovascular Society annual congress June 2022. Also presented at ESC Congress August 2022.

6) Maclachlan H, Bhatia RT, Dhutia H, et al C Outcomes of a nationwide cardiac screening programme in young individuals Heart 2022;108:A174. British Cardiovascular Society annual congress June 2022.

Grants and awards

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1) British Cardiovascular Society Conference – June 2023

Winner Best of the Best Award: Understanding cardiac and sudden death in young individuals: novel insights from the office for national statistics (ONS) in the United Kingdom. Associated cash prize.

2) European Association of Preventative Cardiology- April 2023

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3) European Society of Cardiology Annual Conference– August 2022

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4) British Cardiovascular Society Centenary Conference – June 2022

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5) British Cardiovascular Society Centenary Conference – June 2022

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List of Abbreviations

AC	Arrhythmogenic cardiomyopathy
ACEi	Angiotensin-converting enzyme inhibitors
AED	Automated electrical defibrillator
AHA	American Heart Association
ALCAPA	Anomalous left coronary artery from the pulmonary artery
ARVC	Arrhythmogenic right ventricular cardiomyopathy
BMI	Body mass index
BrS	Brugada syndrome
CAD	Coronary artery disease
CHB	Complete heart block
CMR	Cardiovascular magnetic resonance
CPR	Cardiopulmonary resuscitation
CPVT	Catecholaminergic polymorphic ventricular tachycardia
CRY	Cardiac Risk in the Young
CRY-CCP	Cardiac Risk in the Young Centre for Cardiac Pathology
CV	Cardiovascular
DNA	Deoxyribonucleic acid
DCM	Dilated cardiomyopathy
ECG	Electrocardiogram
ECV	Extra cellular volume
EHRA	European Heart Rhythm Association
EMB	endomyocardial biopsy
EPS	electrophysiological studies

FA	Football Association
FIFA	Fédération Internationale de Football Association
HF	Heart failure
HCM	Hypertrophic cardiomyopathy
ICCs	Inherited cardiac conditions
ICD	Implantable defibrillator
ICD-10	International Classification of Diseases,Tenth Revision
IHD	Ischaemic heart disease
ILR	Implantable loop recorder
ILVH	Idiopathic left ventricular hypertrophy
IOC	International Olympic committee
LV	Left ventricle
LVEF	Left-ventricular ejection fraction
LVH	Left ventricular hypertrophy
LVOT	Left ventricular outflow tract
LQTS	Long QT syndrome
MCCD	Medical Certificate of Cause of Death
MET	Metabolic equivalent of task
MMDS	Mortality Medical Data System
MV	Mitral valve
MVP	Mitral valve prolapse
NSVT	Non sustained ventricular tachycardia
ONS	Office for National Statistics
PPM	Permanent pacemaker
PPS	Pre-participation screening

WPW	Wolff-Parkinson-White
WHO	World Health Organisation
YSCD	Young sudden cardiac death
RVOT	Right ventricular outflow tract
SADS	Sudden arrhythmic death syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCA	Sudden cardiac arrest
SCD	Sudden cardiac death
SCORE	Systematic Coronary Risk Evaluation
SDM	Shared decision-making
SQTS	Short QT syndrome
TTE	Transthoracic echocardiography
UK	United Kingdom
VA	Ventricular arrhythmia
VT	Ventricular tachycardia
VF	Ventricular fibrillation

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Chapter 1: Young Sudden Cardiac Death

1.1 Introduction

Sudden cardiac death (SCD) in young individuals, though rare, carries a devastating impact that reverberates through families, communities, and the general public. The loss of young lives and the potential life-years they could have enjoyed adds to the profound grief experienced by those affected. In particular, young athletes who succumb to sudden cardiac arrest/ death (SCA/ SCD) leave a significant impression on society. When such tragic events are witnessed and televised in real-time, people of all ages are affected, grappling with the implications, and raising questions about the unpredictability of life. The magnitude of these events underscores the need for increased awareness and collective efforts to address the underlying aetiologies, aid early identification and mitigating the risk, especially of exercise related SCD.

Sudden cardiac death (SCD) is defined as an unexpected, nontraumatic death from cardiac causes within 1 hour of symptom onset in individuals with or without pre-existing cardiac disease.[1] Despite the adoption of preventive strategies to curtail the burden of cardiovascular diseases (CV) globally, CV diseases remains an important cause of mortality globally, of which 25% are due to SCD.[2] The aetiology of SCD

varies according to the age (figure 1).

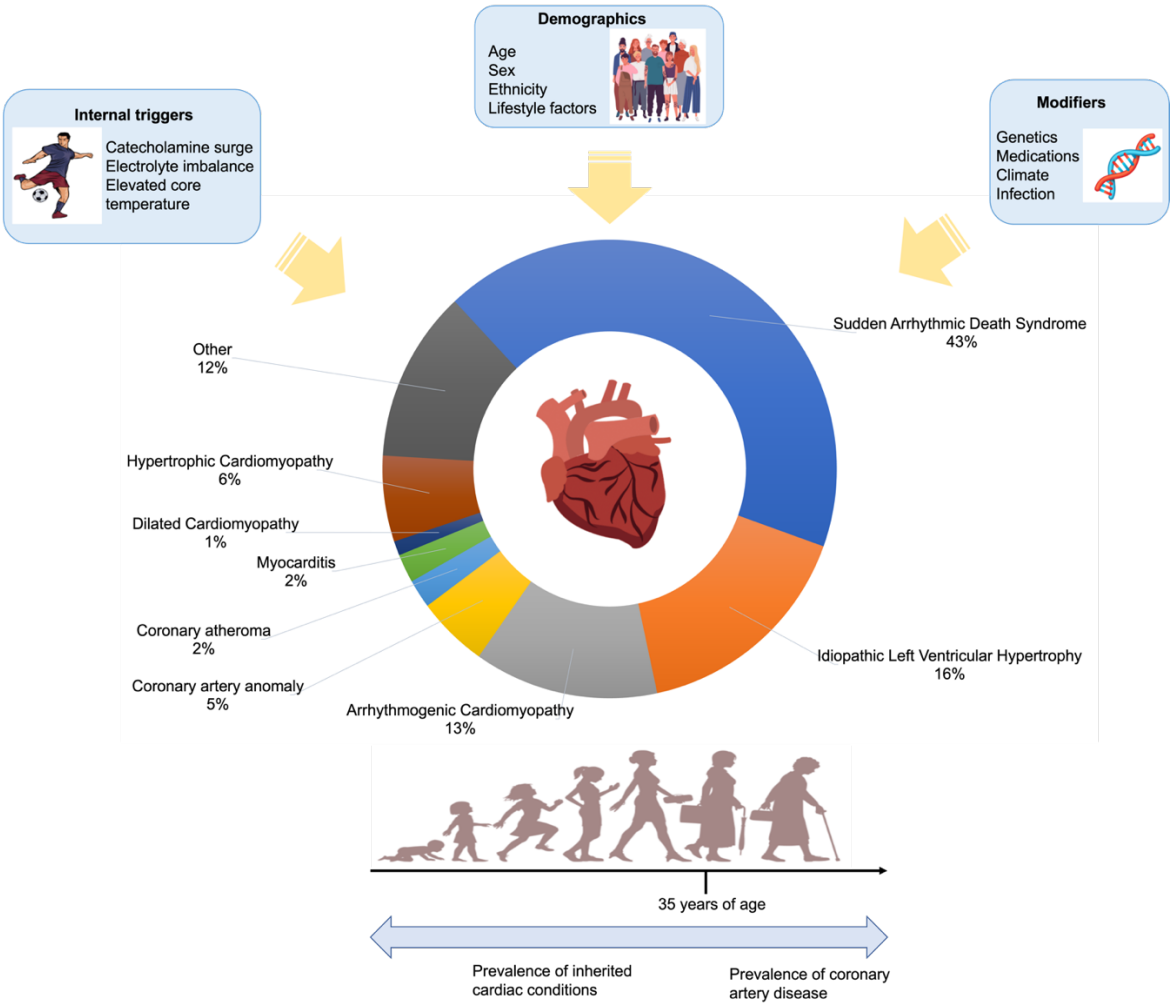


Figure 1: Aetiology of sudden cardiac death in athletic individuals.

'Other' include, mitral valve abnormalities/prolapse; myocardial infarction with normal coronaries; bicuspid aortic valve; aortic dissection; cocaine/steroid use; cardiac sarcoidosis; atrium septal defect (ASD) and in instance where the cause of death could not be attributed to a single disease entity or condition and the post-mortem findings were considered of uncertain significance. Percentages relate to Finocchiaro G, Papadakis M, Robertus JL, et al. Etiology of Sudden Death in Sports: Insights From a United Kingdom Regional Registry. J Am Coll Cardiol. 2016;67(18):2108-2115. and are representative of data from the United Kingdom

In older individuals (>35 years) coronary artery disease (CAD), predominantly attributed to acquired CV risk factors, accounts for most deaths.[3–5] In the young, typically defined as individuals <35 years of age, the majority of SCDs are attributable to non-ischaemic causes, and in particular inherited or congenital cardiac conditions.

The inherited cardiac conditions (ICC's) represent a diverse spectrum of conditions affecting the heart, its conduction system, and vasculature. Whilst a degree of overlap exists between ICC's, they are broadly classified into four categories.

1) **Arrhythmia syndromes**, result from mutations in the sodium, potassium and calcium ion channels that are involved in generating the action potential and include disease such as long QT syndrome (LQTS), short QT syndrome (SQTS), Brugada syndrome (BrS) and catecholaminergic polymorphic ventricular tachycardia (CPVT). These conditions account for a significant proportion of autopsy-negative deaths, termed sudden arrhythmic death syndrome (SADS).
2) **Cardiomyopathies**, result from mutations affecting structural elements in the cardiac muscle cells including the proteins making up the contractile system, ion channels, cytoskeleton and mitochondria. They represent a diverse spectrum of diseases and include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM) and arrhythmogenic cardiomyopathy (AC), which are characterised by abnormal structure and/or function of cardiac muscle. Acquired conditions such as myocarditis are also considered within the inflammatory cardiomyopathies. Inherited channelopathies and

cardiomyopathies are evident in up to 50% of families of victims of SCD. [5–7] In up to 30% of decedents of SCD, no cause is identified at post-mortem. In the presence of a structurally normal heart and a negative toxicology screen, deaths are attributed to SADS. A significant proportion of such deaths are attributed to inherited arrhythmia syndromes.

3) **Inherited arteriopathies**, result from mutations which affect the structure and synthesis of the extracellular matrix such as collagen, elastin, muco-polysaccharides and related biomolecules. These conditions include Marfan syndrome, Ehlers-Danlos syndrome and Loeys-Dietz syndrome, and many other cases of aortopathies that are genetically based, including individuals with bicuspid aortic valve.
4) **Muscular dystrophies**, represent a group of multi-systemic genetic disorders that result in progressive muscle weakness and an increasing burden of disability. These conditions include Duchenne, Myotonic and Beckers muscular dystrophy, and cardiac disease is a common manifestation independent on the degree of skeletal myopathy.

The varied clinical presentations include asymptomatic individuals identified with an abnormality at a routine medical check-up, during community or sports-related cardiac screening, evaluation following a relevant family history, evaluation of individuals presenting with cardiac symptoms and occasionally the first presentation is with a SCA or SCD. In recent years, increased awareness, enhanced diagnostic tests, advancement of genetics and growing expertise in the field, have significantly improved our understanding of the epidemiology, aetiology and management of ICC's, including strategies to prevent SCD.

1.2 Epidemiology and aetiology of young sudden cardiac death

The incidence and causes of SCD in young individuals have historically demonstrated significant heterogeneity, which reflects the cohorts' characteristics, definitions, and methodologies used. Nuances in study designs, which includes poorly defined estimates of the number of deaths (numerator) and assumptions regarding the total number of participants (denominator), have most certainly influenced estimates. Furthermore, historically appreciating the true burden of cardiac morbidity and mortality in young individuals has been impacted by the inclusion or not of resuscitated SCA in studies.

An accurate understanding of the incidence of SCA and SCD is crucial to inform public health policies including preventative strategies such as cardiovascular screening. The gold standard for determining an accurate incidence is with a well-defined denominator which encompasses all concerned individuals during a particular point in time with substantial follow up periods and accurate methods to glean causes of death, which includes, death certificates, medical records and expert cardiac post-mortems. As can be appreciated in table 1, significant variations exist in current studies with estimates of SCA/ SCD in young individuals between 0.61 to 11.2 per 100,000 patient years.

Geography, sex, intensity and type of athletic activity appear to have an important influence. Brugada syndrome is more common in Asian (9/1000) than European populations (2/1000) and AC being more common in Italian populations.[8,9] Male sex is associated with a 2-9-fold increased risk of SCD compared to females. Young

athletes who participate in competitive sports and in particular sports that require a dynamic start-stop proficiency,[10,11] appear to be at increased risk of SCD in the context of an inherited cardiac condition. Study methodology is crucial, as there is up to 41% inter-reporter variability between a general and an expert cardiac pathologist to the attributed cause of death, with general pathologists more likely to diagnose a structural heart disease such as cardiomyopathy, while expert pathologists are more likely to attribute the death to SADS.[12] Moreover, incomplete investigations in survivors of SCAs or in the first-degree relatives of decedents and variable use of molecular autopsy affect the results.

Table 1: Current estimates of SCD incidence in young individuals based. Data relates to individuals in the general population and specifically in athletes. SCA: sudden cardiac arrest.

Study	**Country (region) Cohort characteristics**	**Age range**	**SCD incidence (per 100,000 patient years)**	**Comments**
General population level data				
Papadakis et al[13]	England and Wales Population level data Death certificate based	1-34 years	1.8	Includes sudden cardiac deaths and cardiac deaths in young
Driscoll et al[14]	Olmstead County, Minnesota	1-22 years	1.3	32-year study period

				2.3% sudden deaths
Shen et al[15]	Olmstead County, Minnesota	20-40 years	3.6	29-year study period
Anastasakis et al[16]	Attica, Greece	1-35 years	1.8	8-year study period; death certificates and autopsy reports
Bagnall et al[17]	Australia and New Zealand	1-35 years	1.3	8-year study period; included clinical and genetic evaluation
El-Assad et al[18]	All residents in USA	1-34 years	1.32	16-year study period; death certificate based
Military recruits				
Eckart et al[19]	USA	18-35 years	11.2	25-year study period
Eckart et al[20]	USA	18-35 year	3.5	10-year study period
All athletes				
Corrado et al[21]	Veneto, Italy	12-35 years	2.3 in athletes 0.9 non athletes	21-year study period

Maron et al[22]	National USA registry	8-39 years	0.61	27-year study period
Collegiate athletes				
Harmon et al[23]	USA	17-24 years	1:53,703 athlete years	10-year study period
Drezner et al[24]	USA	14-17 years	4.4	Outcome of study was effectiveness of emergency response planning for SCA
Adolescent athletes				
Malhotra et al[25]	UK FA screening program	12-18 years	6.8	10-year study period All adolescent football players

In addition to the aforementioned genetic diseases, congenital abnormalities are also implicated in the aetiology of SCA and SCD. This includes, anomalous origins of the coronary ostia, bicuspid aortic valve, mitral valve prolapse (MVP) and electrical accessory pathways such as Wolff-Parkinson-White (WPW) syndrome. Furthermore, acquired diseases include myocarditis, performance enhancing drugs and commotio cordis. Historically, the cardiomyopathies were considered to represent the most common cause of mortality in athletes.[22,26] More contemporary data, such as seminal work by Finocchiaro et al.,[7] from a large registry of autopsy findings in the setting of

SCD in athletes, with a mean age of 29 years suggest that SADS is the most prevalent cause of death (42%) (figure 1) in young individuals, with primary myocardial diseases such as hypertrophic cardiomyopathy, idiopathic left ventricular hypertrophy, arrhythmogenic cardiomyopathy accounting for 40% of cases. In contrast to data from North America, deaths attributed to coronary anomalies equated to 5% of deaths. In terms of age, deaths attributed to SADS appear to exhibit an age predilection and accounted for more than 50% of deaths in individuals. Similar trends were observed in individuals aged 18 to 35 years. It is important to acknowledge that all post-mortems in this study were performed by expert cardiac pathologists which facilitates a robust representation of the causes of YSCD in the athletic population.[7] In contrast, almost 80% of all SCDs in athletes aged above 35 (termed master athletes) are secondary to acquired coronary artery disease.[27]

Apart from aortic rupture, mortal events are secondary to ventricular fibrillation (VF). The precise mechanism for arrhythmia is uncertain; however, several exercise related metabolic stresses including surges in blood catecholamine concentration, acid-base disturbances, electrolyte shifts, and increasing core temperature may potentiate abnormal repolarisation and/or ventricular extrasystoles.[28] Among individuals with subclinical or long standing chronic coronary syndromes, ventricular fibrillation may be caused by demand ischaemia or by atherosclerotic plaque rupture secondary to mechanical shearing forces within the coronary arteries.[28,29] Besides age, sex, ethnicity and type of sport, several other factors govern the risk of SCD including the actual cardiac aetiology, cardiorespiratory fitness status, drug history, concomitant infection and environmental climate (figure 1). The relative risk of SCD in male and female athletes harbouring cardiac disease is around 2.5 times higher

than in non-athletes suggesting that exercise is an important trigger for SCD in vulnerable athletes.[21]

1.3 **Preventing SCD – primary and secondary preventative strategies**

A multifaceted approach is required in preventing young sudden cardiac death. This includes primary preventative strategies such as CV screening in the general population including athletes and targeting high risk groups; promoting safe participation in exercise and sport; and guideline directed secondary prevention in those with established CV disease. As will be discussed in my thesis the clinical evaluation in a hospital setting will include an individualised approach, which includes a comprehensive familial evaluation, review of post-mortem findings and tailored down-stream investigations (figure 2).

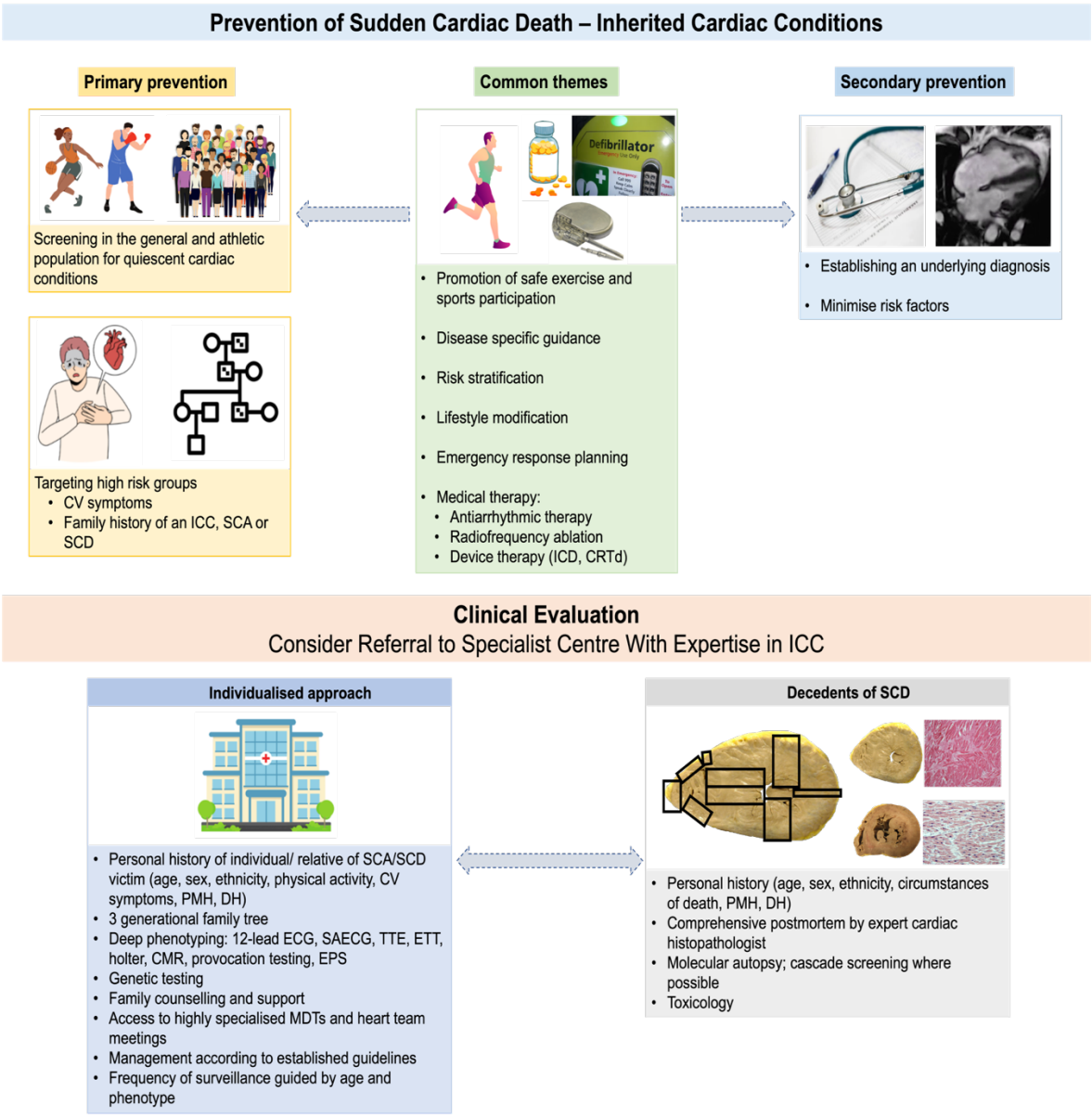


Figure 2: Preventative strategies.

CMR, cardiovascular magnetic resonance; CRTd, cardiac resynhronisation therapy defibrillator; CV, cardiovascular; DH, drug history; ECG, electrocardiogram; EPS, electrophysiological study; ETT, exercise tolerance test; ICC, inherited cardiac condition; ICD, implantable cardioverted defibrillator; MDTs, multidisciplinary team meetings; PMH, past medical history; SAECG, serial average electrocardiogram; SCA, sudden cardiac arrest; SCD, sudden cardiac death; TTE, transthoracic echocardiogram.

1.4 **Systematic population-level screening of low-risk individuals**

Systematic cardiac screening works on the premise that by screening for conditions associated with young sudden cardiac death (YSCD), which might be in the quiescent stages, early and appropriate management can be instigated to prevent SCD. The success of any screening programme is largely dependent upon the application and interpretation of specific criteria.[30] According to the World Health Organisation (WHO), screening for a disease process is recommended if the disease is considered an important public health problem and if the identification of an abnormality in the early, often asymptomatic stages will impact upon the outcome.[30] The natural history of the disease should be known and there should be appropriate treatments for individuals diagnosed with the disease.[30]

At present, in the United Kingdom (UK), there is no government backed national screening programme and this remains a contentious issue, largely in view of the stance taken by policy makers on the varied epidemiology, efficacy around screening investigations such as the 12-lead electrocardiogram (12-lead ECG) and the impact of onward management. These concerns are twinned with balancing the benefits of screening with concerns from false-positive and false-negative findings, as well as overall cost-effectiveness of such programmes. Given that SCD is relatively rare, several thousand athletes would need to be assessed to detect a single individual who may ultimately succumb during exercise. Therefore, any cardiac screening programme in athletes needs to be relatively cheap and simple to conduct whilst having a relatively high sensitivity for detecting athletes with serious cardiac disease.

Athletes are regarded to be at a higher risk of SCD in the context of electrical or structural cardiac abnormalities, due to the haemodynamic demands of exercise.

Moreover, exercise may alter the natural history of certain conditions, as evident in individuals with arrhythmogenic cardiomyopathy and laminopathies.[31–33] Consequently, systematic pre-participation screening (PPS) has been widely adopted by scientific and sporting organisations.[31,34] The American Heart Association (AHA) recommend cardiac screening with history and cardiovascular examination focussing on 14 elements (figure 2).[35,36] The clinical history pertains to identifying CV symptoms such as exertional chest discomfort, dyspnoea, palpitations and syncope. Given the genetic nature of many cardiac disorders implicated in exercise related SCD in the young, particular attention is paid to the family history of premature SCD or recognised heart disease in first-degree relatives <50 years of age with specific references to these conditions during the questioning process. Physical examination is focused to detect high blood pressure, cardiac murmurs, signs of coarctation of the aorta and the Marfan habitus.

In addition, the European Society of Cardiology (ESC) advocates for the routine use of a resting 12 lead electrocardiogram (ECG) as part of PPS algorithms.[31] In comparison to the European model, the AHA screening programme is simple and pragmatic, however, it lacks sensitivity for detecting serious cardiac diseases, because most athletes are asymptomatic prior to sudden death. Furthermore, a family history is not always present because genetic cardiac diseases may have a silent course in first degree relatives for several decades and physical examination is rarely positive in athletes with serious cardiac disease.[37] An American study, comparing the AHA 14 points screening protocol with a protocol that included a 12-lead ECG showed that the AHA model had a much lower sensitivity (18.8%), specificity (68.0%) and positive predictive value (0.3%) compared with the model

including 12-lead ECG which had a sensitivity (87.5%), specificity (97.5%) and positive predictive value (13.6%), respectively.[38]

The ESC stance is based on the Italian experience where PPS in athletes has been legally mandated since 1982 and implementation of the programme in the Padova region resulted in an 89% reduction in the incidence of SCD in athletes, from 3.6/100,000 person years to 0.4/100,000 person years.[39]

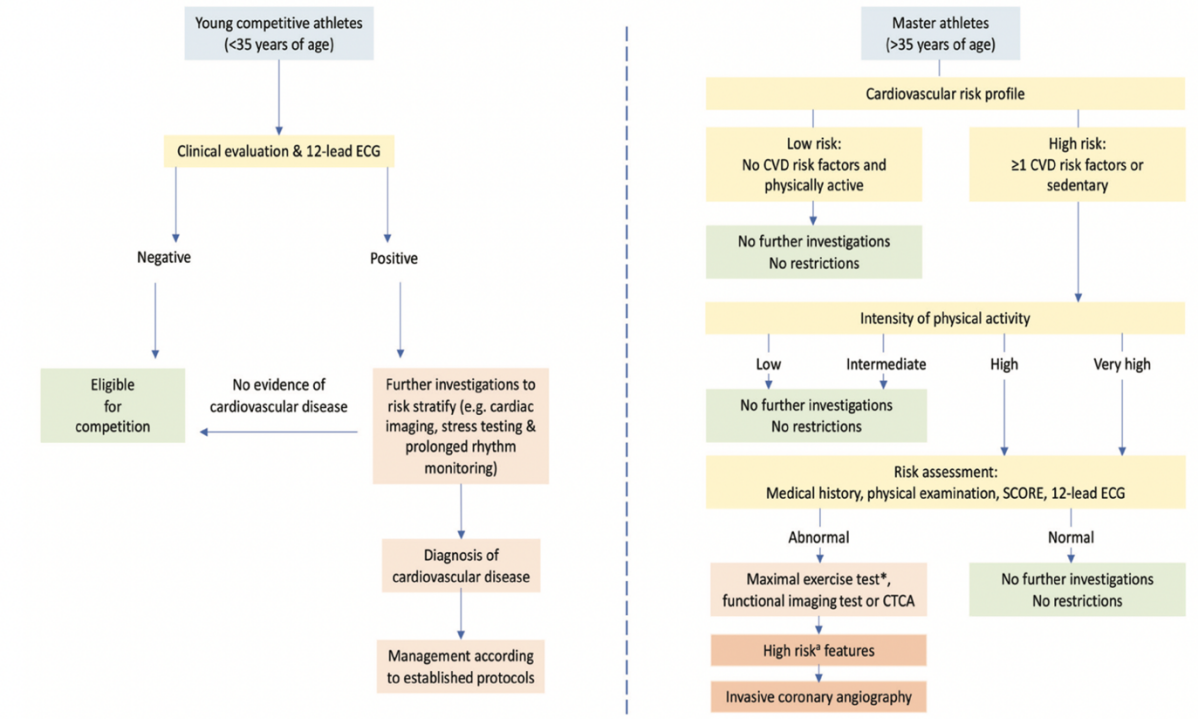
More recently, a large study, with a well-defined denominator in the general population of 26,900 individuals aged 14-35, has demonstrated that the inclusion of a 12-lead ECG into screening algorithms, increases the diagnostic yield of conditions associated with SCD by five-fold.[40] This incremental value is further exemplified as over 80% of young individuals, who were diagnosed with diseases associated with SCD were asymptomatic at initial evaluation and did not have a family history that would otherwise warrant further evaluation.[40] This finding has also been demonstrated in autopsy series, where sudden death is often the first manifestation of an underlying cardiomyopathy in up to 80% of individuals.[41,42] Furthermore, from a cost-effectiveness standpoint, the inclusion of a 12-lead ECG is associated with a 36% reduction in cost per disease detected.[40]

The frequency of cardiac screening, particularly in adolescent athletes has received considerable attention. A large study of over 11,000 adolescent football scholars, yielded a SCD incidence of 6.8 per 100,000 athletes, of which 75% of demises were attributed to cardiomyopathies that were not detected on initial screening. These individuals died on average 7 years following their index cardiac screening.[25] This study remains at the forefront of physicians caring for athletes on a regular basis and

emphasises the need for regular surveillance based on available resources and sport-specific guidance.

Therefore, based on its superior yield and the potential to save lives, cardiac screening including a 12-lead ECG is endorsed by several sporting organisations including the International Olympic committee (IOC) and Fédération Internationale de Football Association (FIFA). Cardiac screening is offered in the UK by charitable organisations, such as Cardiac Risk in the Young (CRY) and sporting governing bodies, such as the Football Association (FA) who mandate such initiatives for their athletes aged 14-35. Similar initiatives exist in most other countries, with Italy, Japan and Israel being the only countries where systematic mandatory cardiac screening happens at population level.

In ‘master-athletes’, defined as those aged >35, there is limited evidence on systematic screening of asymptomatic individuals. However, in view of the higher prevalence of atherosclerotic disease in these individuals, physicians have formulated consensus-based algorithms aimed at identifying those at higher atherosclerotic risk (figure 3). These include, risk-stratification based on the ESC Systematic Coronary Risk Evaluation (SCORE) system[43], physical activity level, functional assessment of exercise capacity and if deemed necessary objective assessment of the epicardial coronary arteries.



*Consider functional test or CCTA if exercise stress test is equivocal or the ECG is uninterpretable. aSingle-photon emission computed tomography: area of ischaemia ≥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 ≥3 dobutamine-induced dysfunctional segments; coronary computed tomography angiography (CCTA): three-vessel disease with proximal stenoses; left main disease; proximal left anterior descending disease. CVD = cardiovascular disease; ECG = electrocardiogram; SCORE = Systematic Coronary Risk Evaluation.

Adapted from (1) Corrado D, et al. Cardiovascular pre-participation screening of young competitive athletes for prevention of sudden death: proposal for a common European protocol. *Eur Heart J.* 2005;26(5):516-524. **(2)** Borjesson M, et al. Cardiovascular evaluation of middle-aged/ senior individuals engaged in leisure-time sport activities. *Eur J CardiovascPrevRehabil.*2011;18(3):446-458. **(3)** Pelliccia A, et al. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease. *Eur Heart J* 2021.

Figure 3: Pre-participation screening protocols.

Adapted from (1) Corrado D, et al. Cardiovascular pre-participation screening of young competitive athletes for prevention of sudden death: proposal for a common European protocol. Eur Heart J. 2005;26(5):516-524. (2) Borjesson M, et al. Cardiovascular evaluation of middle-aged/ senior individuals engaged in leisure-time sport activities. Eur J CardiovascPrevRehabil.2011;18(3):446-458. (3) Pelliccia A, et al. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease. Eur Heart J 2021.

1.5 Challenges related to cardiovascular screening in athletes

The societal impact of a sudden death in an athlete may be considered as an important public health issue. The natural history and management of many cardiac diseases implicated in exercise related SCD in young athletes are recognised. Unlike other screening programmes such as breast cancer however, CV screening in athletes aims to identify a diverse spectrum of diseases for which no single screening test is available.

Although, the 12-lead ECG is a simple test, it is unable to detect concealed electrical pathways, adrenergically mediated arrhythmias (e.g., catecholaminergic polymorphic ventricular tachycardia, CPVT), CAD, anomalous coronary artery origins or Marfan syndrome.[39] There is also evidence that a single cardiovascular assessment between the ages of 16 and 17 years old will fail to identify some individuals with incomplete expressions of a cardiomyopathy.[25]

Conversely, athletic training is associated with a plethora of structural and functional cardiac adaptations that may be associated with repolarisation anomalies on the 12-lead ECG that overlap with those detected in individuals with serious cardiac diseases.[44] In such cases, an erroneous interpretation of the ECG can lead to serious consequences ranging from unnecessary disqualification from sport to false reassurance of an athlete with a life threatening cardiac disorder. Despite these limitations a large proportion of serious cardiac diseases diagnosed in athletes during screening have an electrical basis. In a large screening study of over 11,000 adolescent soccer players, 42 (0.38%) athletes had serious cardiac disease and 36 (86%) had an abnormal ECG compared with only 3 with an abnormal history or examination and 12 (29%) with an abnormal ECG.[25]

1.6 **Improvements in the 12-lead ECG**

Until recently, the ECG interpretation in athletes was based on the 2010 ESC recommendations, which were derived from a cohort of 30,000 predominantly white amateur athletes.[45] These recommendations did not allow for black athletes and individuals or large populations of athletes who train very intensively. As a consequence, some studies reported an acceptably high number of positive results with particular reference to T wave inversion, especially in black athletes.[44] Over the past decade there have been several emerging reports based on large cohorts of athletes that have allowed the refinement of the criteria for interpreting the athlete's ECG. The most recent international recommendations[46] account for:

(i) ethnicity specific repolarisation changes in black athletes,

(ii) the juvenile ECG pattern in adolescent athletes <16 years old,

(iii) more liberal cut off values for a prolonged QT interval,

(iv) a new borderline category for some non-specific markers including axis deviation, voltage criteria for atrial enlargement and right bundle branch block which previously constituted over 50% of all positive results but had a poor diagnostic yield on subsequent investigation. Only athletes with two or more of these borderline anomalies would be considered to have an abnormal ECG.

Compared with the 2010 ESC recommendations the international recommendations are associated with a higher specificity for white (99%) and black (97%) athletes and a sensitivity of 86%.[47] Based on a study of almost 5,000 adult athletes, application of the international recommendations was associated with a 66% reduction in the number of athletes requiring an echocardiogram, 29% reduction in the number

requiring an exercise stress test, a 17% reduction in the number requiring holter monitoring, and a 25% reduction in the number requiring cardiac magnetic resonance imaging (MRI) scans compared with the 2010 ESC recommendations.[48] As such the criteria set out in this consensus document now serve as the foundation for healthcare professionals involved in evaluating the athlete as part of preparticipation screening (PPS).[46]

1.7 Screening high risk individuals

High risk individuals include individuals with CV symptoms and individuals with a family history of an ICC, SCA or SCD. A comprehensive medical history is an essential initial step as part of this evaluation (figure 2). The focus should be on the nature of the cardiovascular symptoms and recognition of “red flags”, including, atypical presentations such as arrhythmic syncope presenting as epileptic seizures, unexplained drownings, and road traffic accidents.

1.8 Evaluation of families after sudden cardiac death

The potentially hereditary nature of conditions predisposing to SCD in young individuals highlights the importance of performing a comprehensive evaluation of the deceased and offering cardiovascular assessment to all first-degree relatives (figure 2). The family’s journey after a SCD includes delicate interactions with numerous public and health services, and formal support networks are still lacking in most countries.

Postmortem evaluation is often the first step in establishing the aetiology of death, and guide down-stream investigations in living family members.[12,49–51] There is growing evidence around the importance of performing a detailed autopsy in victims of SCD by expert histopathologists in accordance with guidelines on sampling, toxicology screen and molecular investigation.[49,50] Interpreting results is complex as many disorders are rare or exhibit subtle findings. In addition, uncertainty can exist to the causal relationship between the pathological findings and the sudden death. In recent years, concerted efforts have been made to standardise autopsy protocols and establish regional centres with the required experience and expertise.[28]

Where available and consent has been provided by the family, stored biological samples of deoxyribonucleic acid (DNA) from the deceased can be evaluated in cases where an inherited cardiac condition is suspected at post-mortem, referred as “molecular autopsy”. Molecular autopsy can be targeted for specific cardiac conditions or include broader panels in cases of SADS. In cases of SADS molecular autopsy may identify a disease-causing mutation in up to 25% of cases, allowing for a probable cause of death to be established and for genetic testing to be offered to first-degree relatives of the deceased, also referred to as familial cascade screening.[49] The combination of genetic information and clinical evaluation can increase the diagnostic yield of ICCs in surviving first-degree relatives.[52]

A three-generation family history should be undertaken. Specific practice-pointers include the age and sex of the individual concerned, circumstances of death (e.g., rest or on exertion), prior medical history and detailed medication history including the potential for illicit drug use. Enquiring about the health of the deceased 24 to 48 hours prior to death might offer diagnostic clues to the cause of death.

Baseline investigations include a 12-lead ECG in the standard lead positions and in the higher lead configuration which has been shown to increase the diagnostic yield of the Brugada phenotype[53,54], transthoracic echocardiography (TTE), ambulatory prolonged rhythm monitoring, and maximal exercise stress testing. Where clinically indicated, further investigations such as, signal-averaged ECG, cardiovascular magnetic resonance (CMR) imaging and sodium channel provocation testing may be performed. In the context of clinical evaluation, genetic testing should be used in individuals with an established or highly suggestive clinical phenotype.

1.9 **Lifestyle interventions**

The diagnosis of an ICC is associated with several lifestyle modifications which individuals need to remain astute towards (table 2). This includes remaining mindful about any medications, metabolic states such as electrolyte imbalance and dehydration, autonomic changes, or other haemodynamic factors such as infection, ischaemia and hypoxaemia, which might promote a pro-arrhythmic state. Furthermore, the benefits of physical activity on the CV system are well established. Despite this, a balance must be struck between the benefits of exercise and the risk of SCD, which need to take into consideration a shared decision-making model that respects the autonomy of the individual after a comprehensive provision of the potential risks and complications associated with intensive exercise. This is particularly relevant in conditions such as AC, where regular high intensity exercise is well documented to being associated with acceleration of the underlying disease process and associated morbidity and mortality.[31] Furthermore, in the context of CV prevention, it is also important to address traditional risk factors such as

hypertension and atherosclerosis, which can have an additive detrimental effect in the prognosis of ICCs in aging individuals.[55]

Table 2: Inherited cardiac conditions – general concepts in disease specific preventative treatment strategies.

	Lifestyle advice	**Medical therapy**	**Interventional and surgical therapies**	**Device therapy**
BrS	Treat febrile episodes >38°C aggressively with cool fluids and paracetamol. Avoid situations where the core temperature may exceed >40°C Avoidance of drugs that may induce ST-segment elevation in right precordial leads (www.brugadadrugs.org) Avoid binge drinking.	Quinidine should be considered to treat electrical storms; or patients who qualify for an ICD but have a contraindication; or patients who refuse an ICD; or for the treatment of supraventricular arrhythmias.	Catheter ablation may be considered in the context of electrical storms or repeated appropriate ICD shocks.	ICD implantation is recommended in survivors of SCA and/or documented spontaneous sustained VT. ICD implantation may be considered in the context of syncope and a spontaneous

	Avoid sleeping within two hours of consuming a heavy meal.			type 1 BrS pattern.
CPVT	Avoidance of competitive sports, strenuous exercise and stressful environments.	β-blockers (e.g., propranolol or nadolol) should be commenced in all patients. Flecainide may be considered as adjunctive therapy, in the context of recurrent syncope or VA	Left cardiac sympathetic denervation may be considered in the context of recurrent syncope, VA, or appropriate shocks despite medical therapy.	ICD implantation is recommended in survivors of SCA, recurrent syncope or VA despite optimal medical therapy.
LQTS	Avoidance of QT-prolonging medications (www.crediblemeds.org) Correction of electrolyte imbalances during systemic illness.	β-blockers should be commenced in all patients with LQTS, including genotype +ve/ phenotype –ve. Sodium channel blockers e.g.,	Left cardiac sympathetic denervation may be considered in the context of in effective treatment with medical	ICD implantation is recommended in survivors of SCA, recurrent syncope or VA despite optimal

	LQTS1: avoid strenuous swimming. LQTS2: avoid loud noises	mexiletine, may be considered as add-on therapy in LQTS3 with a QTc >500 ms.	therapy, contraindication to ICD therapy, or appropriate shocks despite medical therapy.	medical therapy
AC	Avoidance of competitive sport.	In patients with PVCs and NSVT, β-blockers should be up-titrated to the maximal tolerated dose. Amiodarone should be considered as add-on therapy where required.	Catheter ablation should be performed in the context of frequent symptomatic PVCs or VT unresponsive to medical therapy.	ICD implantation is recommended in survivors of SCA, recurrent syncope or VA despite optimal medical therapy
DCM	Avoidance of electrolyte imbalance in the context of systemic illness.	In individuals with LVSD- optimal medical therapy as per HF guidelines, including, ACEi, β-	In the context of age, risk factors, VA and LVSF, consider coronary angiography to	ICD is considered with: (i) haemodynamically

		blockers and MRA. Consider add-on therapy with amiodarone in the presence of refractory VA and/or recurrent appropriate shocks despite optimal device programming.	exclude bystander coronary artery disease. Consider catheter ablation in the context of a VA focus/ refractory to medical therapy.	compromising VA and survival expected >1 year (ii) NYHA II-III, LVEF ≦35% for ≥3 months despite optimal HF medical therapy (iii) consider CRTp or CRTd depending on QRS duration (iii) genotype specific cases e.g., LMNA mutation
HCM	Avoidance of competitive sport. Patients with LVOT obstruction should	β-blockers and disopyramide to treat LVOT obstruction.	Alcohol septal ablation and/or myectomy considered on a case-by-case	ICD implantation is recommended in

	remain well-hydrated, avoid excessive alcohol consumption and weight loss should be encouraged	Verapamil may be used if intolerant or contraindication to β-blockers. Thromboembolic risk should be reviewed as a continuum. Prompt restoration of sinus rhythm is preferred in patients with LVOT obstruction	basis, with care delivered in experienced centres.	(i) survivors of SCA (ii) based on ESC-HCM risk score in patients aged ≥16 years

AC: arrhythmogenic cardiomyopathy; BrS: Brugada syndrome; β-blockers: beta-blockers; CAD: coronary artery disease; CPVT: catecholaminergic polymorphic ventricular tachycardia; CRT: cardiac resynchronization therapy (p: pace, d: defibrillator); DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; ICD: implantable cardioverter defibrillator; LQTS: long QT syndrome; LVOT: left ventricular outflow tract; LVSD: left-ventricular systolic dysfunction; LVSF: left-ventricular systolic function; MRA: mineralocorticoid receptor antagonist; NYHA: New-York Heart Association dyspnoea class; PVC: premature ventricular contraction; SCA: sudden cardiac arrest; VA: ventricular arrhythmia; VT: ventricular tachycardia.

1.10 **Therapeutics**

The effective management of ICCs often includes a combination of medical and advanced device treatments to manage atrial and ventricular arrhythmia (VA), thromboembolic risk and heart failure (HF). A brief account of some disease specific treatment strategies is discussed below and in table 2.

In general, betablockers, have consistently demonstrated efficacy in suppressing ventricular ectopy and arrhythmia burden, irrespective of left-ventricular systolic impairment and are considered first-line therapy to reduce the risk of SCD.[1] Class 1a anti-arrhythmic medications (e.g., quinidine, procainamide and disopyramide) block sodium channels and also cause delays in potassium signalling, which can result in prolongation of the QT interval and may commonly results in anticholinergic side effects. Class III agents, namely amiodarone, whilst utilised widely in the acute setting of VAs, should be used with caution in individuals requiring concomitant therapies associated with prolongation of the QT interval and in individuals with significant conduction tissue disease. Individuals who are on established therapy with amiodarone, require regular monitoring for its systemic side effects e.g., ocular, pulmonary, liver and thyroid dysfunction, which might necessitate cessation of the drug. Another class III agent, Sotalol, can be utilised effectively to reduce sustained ventricular arrhythmias.[1,56]

Conditions such as DCM, HCM and AC can result in adverse cardiac re-modelling, such as dilated atria, valvular heart disease, diastolic, biventricular systolic impairment and promote pro-thrombotic states. These structural changes often

manifest clinically with cardinal cardiovascular symptoms such as dyspnoea, palpitations and systemic features due to thromboembolic complications. As such, optimisation of medical therapy should include angiotensin-converting enzyme inhibitors (ACEi), mineralocorticoid antagonists and anticoagulation based on established evidence-based guidelines.[1,51,57] Based on arrythmia burden and findings from imaging studies such as CMR, catheter ablation therapy may be considered. Depending on the arrhythmogenic substrate, combination therapy with medical and interventional techniques are often required to manage SCD risk.

Individuals considered to be at a high risk for SCD, often warrant a primary preventative implantable defibrillator (ICD). The indications are disease specific, with decisions made based on taking into account symptoms, family history, genetic variants identified, imaging studies, especially scar burden on CMR, the underlying arrhythmic substrate, QRS duration and left-ventricular ejection fraction (LVEF).

Accurate risk stratification is vital and regular surveillance in centres of excellence with adequate expertise to ensure appropriate consideration of ICD therapy, which takes into account the risks of procedural complications, long-term device-related risks in younger individuals and the benefits of these life-saving devices. Historically, these devices have been inserted via transvenous access. In recent years, with the advent of subcutaneous ICDs, problems due to vascular access can be negated and may be considered in individuals where pacing therapy or anti-tachycardia pacing is not required. In addition, subcutaneous ICDs are often considered in younger individuals and where there are concerns regarding infection. Wearable cardioverter defibrillators have also demonstrated prevention of SCD and may be considered for adult patients with impaired left ventricular systolic function who are not candidates

for an ICD e.g., as a bridge to cardiac transplantation, acute myocarditis and a pro-arrhythmic state post myocardial infarction.

Long QT syndrome: Betablockers, such as nadolol and propranolol are recommended in all patients with a clinical diagnosis of LQTS and should be considered even in genotype positive/phenotype negative individuals. Combination therapy with mexiletine may be beneficial in individuals with the LQTS3 sub-type. ICDs should be considered in survivors of cardiac arrest but may also be considered in individuals with high-risk markers e.g., QTc of ≥ 500ms, history of syncope, young age at presentation, and LQTS2 and LQTS3 genotype. From a surgical perspective, cardiac sympathetic denervation should be considered when betablockers are not effective, tolerated or contraindicated, ICD therapy is contraindicated or refused and in individuals who have received appropriate ICD shocks despite optimal medical therapy.[1]

Short QT syndrome: ICD implantation is recommended in patients who are survivors of cardiac arrest and/or documented sustained ventricular tachycardia. Whilst evidence from a primary preventative perspective remains uncertain and decisions should be adjudicated on a case-by-case basis.

Brugada syndrome: The only efficacious therapy to reduce the risk of SCD is an ICD and is recommended in survivors of cardiac arrest, individuals with documented ventricular tachycardia or fibrillation, and those presenting with syncope and have demonstrated a type 1 BrS pattern on ECG. Medications such as quinidine should be considered in individuals who have demonstrated ventricular arrhythmias, electrical storms and those who have a contraindication to ICD insertion or refuse it for personal reasons. Epicardial ablation of the right ventricular outflow tract (RVOT)/

right ventricle (RV) has emerged as a promising tool for the management of the disease.[58]

Catecholaminergic polymorphic ventricular tachycardia: Therapy includes betablockers, which may be combined with flecanide in refractory cases. Invasive options also include left cardiac sympathetic denervation and may be considered based on symptoms and response to medical therapy. ICD therapy is recommended in survivors of cardiac arrest and in those who are not responding to medical therapy. However, unique to the adrenergic surges that ICD shocks can generate, the substrate for VA in individuals with CPVT may be further perpetuated, and ICDs should be programmed with long delays before delivering shocks.

Hypertrophic cardiomyopathy: Risk predictor tools are available in few inherited cardiac conditions. In HCM, the ESC 5-year risk score offers a structured approach to SCD prevention and has been widely adopted in clinical practice. It incorporates a number of risk factors and provides an indication to the responsible clinician as to whether an ICD is not indicated, may be considered or should be considered (https://doc2do.com/hcm/webHCM.html).[59] Our understanding of an individual's risk of SCD continues to evolve and practice varies from Europe to North America, where the findings of an apical aneurysm, reduced left ventricular systolic function, and the presence of extensive late gadolinium enhancement are incorporated into risk-stratification algorithms in individuals with HCM.[60] Suppression of VA may be achieved by monotherapy or combination therapy with betablockers, calcium channel antagonists or amiodarone. In select cases with a clearly identifiable focus, electrophysiological studies (EPS) and ablation may be considered.

A subgroup of patients with HCM may reveal an obstructive phenotype due to asymmetrical LV hypertrophy, which typically results in turbulence of blood flow across the left ventricular outflow tract (LVOT), and manifests itself clinically with symptoms of dyspnea, angina, pre-syncope, syncope and even sudden death. The main stay of medical therapy to treat LVOT obstruction include, betablockers and disopyramide; whilst invasive strategies which include alcohol septal ablation and surgical myectomy are considered on a case-by-case basis, and are largely driven by anatomical and physiological suitability. Whilst, symptoms and quality of life may be improved, none of these therapies have demonstrated a prognostic benefit in reducing risk of SCD.

Arrhythmogenic cardiomyopathy: Risk stratification in AC has been evolving and in 2019, similar to HCM, a risk calculator was proposed to guide clinical practice.[61] The calculator uses seven non-invasive parameters that are readily available to the clinician. Rather than predicting the risk of SCD, however, the model estimates the risk of sustained ventricular arrhythmias as a surrogate for life-threatening events.

1.11 Emergency response planning and secondary prevention

Despite primary preventative strategies to mitigate SCA and SCD, effective secondary prevention strategies which include timely recognition of a cardiac arrest, commencing cardiopulmonary resuscitation (CPR), early defibrillation and appropriate post resuscitation care are associated with improved survival, enhanced cardiac and neurological outcomes and in turn, a better quality of life.[62] Contemporary studies suggest that prompt CPR and early defibrillation can be

associated with survival rates of up to 89%, particularly in younger, athletic individuals.[63] The time from cardiac arrest to the delivery of first shock using an automated electrical defibrillator (AED) is critically important. Public access AED programmes aim to reduce this collapse-to-shock time to less than 5 minutes. A survey of 1710 US high schools with an on-site AED programme demonstrated a survival benefit with early defibrillation. Of the 36 cases of cardiac arrest observed amongst young students and older non-students, 64% survived to hospital discharge with mean collapse-to-shock time of 3.6 minutes.[24] Public access to AEDs as a part of emergency response planning has shown to be effective, and major sporting and cardiac organisations recommend implementation of such programmes in all sporting venues and fitness centres.

The combination of increasing education and training regarding resuscitation techniques and by increasing the uptake of automated external defibrillators (AEDs) particularly in community settings, should continue to be part of societies emergency response planning.

In elite sport, a recent study highlighted the disparity in AED provision and training between premiership clubs in contrast to lower division clubs.[64] This issue is further exemplified at the grassroot level and in the general population. Potential solutions have included the utility of mobile phone applications, which alert nearby volunteer first-responders about out of hospital cardiac arrests and the location of the nearest defibrillator. Such technology has demonstrated an increased survival to hospital discharge.[65]

Chapter 2: Context of proposed work

SCD in young individuals aged 14-35 has been attributed to a diverse spectrum of inherited and acquired cardiac conditions which express great heterogeneity in their clinical manifestations. However, significant variations exist in the reported incidence and causes of cardiac mortality in the young globally. This is particularly relevant in the United Kingdom (UK) where there is a lack of large-scale population-based studies addressing this issue.

In the setting of a sudden unexpected cardiac death, the autopsy, in the absence of significant pre-morbid medical conditions or investigations, plays a pivotal role in establishing a diagnosis of an inherited cardiac condition, may lead to the discovery of new disease entities or new variants of already known entities and of paramount importance, guides the onward evaluation in surviving members of the family.

More broadly, in the general population, identifying individuals who may be harbouring quiescent cardiac conditions, which may be genetic or in the context of the novel COVID-19 pandemic, may be acquired, and are associated with SCD is challenging. In the UK, this typically involves attendance at a voluntary primary preventative cardiac screening initiative, which may be mandatory in the case of elite athletes and targeting high risk groups with either established CV symptoms or a family history of premature CV morbidity and/ or mortality. Finally, an integral theme which is omnipresent in my thesis reflects my period in clinical research being closely intertwined with the COVID-19 pandemic, which naturally raised concern around the potential for inflammatory cardiac conditions in young individuals

including athletes, with the potential for an arrhythmogenic substrate and propensity for VA, particularly during high intensity exercise and competitive sport.

2.1 **Aims of the thesis**

The aims of my thesis are to address three integrated themes in the field of young SCD.

2.1.1 The first theme linked to national mortality data from the Office for National Statistics (ONS) in England and Wales

(i) Will investigate the incidence and aetiology of YSCD over two decades since the incorporation of ICD-10 codes into clinical practice.

(ii) Will establish temporal trends in cardiac mortality in young individuals.

(iii) Twinned with the above aims, I will draw inferences from the largest global SCD autopsy registry.

2.1.2 The second theme linked to autopsy data from the largest systematic SCD registry globally.

(iv) Will specifically address the causes and circumstances of SCD in female athletes who are a relatively understudied group.

(v) Will report on the circumstances of SCD in young individuals whose autopsy was consistent with HCM.

(vi) Will report on the prevalence and nature of mitral valve (MV) abnormalities in SCD victims with post-mortem findings consistent with HCM and idiopathic left ventricular hypertrophy (ILVH).

(vii) Examine the presenting features, and circumstances of death in a large cohort of decedents who experienced SCD in the community and were subsequently diagnosed with myocarditis at autopsy. This period will include a 24-month period which overlapped with the COVID-19 pandemic in the UK.

2.1.3 The third theme will address novel considerations brought upon us by the COVID-19 pandemic, in the arena of cardiac screening, specifically concerns around inflammatory cardiac sequalae and the risk of adverse cardiac outcomes including SCA/SCD in elite sport.

(viii) Aim to address the prevalence and diagnostic significance of de-novo 12-lead ECG changes following COVID-19 infection in elite soccer players.

2.2 **Hypotheses**

The nature of the research carried out lends itself to the following hypotheses:

1) An accurate representation of the incidence and aetiology of cardiac and sudden cardiac death in England and Wales is crucial for guiding health care policy makers in allocating resources effectively.
2) SADS is an underestimated cause of death in young individuals, with an increasing incidence particularly since the awareness and referral pathways around expert histological evaluation.
3) Continued variation and ambiguity exist in the reported cause of death in the young based on large scale population level data.

4) Differences exist in the causes and circumstances of SCD based on sex and age.
5) Mitral valve abnormalities are more common in individuals with HCM than those with ILVH and may be considered as additional macroscopic features to differentiate between these entities, that are not only common causes of SCD, but can be extremely challenging to differentiate between.
6) Establishing a diagnosis of myocarditis antemortem is challenging. However, missed opportunities for timely diagnosis and intervention in cases of myocarditis may exist and contribute to the risk of SCD in individuals who are subsequently diagnosed at autopsy.
7) No significant increment in mortality from myocarditis cases were observed at the Cardiac Risk in the Young Centre for Cardiac Pathology (CRY-CCP) during the COVID-19 pandemic.
8) A cardiac screening programme in elite athletes, based on a clinical evaluation and 12-lead ECG with availability of serial ECGs for comparison is able to detect athletes at risk of inflammatory cardiac sequelae due to SARS-CoV-2 infection.

Chapter 3: Understanding Cardiac and Sudden Death in Young Individuals: Novel Insights from the Office for National Statistics (ONS) in England and Wales and Cardiac Risk in the Young (CRY), 21 years in Review

3.1 Abstract

Background: Previous data from the Office for National Statistics (ONS) reported an incidence of sudden cardiac death (SCD) in the young of 1.8 per 100,000 per year.

Aim: We aimed to report on the incidence of cardiac and sudden cardiac death in individuals under the age of 35 years in England and Wales between 2001 and 2021, with the goal of identifying any shifts in incidence and causes of SCD.

Methods: Annual ONS mortality data relating to cardiovascular (CV) and possible CV deaths in individuals aged <35 years was analysed according to international classification of diseases-10 (ICD-10) codes. We classified these deaths into four classes; A1: definite cardiac deaths with no structural heart disease identified at post-mortem (consistent with sudden arrhythmic death syndrome, SADS), A2: definite cardiac deaths with structural heart disease identified at post-mortem, A3: definite cardiac deaths with indeterminate cause, and B: possible cardiac deaths. We calculated incidence rates based on ONS census data of the annual resident population for individuals under 35 years of age in England and Wales. Inferences were drawn from the Cardiac Risk in the Young Centre for Cardiac Pathology (CRYCCP) nationwide registry of sudden cardiac death victims.

Results: Between 2001-2021, there was a mean of 414.19 (SD 27.45) definite cardiac deaths per annum (classes A1+A2+A3). Based on annual census population estimates (mean 24,68, 494.04 ± 78,880.18), this equates to an incidence of cardiac and SCD in the young of 1.68 per 100,000 individuals per annum. The most prevalent cardiac conditions were ischaemic heart disease (28.4%), cardiomyopathies (25.9%), SADS (21.8%), myocarditis (10.7%), aortopathy including dissection (4.9%), valvular heart disease (3.4%) and hypertensive heart disease (1.7%). There was a mean of 573.28 (SD 76.67) deaths per annum which may have signified a proportion of possible cardiac deaths (class B) and comprised primarily of deaths from ill-defined and unspecified causes of mortality (33.5%), epilepsy (32.4%), sudden infant death syndrome (24.2%) and drowning (7%). A male preponderance was observed for both definite and possible cardiac deaths; male to female ratios of 2.31:1 and 1.68:1, respectively. An overall downward trend in total definite and possible cardiac mortality was noted. The incidence of SADS increased till 2010 by 8.5% annually ($p<0.001$) and mortality attributed to structural heart disease demonstrated a significant downward trend by 2.5% per year ($p<0.001$).

Conclusions: The overall incidence of young cardiac and sudden cardiac death over 20 years in England and Wales is 1.68/100,000/year with a decreasing trend in mortality over the study period. The incidence of SADS is on the rise whilst a decline in structural causes was noted. The impact of cardiac and SCD in young individuals underscores the need to expand and sustain access to preventative strategies and targeted risk management.

3.2 Introduction

Accurate representation of the incidence and aetiology of cardiac and sudden cardiac death (SCD) is critical in managing resource allocation by health policy makers to address issues such as screening for potentially lethal conditions, standardisation of post-mortem evaluations and improvement in resuscitation facilities. This is particularly relevant in the young population (<35 years of age), where the impact of sudden death is amplified by the significant life years lost, often in the absence of any warning signs.

In the absence of systematic registries, the precise quantification of SCD remains challenging. Despite the establishment of international definitions for SCD and advances in data collection, studies still demonstrate significant heterogeneity with disparate age cutoffs and diverse methodology. Several population-based studies have provided estimates of the incidence of SCD in the young ranging from 1 to 10 deaths per 100,000 per year. Moreover, discrepancies exist relating to the causal pathology of SCD in the young, with earlier studies emphasizing the predominance of structural heart disease such as hypertrophic cardiomyopathy (HCM), but contemporary studies shifting the emphasis towards structurally normal hearts and sudden arrhythmic death syndrome (SADS), commonly attributed to ion-channelopathies.

Papadakis et al., reported the incidence of cardiac and SCD in the young in England and Wales to be 1.8 per 100,000 per year between 2002 and 2005 based on mortality data from the Office for National Statistics (ONS).[13] Furthermore, based on this data 12-young cardiac deaths per week are estimated to occur on a weekly

basis in the United Kingdom, which takes into account estimated mortality data from Scotland and Northern Ireland. This seminal study by Papadakis et al.,[13] has supported initiatives, for cardiovascular screening in the UK in young individuals who may be harboring quiescent cardiac conditions associated with young SCD.

Since initial publication of this data[13], there have been several changes in the UK population demographics, advancement in medical diagnostics and therapeutic strategies, preventative measures which include screening programmes largely driven by charitable initiatives such as by Cardiac Risk in the Young (CRY) which has now screened in excess of 250,000 young individuals in the UK over the past two decades, as well as a greater emphasis on expert cardiac histopathologists performing post-mortem examinations to elucidate the exact cause of young SCD.

3.3 **Aim**

The aim of this study was to investigate the incidence of cardiac and SCD among individuals under 35 years of age in England and Wales from 2001 to 2021, inclusive. Importantly, we aimed to identify any temporal trend shifts in the incidence and causes of death, which has not been previously reported using large scale population data from the Office for National Statistics (ONS).

3.4 **Personal contribution**

I formulated the study hypothesis, obtained, reviewed and analysed a large dataset from the ONS and the CRY-CCP sudden death database, performed quality control, statistical analysis, manuscript preparation and subsequent manuscript revisions. RTB presented part of the findings from this work at national and international

meetings (mortality data specifically from 2013 to 2021) with plans to release the findings from the entire dataset at international meetings in 2024.

3.5 **Methods**

3.5.1 ONS Mortality Statistics

ONS mortality statistics for England and Wales for 21 consecutive years (2001 to 2021) were obtained and analysed according to year, age (<35 years), gender, and cause of death. This was facilitated by utilising annual mortality statistics from 21st century mortality files (2001-2012) and Nomis ONS software (2013-2021), followed meticulous merger of datasets. Mortality data utilised for this study related to conditions directly leading to death as recorded at the time of certification and registration by a medical practitioner using the Medical Certificate of Cause of Death (MCCD) form- part 1, which is compatible with that recommended by the World Health Organization (WHO). Data will be made available upon reasonable request to the corresponding author.

3.5.2 Information collected at death registration

In England and Wales following an individual's demise, mortality statistics are based on information recorded when deaths are certified and registered. This usually occurs when a medical practitioner competes the medical certificate cause of death (MCCD), which is taken by a relative to the medical registrar. It is usual practice for this process to occur within five days of death. In certain situations, where a MCCD cannot be issued immediately e.g., in the setting of sudden unexpected death, cases are referred to the coroner (table 3). The coroner will decide on whether the cause of

death is clear, if a post-mortem is required or whether an inquest is required. If the cause of death is clear, the certifying doctor, who must have seen the deceased during the last two weeks of life will facilitate completion of a MCCD which will be utilised by ONS to code the death. Simultaneously, the coroner will issue a certificate to the registrar stating a post-mortem is not required. Often the coroners will recommend a comprehensive post-mortem examination to elucidate the cause of death. In all cases of sudden unexpected deaths in England and Wales, a post-mortem is required and recommended by the coroner. After the post-mortem, the coroner will release the body for funeral. However, if the cause of death is still unknown, or perhaps the death might have been violent or an unnatural death the coroner will hold an inquest. These findings from the above stringent processes accordingly are used in coding ONS mortality statistics.

Table 3: Reasons for referral to the coroner
1. The cause of death is unknown e.g., suspected sudden unexpected cardiac death
2. The deceased was not seen by the certifying doctor either after death or within the 14 days before
3. The death was violent, unnatural or suspicious
4. The death may have been due to an accident
5. The death may have been due to self-neglect or neglect by others
6. The death may have been due to an industrial disease or related to the deceased's employment
7. The death occurred during an operation or before recovery from the effects of an anaesthetic
8. The death may have been a suicide

9. The death occurred during or shortly after detention in police or prison custody
10. There was no doctor available who was legally qualified to certify the death

3.5.3 ONS Software Updates and ICD-10 Codes

International Classification of Diseases (ICD) 10th Revision code (ICD-10) coding was introduced in January 2001 and has undergone amendments as authorized by the WHO. Between 2001 and 2010, Mortality Medical Data System (MMDS) ICD-10 version 2001.2 software was utilized to code cause of death. From January 2011, this was updated to version 2010. Furthermore, from January 2014, coding software was updated to IRIS version 2013. In accordance with ONS, these amendments in coding and updates in software, and updates in final cause of deaths, reflect minor alterations in overall mortality data published by ONS in the past two decades, including data previously reported elsewhere.[13]

3.5.4 Geographical considerations

For the purpose of this study, data only relates to England and Wales. Naturally this lends itself to include some deaths of residents of other UK countries and potentially visitors, where the deaths occurred in England and Wales. Based on mortality statistics published by the ONS, between 2015 to 2021 the percentage of deaths of residents outside of England and Wales is estimated between 0.1% to 0.2%.

3.5.5 Mortality codes

Following scrutiny of the entire ICD-10 compendium, classification codes considered to represent cardiac deaths were selected by authors (R.T.B., M.P., S.S., E.R.B., and M.N.S.) (tables 4-7). To ensure consistency, we employed a similar

methodology as previously reported[13] and further subdivided causes of death into four classes: class A1 – definite cardiac deaths with no structural heart disease identified at post-mortem compatible with a diagnosis of sudden arrhythmic death syndrome (SADS); class A2 – definite cardiac deaths with structural heart disease identified at post-mortem comprising sudden and non-sudden deaths with likely causation by structural heart disease; class A3 – definite cardiac deaths with indeterminate cause comprising sudden and non-sudden deaths where the presence or absence of underlying heart disease was either unrecorded or ill-defined; and class B – possible cardiac deaths. Deaths attributed to class B were a reflection that these deaths may represent potential misclassifications in cardiac mortality, with an emphasis on SADS, where the heart was structurally normal at autopsy, or the death occurred whilst drowning or in the context of a reported seizure. Details relating to the exact ICD-10 codes utilized in this analysis are listed in table 4 to table 7.

Table 4 ICD-10 codes utilised to form Class A1- cardiac death with normal heart. WPW: Wolff-Parkinson-White.

R96	Other sudden death, cause unknown
I44.0	Atrioventricular block, first degree
I44.1	Atrioventricular block, second degree
I44.2	Atrioventricular block, complete
I44.3	Other and unspecified atrioventricular block
I45.5	Other specified heart block
I45.6	Pre-excitation syndrome (WPW)
I45.8	Other specified conduction disorders

I45.9	Conduction disorder, unspecified
I46.1	Sudden cardiac death, so described
I46.9	Cardiac arrest, unspecified
I47.0	Re-entry ventricular arrhythmia
I47.1	Supraventricular tachycardia
I47.2	Ventricular tachycardia
I49.0	Ventricular fibrillation and flutter
I49.9	Cardiac arrhythmia, unspecified
R00	Abnormalities of heart beat
R00.1	Bradycardia, unspecified
R55	Syncope and collapse

Table 5 ICD-10 codes utilised to form Class A2- cardiac death with structural disease	
I01.1	Acute rheumatic endocarditis
I05.2	Mitral stenosis with insufficiency
I06.1	Rheumatic aortic insufficiency
I06.8	Other rheumatic aortic valve diseases
I07.0	Tricuspid stenosis
I09.8	Other specified rheumatic heart diseases
I11.0	Hypertensive heart disease with congestive heart failure
I11.9	Hypertensive heart disease without congestive heart failure
I21.9	Acute myocardial infarction, unspecified
I24.1	Dressler's syndrome
I24.8	Other forms of acute ischaemic heart disease

I24.9	Acute ischaemic heart disease, unspecified
I25.0	Atherosclerotic cardiovascular disease, so described
I25.1	Atherosclerotic heart disease
I25.5	Ischaemic cardiomyopathy
I25.8	Other forms of chronic ischaemic heart disease
I25.9	Chronic ischaemic heart disease, unspecified
I34.0	Mitral (valve) insufficiency
I34.1	Mitral (valve) prolapse
I34.8	Other nonrheumatic mitral valve disorders
I34.9	Nonrheumatic mitral valve disorder, unspecified
I35.0	Aortic (valve) stenosis
I35.1	Aortic (valve) insufficiency
I35.2	Aortic (valve) stenosis with insufficiency
I35.8	Other aortic valve disorders
I35.9	Aortic valve disorder, unspecified
I37.1	Pulmonary valve insufficiency
I37.8	Other pulmonary valve disorders
I37.9	Pulmonary valve disorder, unspecified
I40.0	Infective myocarditis
I40.1	Isolated myocarditis
I40.9	Acute myocarditis, unspecified
I51.4	Myocarditis, unspecified
I42.0	Dilated cardiomyopathy
I42.1	Obstructive hypertrophic cardiomyopathy

I42.2	Other hypertrophic cardiomyopathy
I42.3	Endomyocardial (eosinophilic) disease
I42.4	Endocardial fibroelastosis
I42.5	Other restrictive cardiomyopathy
I42.6	Alcoholic cardiomyopathy
I42.8	Other cardiomyopathies
I42.9	Cardiomyopathy, unspecified
I51.1	Rupture of chordae tendinae, not elsewhere classified
I71.0	Dissection of aorta [any part] (Marfans)
I71.1	Thoracic aortic aneurysm, ruptured (Marfans)

Table 6 ICD-10 codes utilised to form Class A3- cardiac death with an indeterminate cause	
I44.7	Left bundle-branch block, unspecified
I45.2	Bifascicular block
I45.4	Nonspecific intraventricular block
I50.0	Congestive heart failure
I50.1	Left ventricular failure
I50.9	Heart failure, unspecified
I51.6	Cardiovascular disease, unspecified
I51.8	Other ill-defined heart diseases
I51.9	Heart disease, unspecified
I99	Other and unspecified disorders of circulatory system
R57.0	Cardiogenic shock

I10	Essential (primary) hypertension

Table 7 ICD-10 codes utilised to form Class B- possible cardiac death. SIDS: sudden infant death syndrome	
R99	Other ill-defined and unspecified causes of mortality
R95	SIDS
G40.6	Grand mal seizures, unspecified (with or without petit mal)
G40.9	Epilepsy, unspecified
G41.8	Other status epilepticus
G41.9	Status epilepticus, unspecified
J46	Status asthmaticus
R06	Abnormalities of breathing
R06.8	Other and unspecified abnormalities of breathing
R09.8	Other specified symptoms and signs involving the circulatory and respiratory systems
R56	Convulsions, not elsewhere classified
W65	Drowning and submersion while in bathtub
W66	Drowning and submersion following fall into bathtub
W67	Drowning and submersion while in swimming pool
W68	Drowning and submersion following fall into swimming pool
W69	Drowning and submersion while in natural water
W70	Drowning and submersion following fall into natural water
W73	Other specified drowning and submersion
W74	Unspecified drowning and submersion

3.5.6 Statistical analysis

Statistical analysis was conducted using R programming language version 4.2.2. Data are expressed in means and standard deviations. Mortality data was consolidated, and incidence rates per 100,000 individuals were calculated using extensive datasets for mid-year estimates of the annual resident population of England and Wales from ONS census data. The most updated mid-year population estimates for each year were utilized, which take into account births, deaths, net migration and ageing of the population. The chi-squared test or Fisher's exact test was used to analyse group differences of proportions.

For modelling purposes, time was defined as years since 2001. Incidence rates of each category was further analysed and modelled using Poisson log-linear models considering the number of cases in each category as the response variable and the mid-year population as an offset. Time since 2001 was considered the independent variable. The piece-wise function of time was considered when cases showed non-linear trends.

3.6 **Results**

3.6.1 Incidence of cardiac and sudden death

Over the twenty-one-year period, there was a mean of 414.19 (SD 27.45) definite cardiac deaths (classes A1 + A2 + A3) per annum, equating to 7.96 deaths per week in England and Wales (table 8). Based on annual ONS census data relating to the resident population of England and Wales during this period (mean 24,681,494.04 ±

78,880.18), the incidence of cardiac and SCD in the young was 1.68 (SD 0.11) per 100,000 individuals per year. The greatest contribution to the definite cardiac deaths arose from individuals with a structurally abnormal heart (class A2), with a mean number of deaths per annum of 309.9 (SD 42.61), followed by SADS 90.09 (SD 24.84) and finally cardiac deaths with an indeterminate cause (class A3) with a mean number of deaths per annum of 14.19 (SD 5.37).

In terms of possible cardiac deaths (Class B), there was a mean of 573.28 (SD 76.67) deaths per annum, equating to 11.02 deaths per week, and with an incidence of 2.32 (SD 0.31) deaths per 100,000 individuals per annum in England and Wales.

Table 8: Number of deaths according to class per year. SD: standard deviation

Class	Number of deaths per year																					Total	Mean deaths	Mean mortality rate
	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	No. Deaths	per annum (SD)	per 100000 per annum
A1	58	51	56	57	62	65	68	81	78	121	105	100	112	110	114	106	101	103	128	113	103	1892	90.09 (24.84)	0.36 (0.10)
A2	361	376	386	341	333	383	342	321	320	315	284	287	303	278	286	268	271	270	249	254	280	6508	309.9 (42.61)	1.25 (0.17)
A3	18	21	23	20	23	19	10	9	20	20	13	10	7	14	11	9	9	10	10	10	12	298	14.19 (5.37)	0.05 (0.02)
A1+A2+A3	437	448	465	418	418	467	420	411	418	456	402	397	422	402	411	383	381	383	387	377	395	8698	414.19 (27.45)	1.67 (0.11)
B	803	621	607	610	648	591	637	638	598	549	561	507	555	586	531	551	469	523	501	475	478	12039	573.28 (76.67)	2.32 (0.31)
Total	1240	1069	1072	1028	1066	1058	1057	1049	1016	1005	963	904	977	988	942	934	850	906	888	852	873	20737	987.47 (94.75)	4.00 (0.38)

3.6.2 Aetiology of cardiac and sudden death

Over 21-years, the most prevalent conditions were ischaemic heart disease (28.4%), cardiomyopathies (25.9%), SADS (21.8%), myocarditis (10.7%), dissection of the aorta including in individuals with Marfans syndrome (4.9%), valvular heart disease (3.4%) and hypertensive heart disease (1.7%) (figure 4). Within the ischaemic heart

disease category, 14.4% of deaths were attributed to acute myocardial infarction. In the heterogenous cardiomyopathy group, dilated cardiomyopathy (9.4%) was the most prevalent, followed by cardiomyopathy unspecified (7.0%), hypertrophic cardiomyopathy (5.3%) and other cardiomyopathies (4.2%). It is worth acknowledging that entities such as arrhythmogenic cardiomyopathy continue to be classified under I42.8 other cardiomyopathies or 142.9 cardiomyopathy, unspecified.

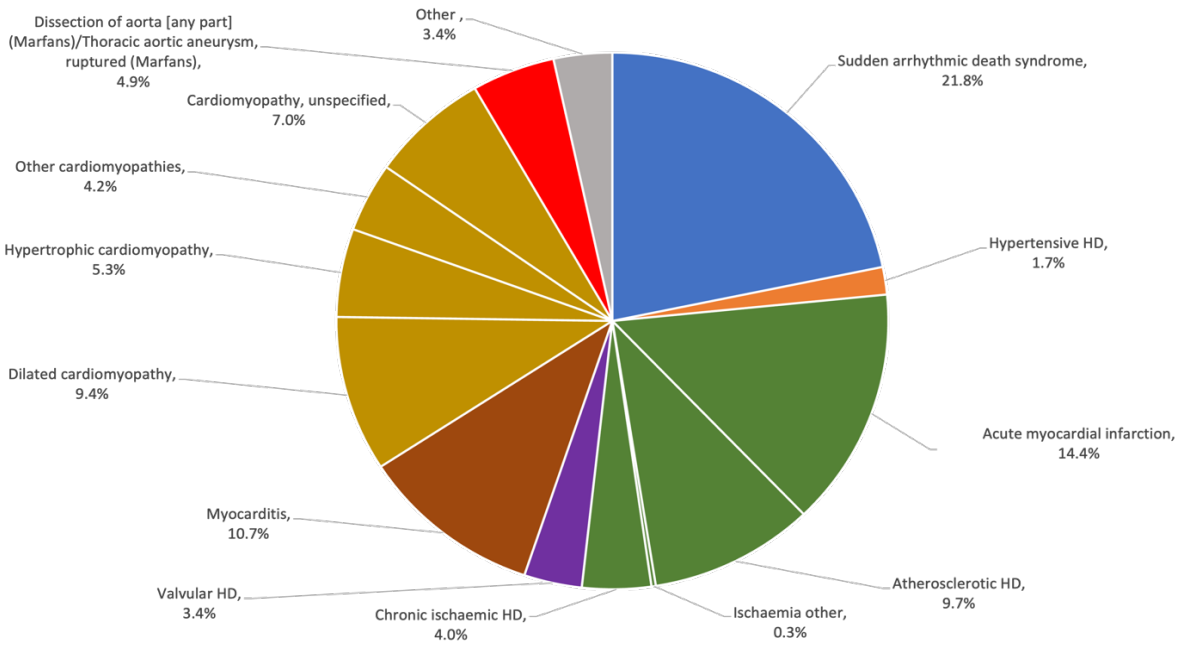


Figure 4: Causes of cardiac death in the young expressed as % of total number of definite cardiac deaths (A1+A2+A3). HD, heart disease.

3.6.3 Aetiology of possible cardiac deaths

The most prevalent conditions in this category included ill-defined and unspecified causes of mortality (33.5%), epilepsy (32.4%), sudden infant death syndrome (24.2%) and drowning (7%) (figure 5). A smaller proportion died due to grand mal

seizures or status epilepticus (2.8%), abnormalities of breathing or status asthmaticus (1.5%) and convulsions, not classified elsewhere (0.1%).

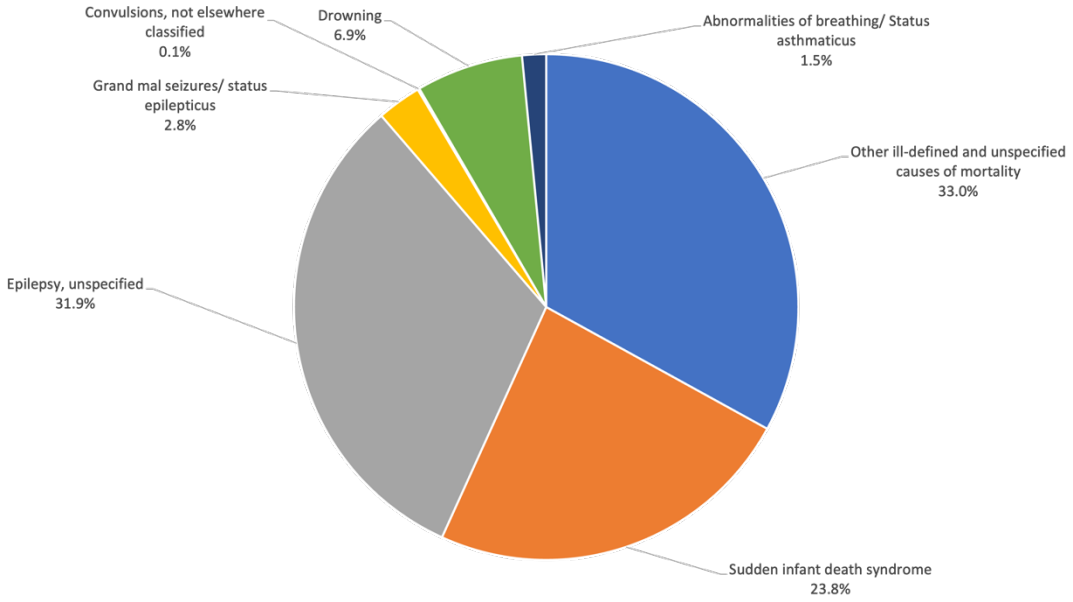


Figure 5: Causes of death in the young expressed as percentages of the total number of deaths in Class B (possible cardiac deaths).

3.6.4 Temporal trends in mortality

3.6.4.1 Sudden arrhythmic death syndrome- class A1

Based on absolute mortality numbers and mid-year census population data, incidence rates for class A1 demonstrated an upward trend (Figure 6).

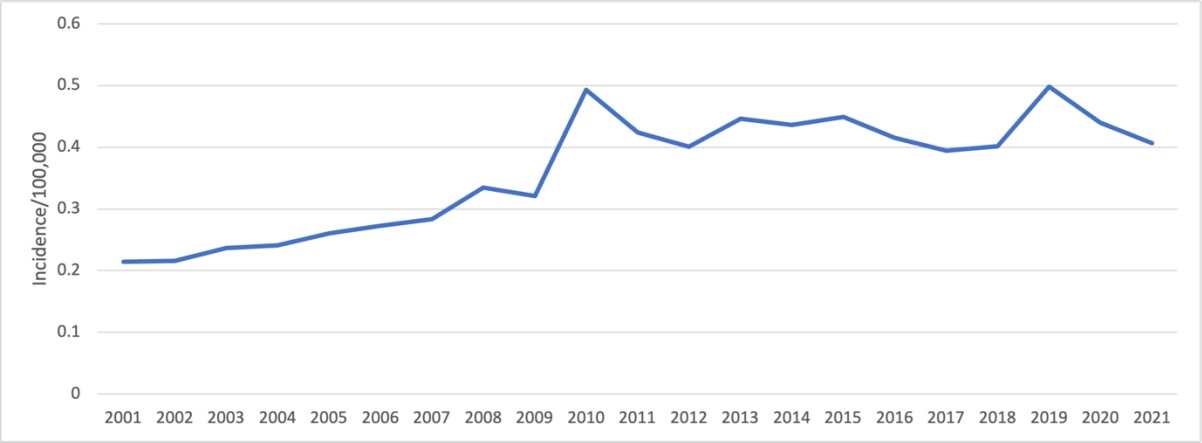


Figure 6: Overall incidence trends in class A1.

Table 9 demonstrates the parameter estimates of the fitted log-linear model for category A1. The fitted model included a significant piece-wise function for time after 2010 (delta deviance = 22, df = 1), as cases demonstrated a non-linear trend. The model demonstrated an increasing incidence rate in SADS up until 2010, after which the incidence rates flattened thereafter till 2021 (figure 7). The estimated rate ratio for the period up to 2010 was 1.085 (95% CI: 1.062 - 1.108), indicating an 8.5% (95% CI: 6.2% - 10.8%) annual increase in the incidence rates up to 2010; p value < 0.001. The estimated rate ratio after 2010 was 1.006 (95% CI: 0.992 - 1.020), indicating a 0.6% increase (95%CI: -0.8% - 2%); p value = 0.424. Although the p value is not significant, delta deviance is significant (delta deviance = 22, df = 1).

Table 9 Parameter estimates of the fitted log-liner model for Class A1.

	Estimate	Std. Error	z value	Pr(>|z|)
Intercept	-12.401229	0.044646	-277.768	<0001
Time up to 2010	0.081161	0.010974	7.396	< 0001
Time after 2010	0.005733	0.007165	0.800	0.424

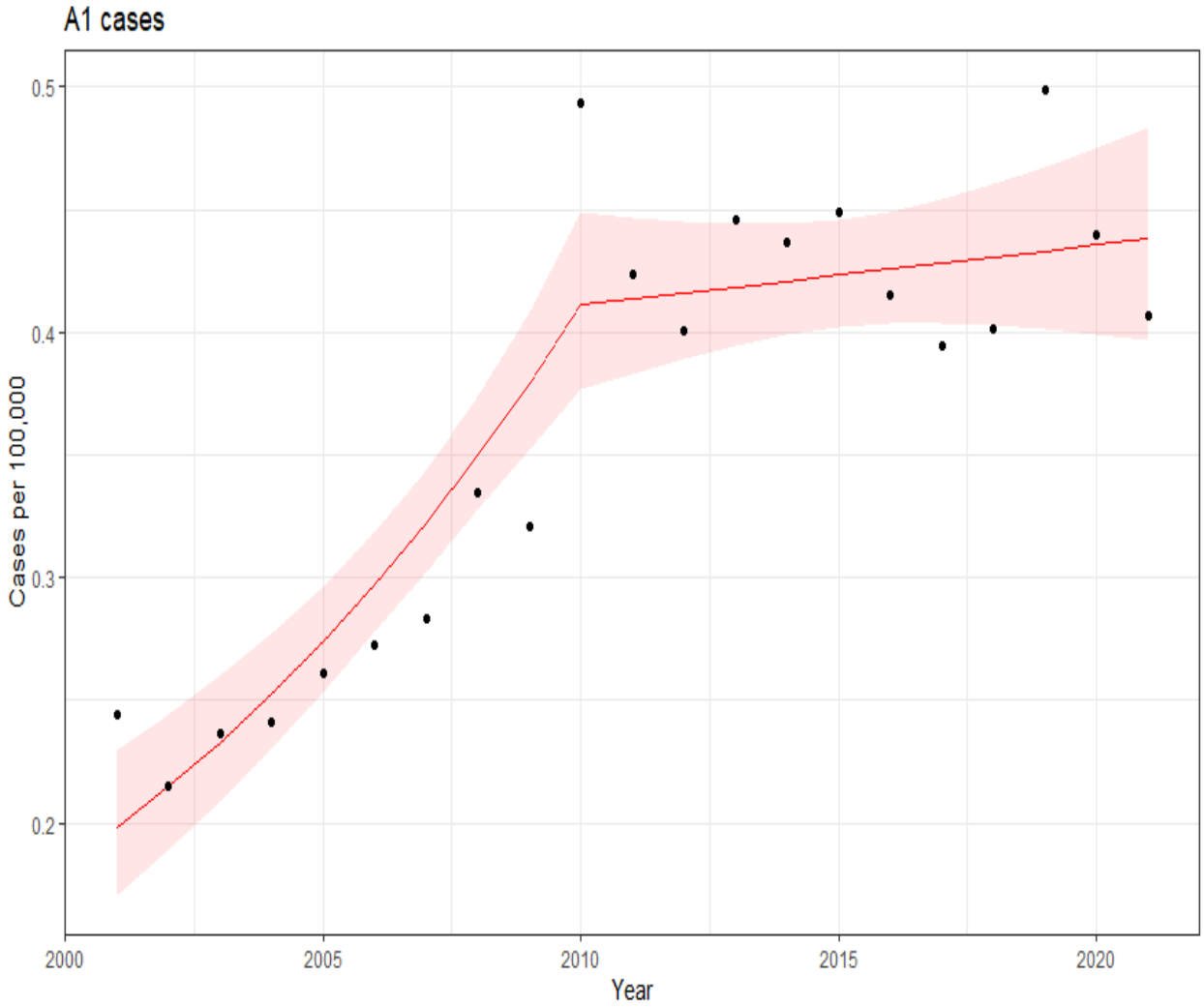


Figure 7: Incidence rates for Class A1 modelled using Poisson log-linear model. The number of cases in Class A1 was utilised as the response variable and the mid-year population as an offset. Time since 2001 was considered the independent variable. The piece-wise function of time was considered when cases showed non-linear trends. The solid red line represents the model output, and the respective 95% confidence intervals either side demonstrated by the shaded area. The black dots correlate with absolute mortality counts.

Table 10 demonstrates the estimated incidence using fitted log-linear mode for the category A1 cases in each year as depicted in figure X. Overall, the incidence rate was 0.20% (95% CI: 0.17 - 0.23) in 2001 and it rose to 0.41% (95% CI: 0.38 - 0.45) in 2010. Thereafter, there has been a more gradual increment to 0.44% (95%CI: 0.40 - 0.48) in 2021.

Table 10: Estimated incidence rates from 2001 to 2021 for Class A1.

	Year	Incidence	95% CI lower margin	95% CI upper margin
1	2001	0.20	0.17	0.23
2	2002	0.21	0.19	0.24
3	2003	0.23	0.21	0.26
4	2004	0.25	0.23	0.28
5	2005	0.27	0.25	0.30
6	2006	0.30	0.28	0.32
7	2007	0.32	0.30	0.34
8	2008	0.35	0.33	0.37
9	2009	0.38	0.35	0.41
10	2010	0.41	0.38	0.45
11	2011	0.41	0.38	0.45
12	2012	0.42	0.39	0.44
13	2013	0.42	0.39	0.44
14	2014	0.42	0.40	0.44
15	2015	0.42	0.40	0.45
16	2016	0.43	0.40	0.45

17	2017	0.43	0.40	0.45
18	2018	0.43	0.40	0.46
19	2019	0.43	0.40	0.47
20	2020	0.44	0.40	0.48
21	2021	0.44	0.40	0.48

3.6.4.2 Cardiac death with structural disease – class A2

Based on absolute mortality numbers and mid-year census population data, incidence rates for class A2 demonstrated a downward trend (Figure 8).

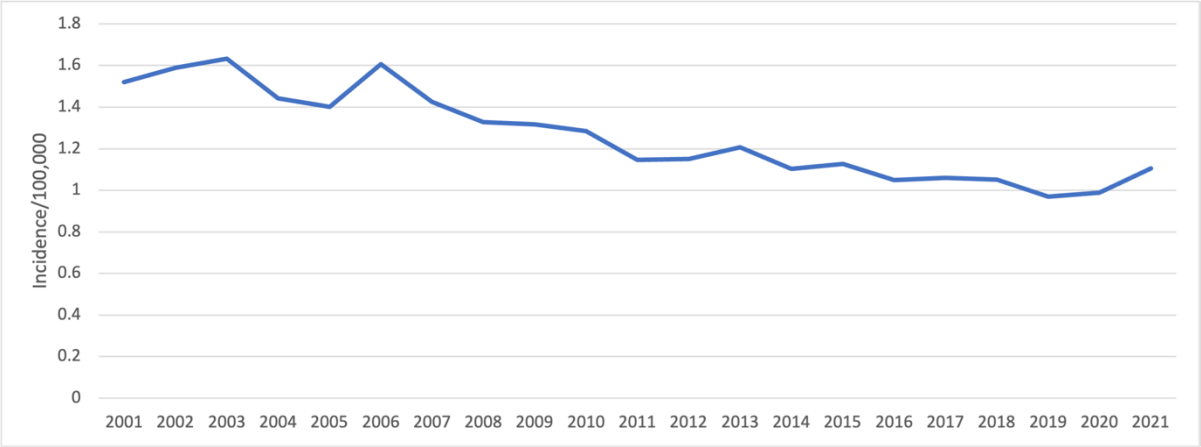


Figure 8: Overall incidence trends in class A2.

Table 11 demonstrates the parameter estimates of the fitted log-linear model for class A2. The model (figure 9) demonstrates a significant downward trend in incidence rates over 21-years. The estimated rate ratio of the downwards trend was 0.975 (95% CI: 0.971 - 0.979) per year, indicating a 2.5% (95% CI: 2.1% - 2.9%) incidence rate reduction per year over the time period; p value <0.001.

Table 11: Parameter estimates of the fitted log-linear model for class A2 cases.				
	Estimate	Std. Error	z value	Pr(>|z|)
Intercept	-11.037944	0.022718	-485.87	<0001
Time since 2001	-0.025456	0.002058	-12.37	<0001

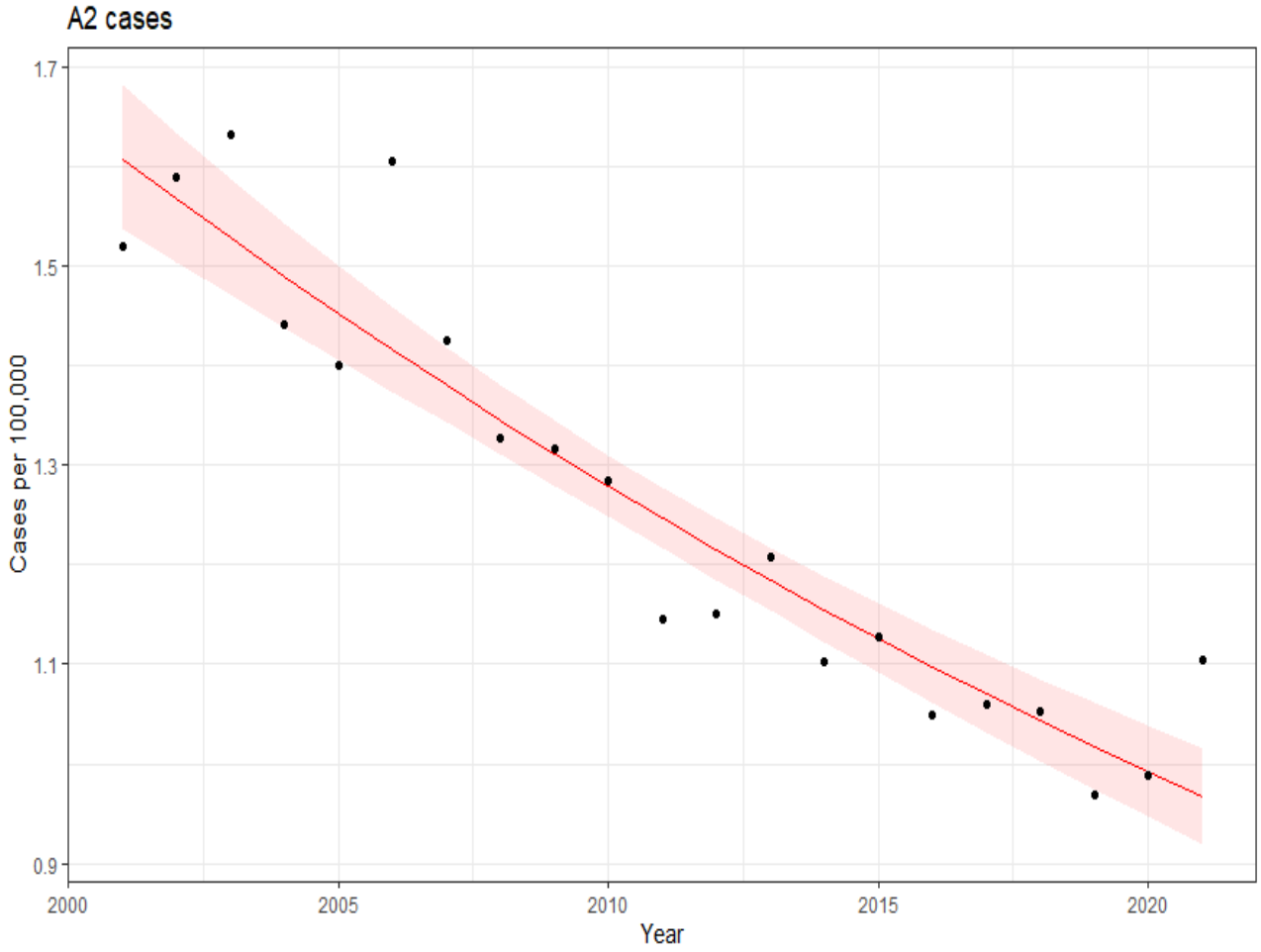


Figure 9: Incidence rates for Class A2 modelled using Poisson log-linear model. The number of cases in Class A2 was utilised as the response variable and the mid-year population as an offset. Time since 2001 was considered the independent variable. The solid red line represents the model output, and the respective 95% confidence intervals either side demonstrated by the shaded area. The black dots correlate with absolute mortality counts.

Table 12 demonstrates the estimated incidence using fitted log-linear mode for the category A2 cases in each year as depicted in figure 9. Overall, the incidence rate was 1.61 (95% CI: 1.54 – 1.68) in 2001 and it has reduced to 0.97 (95% CI: 0.92 – 1.02) in 2021.

Table 12: Estimated incidence rates from 2001 to 2021 for Class A2.

	Year	Incidence	95% CI lower margin	95% CI upper margin
1	2001	1.61	1.54	1.68
2	2002	1.57	1.50	1.63
3	2003	1.53	1.47	1.59
4	2004	1.49	1.44	1.54
5	2005	1.45	1.41	1.50
6	2006	1.42	1.37	1.46
7	2007	1.38	1.34	1.42
8	2008	1.35	1.31	1.38
9	2009	1.31	1.28	1.34
10	2010	1.28	1.25	1.31
11	2011	1.25	1.22	1.28
12	2012	1.22	1.18	1.25
13	2013	1.18	1.15	1.22
14	2014	1.15	1.12	1.19
15	2015	1.13	1.09	1.16
16	2016	1.10	1.06	1.14

17	2017	1.07	1.03	1.11
18	2018	1.04	1.00	1.09
19	2019	1.02	0.97	1.06
20	2020	0.99	0.95	1.04
21	2021	0.97	0.92	1.02

3.6.4.3 Cardiac deaths with an indeterminant cause – class A3

Based on absolute mortality numbers and mid-year census population data, incidence rates for class A3 demonstrated a downward trend (Figure 10).

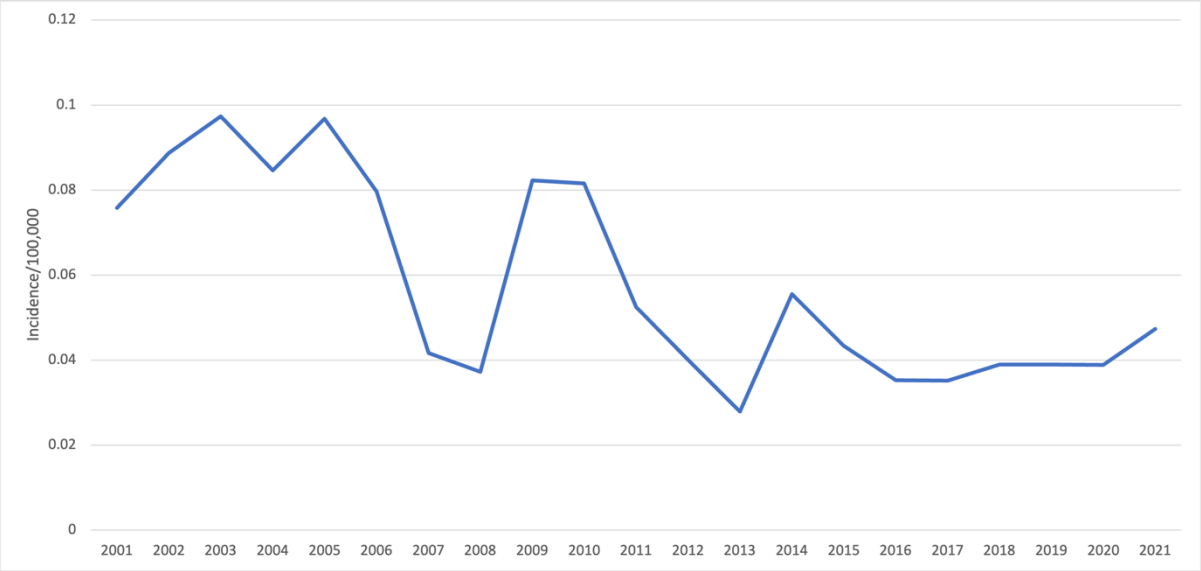


Figure 10: Overall incidence trends in class A3.

Table 13 demonstrates the parameter estimates of the fitted log-linear model for category A3 cases. The model demonstrated a significant downward trend in incidence rates over the 21-year time period (figure 11). The estimated rate ratio of the downwards trend was 0.951 (95% CI: 0.933 - 0.970) per year, indicating a 4.9%

(95% CI: 3% - 6.7%) incidence rate reduction per year over the time period; p value <0.001.

Table 13: Parameter estimates of the fitted log-linear model for category A3 cases.

	Estimate	Std. Error	z value	Pr(>|z|)
Intercept	-13.90556	0.10033	-138.60	< 0001
Time since 2001	0.04998	0.00978	-5.11	< 0001

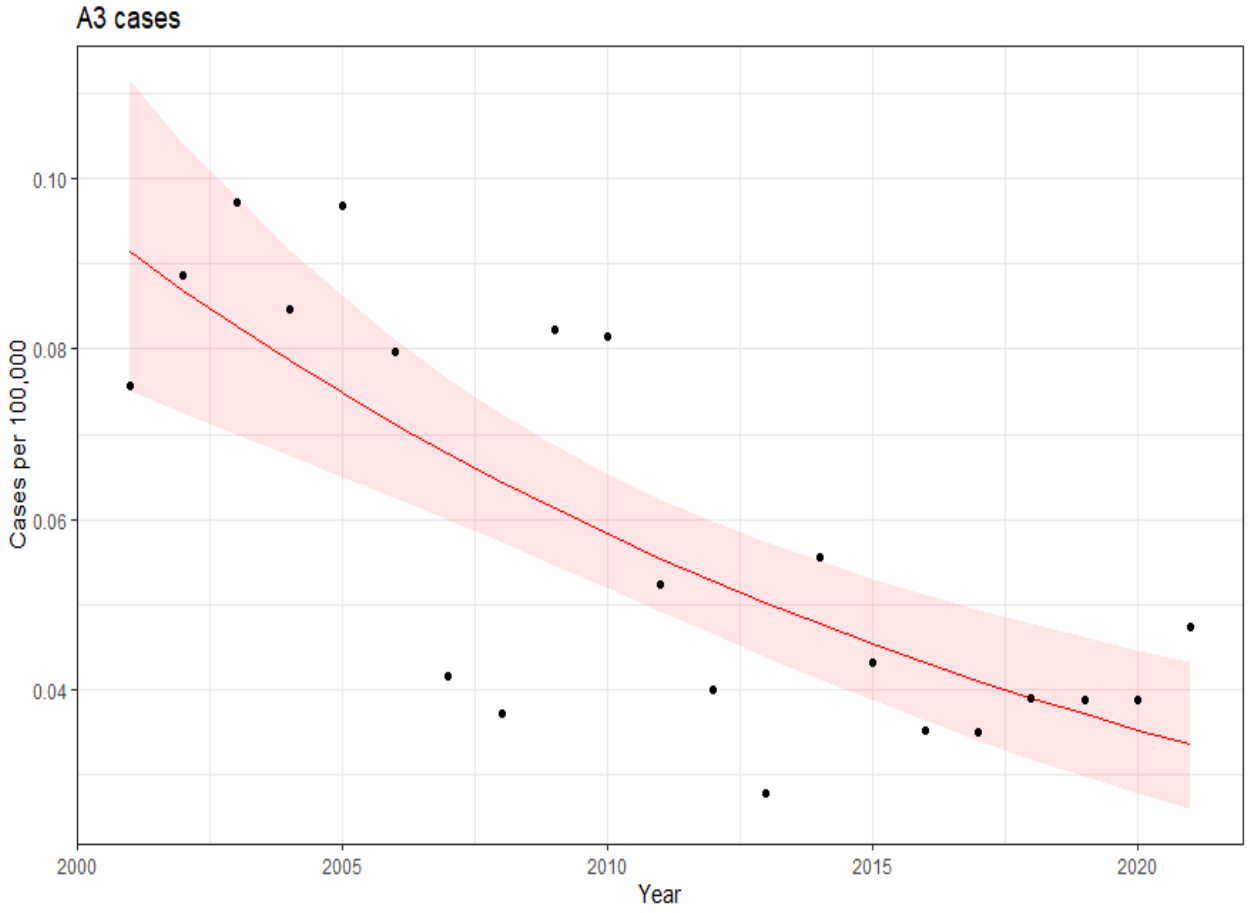


Figure 11: Incidence rates for Class A3 modelled using Poisson log-linear model. The number of cases in Class A3 was utilised as the response variable and the mid-year population as an offset. Time since 2001 was considered the independent

variable. The solid red line represents the model output, and the respective 95% confidence intervals either side demonstrated by the shaded area. The black dots correlate with absolute mortality counts.

Table 14 demonstrates the estimated incidence using fitted log-linear mode for the category A3 cases in each year. The incidence rate was 0.09 (95% CI: 0.08 – 0.11) in 2001 and it has reduced to 0.03 (95% CI: 0.03 – 0.04) in 2021.

Table 14: Estimated incidence rates from 2001 to 2021 for Class A3.

	Year	Incidence	95% CI lower margin	95% CI upper margin
1	2001	0.09	0.08	0.11
2	2002	0.09	0.07	0.10
3	2003	0.08	0.07	0.10
4	2004	0.08	0.07	0.09
5	2005	0.07	0.06	0.09
6	2006	0.07	0.06	0.08
7	2007	0.07	0.06	0.08
8	2008	0.06	0.06	0.07
9	2009	0.06	0.05	0.07
10	2010	0.06	0.05	0.07
11	2011	0.06	0.05	0.06
12	2012	0.05	0.05	0.06
13	2013	0.05	0.04	0.06
14	2014	0.05	0.04	0.06

15	2015	0.05	0.04	0.05
16	2016	0.04	0.04	0.05
17	2017	0.04	0.03	0.05
18	2018	0.04	0.03	0.05
19	2019	0.04	0.03	0.05
20	2020	0.04	0.03	0.04
21	2021	0.03	0.03	0.04

3.6.4.4 Total definite cardiac deaths – class A1+A2+A3

Based on absolute mortality numbers and mid-year census population data, incidence rates for class A1+A2+A3 overall demonstrated an downward trend (Figure 12).

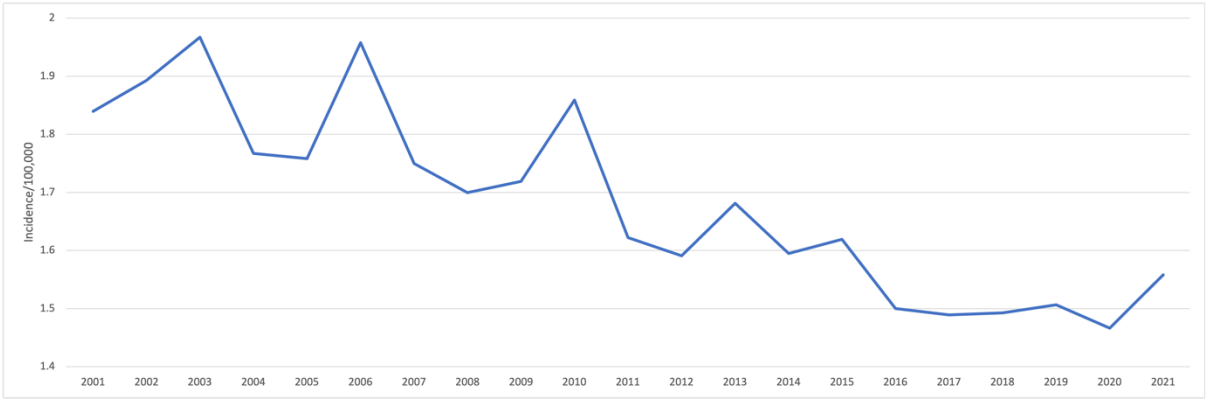


Figure 12: Overall incidence trends in class A1+A2+A3.

Table 15 demonstrates the parameter estimates of the fitted log-linear model for category A1, A2 and A3 cases. The model demonstrates a significant downward trend in incidence rates over the 21-year time period. The estimated rate ratio of the downwards trend was 0.987 (95% CI: 0.983 - 0.990) per year, indicating a 1.3%

(95% CI: 1.0% - 1.7%) incidence rate reduction per year over the time period; p value <0.001.

Table 15: Parameter estimates of the fitted log-linear model for category A1, A2 and A3 cases.

	Estimate	Std. Error	z value	Pr(>|z|)
Intercept	-10.861882	0.020257	-536.210	< 0001
Time since 2001	-0.013420	0.001773	-7.568	< 0001

Figure 13: Incidence rates for Class A1+A2+A3 modelled using Poisson log-linear model. The number of cases in Class A1+A2+A3 was utilised as the response variable and the mid-year population as an offset. Time since 2001 was considered the independent variable. The solid red line represents the model output, and the

respective 95% confidence intervals either side demonstrated by the shaded area. The black dots correlate with absolute mortality counts.

Table 16 demonstrates the estimated incidence using fitted log-linear mode for category A1, A2 and A3 cases in each year. The incidence rate was 1.92 (95% CI: 1.84 – 2.00) in 2001 and it has come down to 1.47 (95% CI: 1.41 – 1.53) in 2021.

Table 16: Estimated incidence rates from 2001 to 2021 for Class A1, A2 and A3.

	Year	Incidence	95% CI lower margin	95% CI upper margin
1	2001	1.92	1.84	2.00
2	2002	1.89	1.82	1.96
3	2003	1.87	1.80	1.93
4	2004	1.84	1.79	1.90
5	2005	1.82	1.77	1.87
6	2006	1.79	1.75	1.84
7	2007	1.77	1.73	1.81
8	2008	1.75	1.71	1.79
9	2009	1.72	1.69	1.76
10	2010	1.70	1.66	1.74
11	2011	1.68	1.64	1.71
12	2012	1.65	1.62	1.69
13	2013	1.63	1.60	1.67
14	2014	1.61	1.57	1.65
15	2015	1.59	1.55	1.63

16	2016	1.57	1.52	1.61
17	2017	1.55	1.50	1.59
18	2018	1.53	1.48	1.58
19	2019	1.51	1.45	1.56
20	2020	1.49	1.43	1.54
21	2021	1.47	1.41	1.53

3.6.4.5 Possible cardiac deaths – class B

Based on absolute mortality numbers and mid-year census population data, incidence rates for class B1 demonstrated a downward trend (Figure 14).

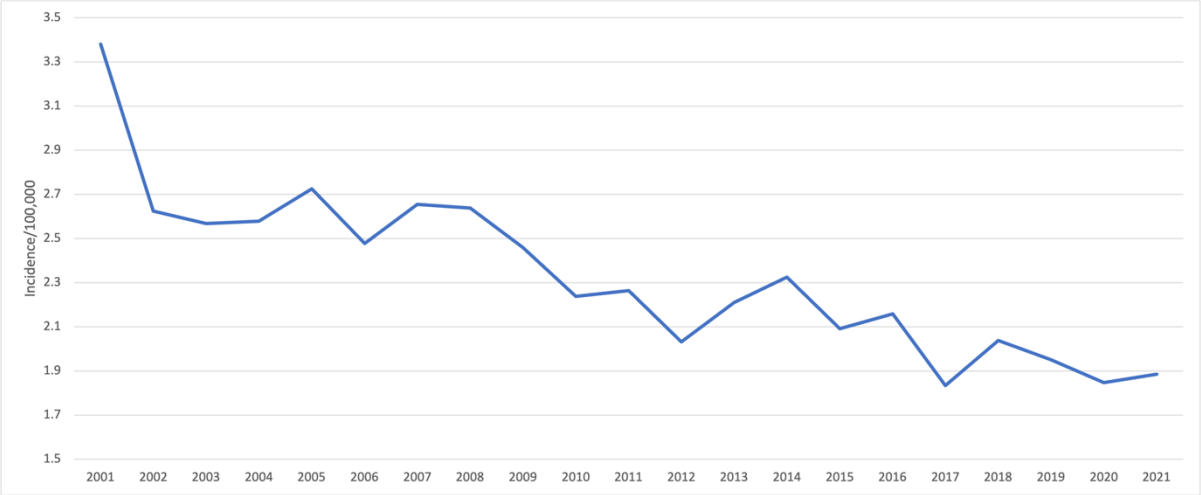


Figure 14: Overall incidence trends in class B

Table 17 demonstrates the parameter estimates of the fitted log-linear model for category B cases. The model demonstrated a significant downward trend in incidence rates over the time period. The estimated rate ratio of the downwards trend was 0.977 (95% CI: 0.974 - 0.980) per year, indicating a 2.3% (95% CI: 2.0% - 2.6%) incidence rate reduction per year over the time period; p value <0.001.

Table 17: Parameter estimates of the fitted log-linear model for category B cases.				
	Estimate	Std. Error	z value	Pr(>|z|)
Intercept	-10.443924	0.016797	-621.78	<0001
Time since 2001	-0.023186	0.001511	-15.34	<0001

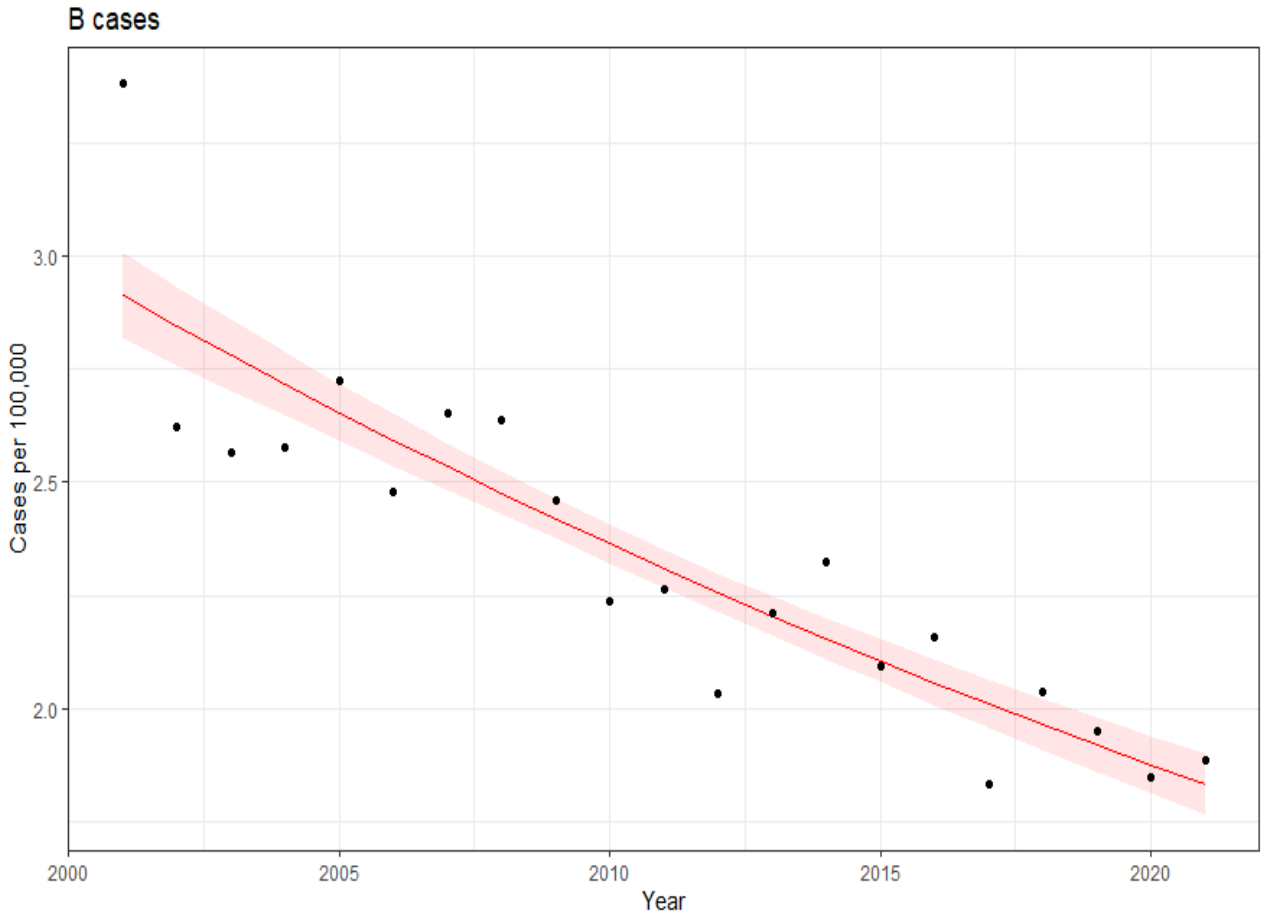


Figure 15: Incidence rates for Class B modelled using Poisson log-linear model. The number of cases in Class B was utilised as the response variable and the mid-year population as an offset. Time since 2001 was considered the independent variable. The solid red line represents the model output, and the respective 95% confidence

intervals either side demonstrated by the shaded area. The black dots correlate with absolute mortality counts.

Table 18 demonstrates the estimated incidence using fitted log-linear mode for the category B cases in each year. The incidence rate was 2.91 (95% CI: 2.82 – 3.01) in 2001 and it has come down to 1.83 (95% CI: 1.77 – 1.90) in 2021.

Table 18: Estimated incidence rates from 2001 to 2021 for Class B.

	Year	Incidence	95% CI lower margin	95% CI margin margin
1	2001	2.91	2.82	3.01
2	2002	2.85	2.76	2.93
3	2003	2.78	2.70	2.86
4	2004	2.72	2.65	2.79
5	2005	2.65	2.59	2.72
6	2006	2.59	2.54	2.65
7	2007	2.53	2.48	2.59
8	2008	2.48	2.43	2.52
9	2009	2.42	2.38	2.46
10	2010	2.36	2.32	2.41
11	2011	2.31	2.27	2.35
12	2012	2.26	2.22	2.30
13	2013	2.21	2.16	2.25
14	2014	2.15	2.11	2.20
15	2015	2.11	2.06	2.15

16	2016	2.06	2.01	2.11
17	2017	2.01	1.96	2.06
18	2018	1.96	1.91	2.02
19	2019	1.92	1.86	1.98
20	2020	1.87	1.81	1.94
21	2021	1.83	1.77	1.90

3.6.4.6 Total mortality trends for definite and possible cardiac death: classes A1, A2, A3 and B

Based on absolute mortality numbers and mid-year census population data, incidence rates for all mortality in classes A and B demonstrated a downward trend (Figure 16).

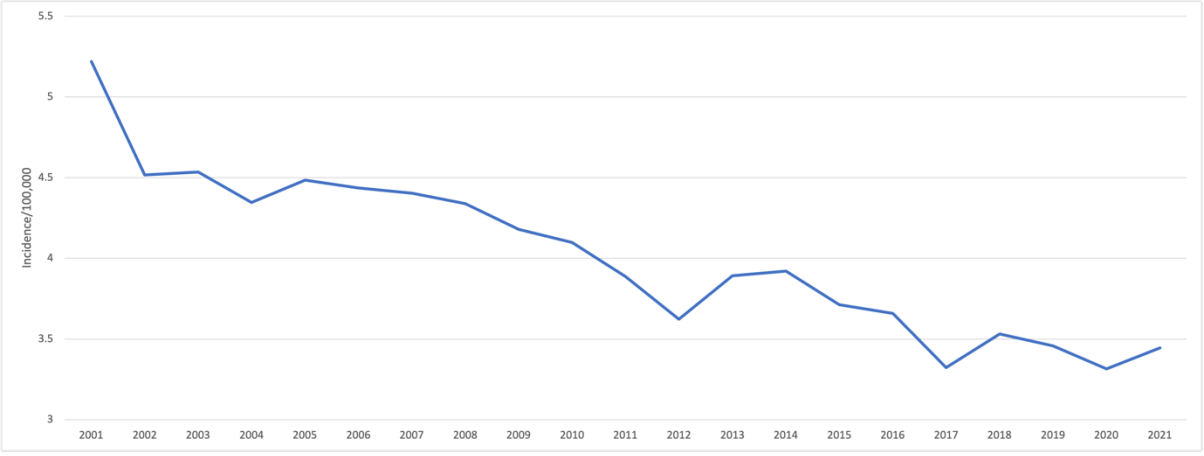


Figure 16: Overall incidence trends in class A1+A2+A3+B.

Table 19 demonstrates the parameter estimates of the fitted log-linear model for the total cases. The fitted model showed a significant downward linear trend in the rate of total cases over the 21-year study period (figure 17). The estimated rate ratio of

predictor variable time since 2001 was 0.983 (95% CI: 0.981 - 0.985) per year, indicating a reduction of 1.7% (95% CI: 1.5% - 1.9%) per year in the incidence rate over the study period.

Table 19: Parameter estimates of the fitted log-linear model for total cases.

	Estimate	Std. Error	z value	Pr(>|z|)
Intercept	-9.6044332	0.0108992	-881.21	<0001
Time since 2001	-0.0174081	0.0009648	-18.04	<0001

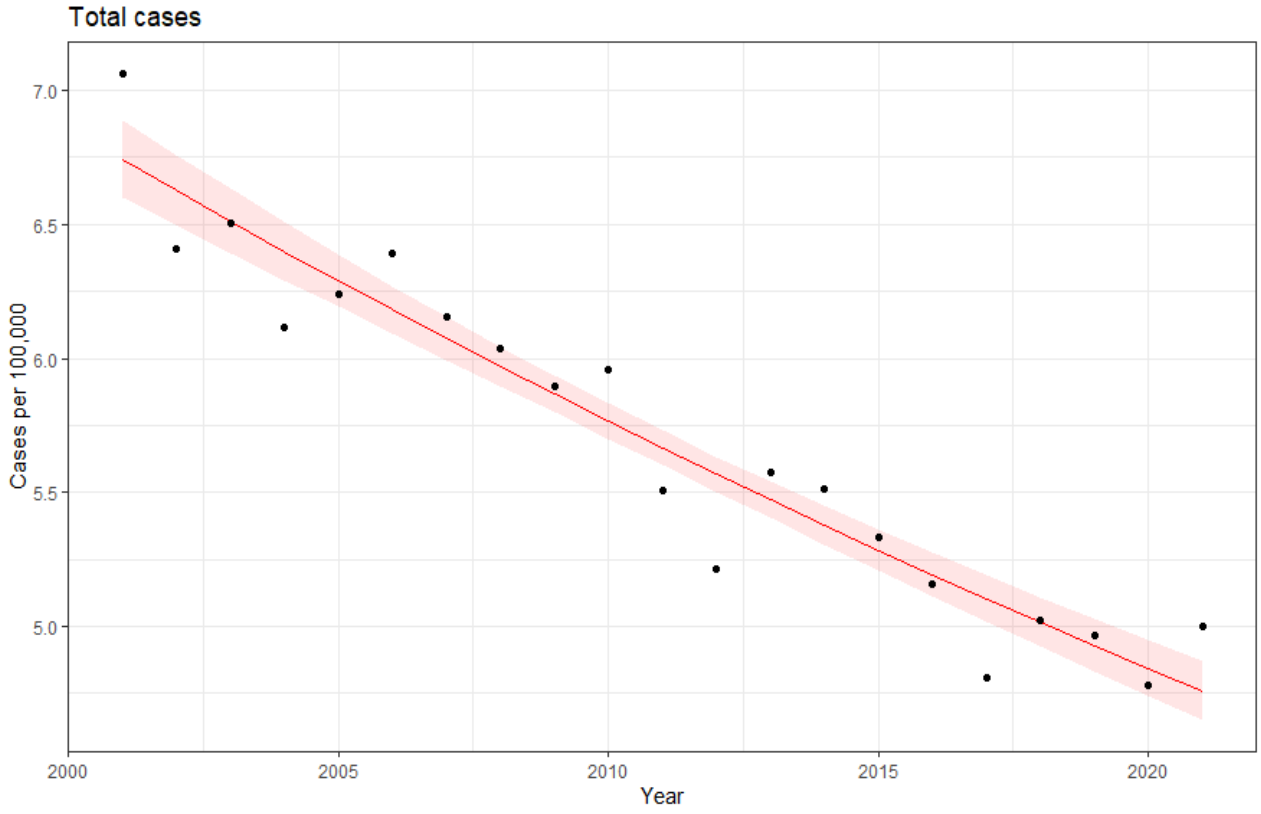


Figure 17: Incidence rates for overall incidence trends in class A1+A2+A3+B modelled using Poisson log-linear model. The number of cases in classes A1+A2+A3+B was utilised as the response variable and the mid-year population as an offset. Time since 2001 was considered the independent variable. The solid red line represents the model output, and the respective 95% confidence intervals either

side demonstrated by the shaded area. The black dots correlate with absolute mortality counts.

Table 20 demonstrates the estimated incidence from the fitted log-linear mode for the total cases in each study year. The incidence rate was 6.74 (95% CI: 6.60 – 6.89) in 2001 and it has come down to 4.76 (95% CI: 4.65 - 4.87) in 2021.

Table 20: Estimated incidence rates from 2001 to 2021 for total cases (Class A1+A2+A3+B)

	Year	Incidence	95% CI lower margin	95% CI upper margin
1	2001	6.74	6.60	6.89
2	2002	6.63	6.50	6.76
3	2003	6.51	6.39	6.63
4	2004	6.40	6.29	6.51
5	2005	6.29	6.19	6.39
6	2006	6.18	6.09	6.27
7	2007	6.07	5.99	6.16
8	2008	5.97	5.90	6.04
9	2009	5.87	5.80	5.94
10	2010	5.77	5.70	5.83
11	2011	5.67	5.60	5.73
12	2012	5.57	5.50	5.63
13	2013	5.47	5.40	5.54
14	2014	5.38	5.31	5.45

15	2015	5.28	5.21	5.36
16	2016	5.19	5.11	5.27
17	2017	5.10	5.02	5.19
18	2018	5.02	4.93	5.11
19	2019	4.93	4.83	5.03
20	2020	4.84	4.74	4.95
21	2021	4.76	4.65	4.87

3.6.5 Causes of death by gender

Definite cardiac deaths were more prevalent in males with a male to female ratio of 2.31: 1. Possible cardiac deaths were also more prevalent in males with a male to female ratio of 1.68:1. Taking into account calculations for proportional (%) distribution of underlying cause of death by gender, based on the denominator of total deaths in each gender category, statistically significant differences were observed in several pathologies (figure 18 and table 21). There was a notable discrepancy in mortality rates from IHD, with 14.62% of males succumbing to this entity compared to 6.61% of females (p value < 0.0001). A significant gender difference was observed in mortality related to aortopathy, where 2.30% of males passed away from this entity as opposed to 1.54% of females (p value = 0.0002). Interestingly, females exhibited a higher mortality rate due to myocarditis, with 5.63% of females affected compared to 3.87% of males (p value < 0.0001). Similarly, epilepsy-related deaths demonstrated a gender discrepancy, with 21.25% of females affected compared to 17.05% of males (p value < 0.0001). There were no statistically significant differences observed between genders in cases of SADS, cardiomyopathies, or other ill-defined causes of death.

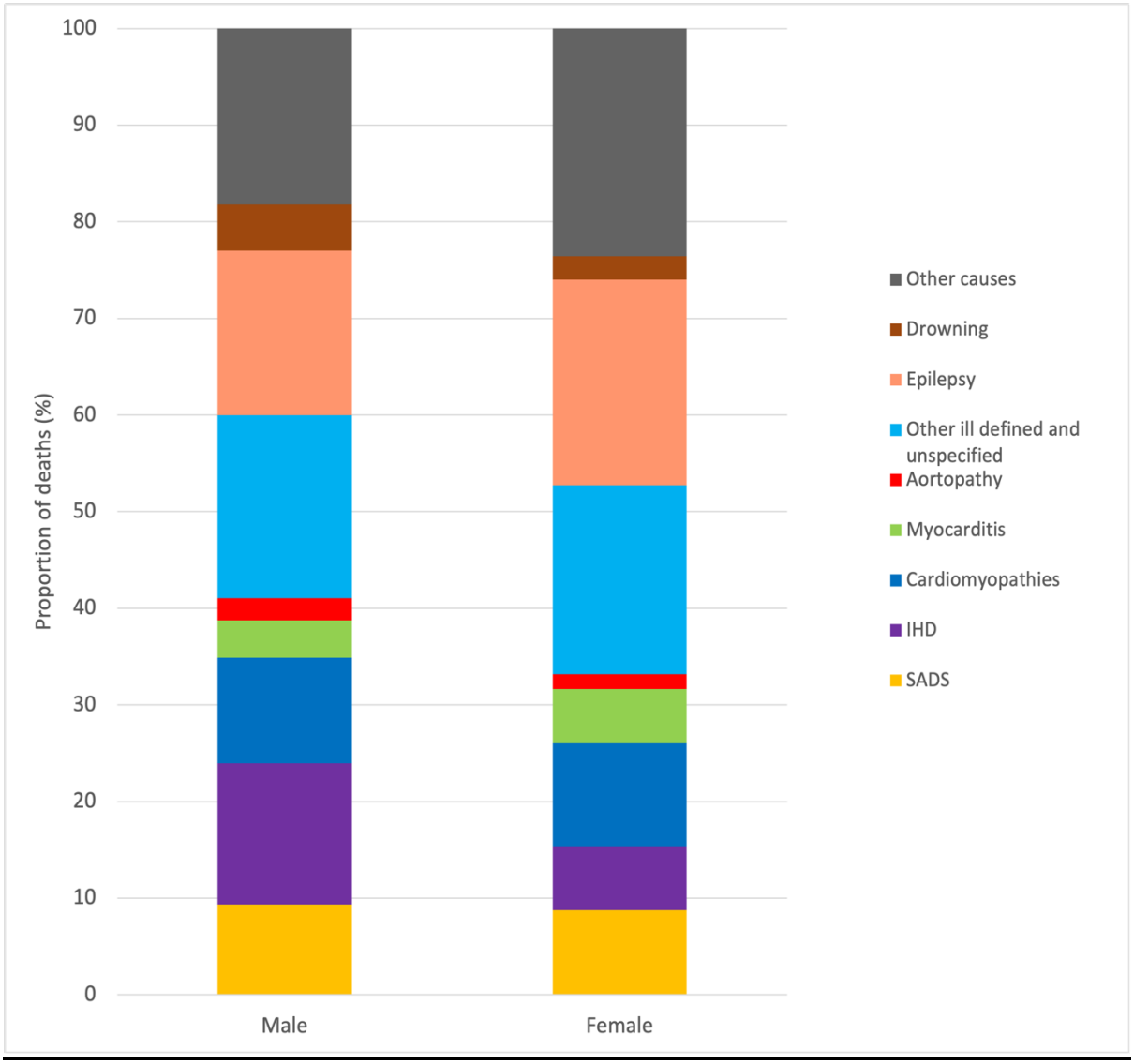


Figure 18: Proportional (%) distribution of underlying cause of death by gender. IHD, ischaemic heart disease; SADS, sudden arrhythmic death syndrome.

Table 21: Statistical comparison of proportional (%) distribution of underlying cause of death by gender. IHD, ischaemic heart disease; SADS, sudden arrhythmic death syndrome.

	Proportion of male deaths (%) [1]	Proportion of female deaths (%) [2]	p value[3]
SADS	9.32%	8.73%	p=0.1685
IHD	14.62%	6.61%	**p<0.0001**
Cardiomyopathies	10.91%	10.66%	p=0.5943
Myocarditis	3.87%	5.63%	**p<0.0001**
Aortopathy	2.30%	1.54%	**p=0.0002**
Other ill defined	18.92%	19.56%	p=0.2743
Epilepsy	17.05%	21.25%	**p<0.0001**
Drowning	4.78%	2.44	**p<0.0001**
Other causes	18.19	23.55	**p<0.0001**

[1] Total male deaths in classes A1+A2+A3+B= 13617

[2] Total female deaths in classes A1+A2+A3+B= 7120

[3] p value <0.05 deemed statistically significant

3.6.6 Causes of death by age

When age groups were consolidated into 9-to-10-year age brackets apart from the individuals over the age of 30 years, causes of death demonstrated variation with age (figure 19). Ischaemic heart disease peaked in the 30-to-34-year age group and demonstrated an upward trend with advancing age. Cardiomyopathies peaked during the 10-to-19-year age group and SADS peaked in the 10 to 19 and 20 to 29 year age groups. Epilepsy and drowning peaked in the 10–19-year age group. Myocarditis as a cause of cardiac mortality in the young was omnipresent throughout all age groups and aortopathies demonstrated a subtle increment with advancing age.

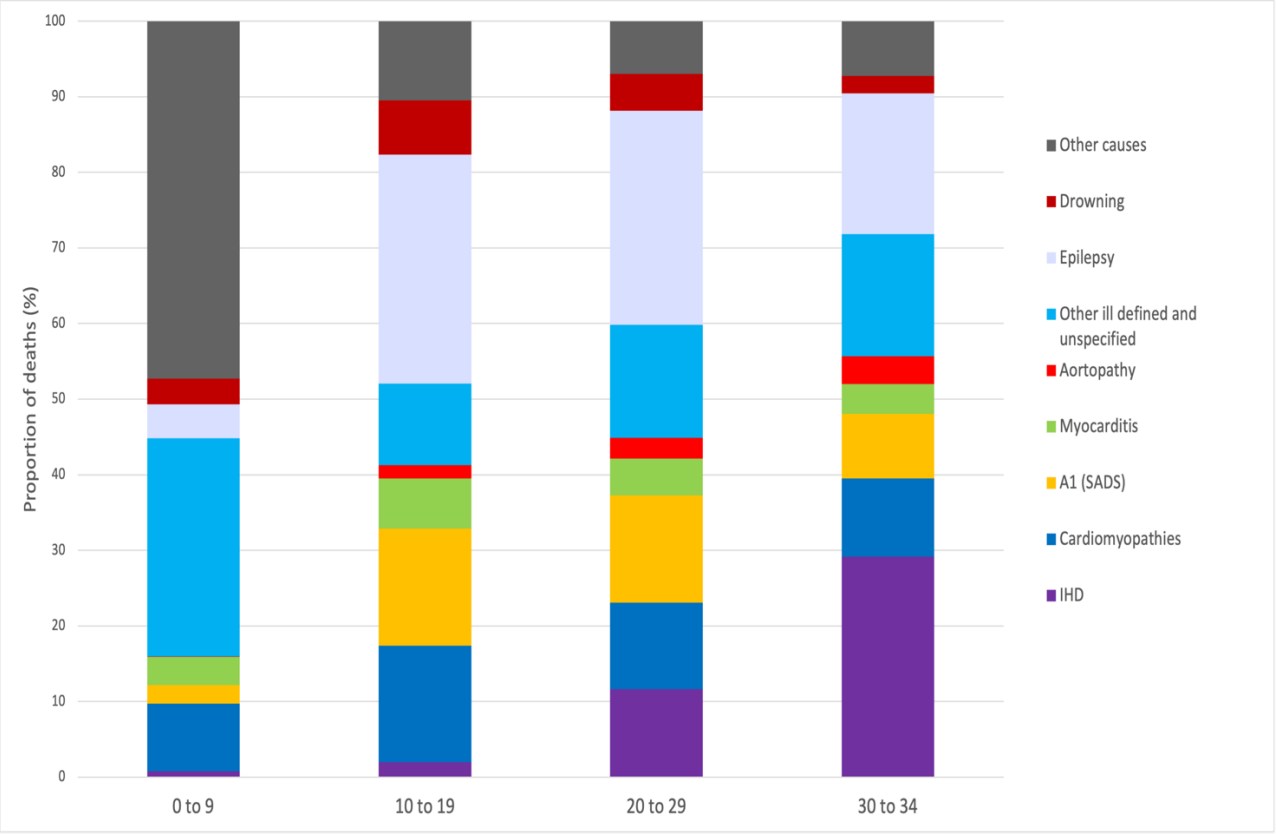


Figure 19 Proportional (%) distribution of underlying cause of death by age. IHD, ischaemic heart disease. SADS, sudden arrhythmic death syndrome.

Poisson log-linear models were used to investigate the relationship between the cause of death and age. The age variable as noted was categorised into four categories; 0 to 9 years; 10 to 19 years; 20 to 29 years; and 30 to 34 years. The common causes of death investigated by the models were as listed in figure 19. The dependent variable for the Poisson log-linear models was the number of deaths that occurred in each cause of death. The independent variable was the age category. The total number of deaths was considered as an offset in the Poisson log-linear models. This means that the model was adjusted for the total number of deaths, so that the results could be interpreted as the effect of age category on the number of deaths in each cause of death category, after controlling for the overall number of deaths.

The four age categories resulted six comparisons as mentioned below.

- Age 0-9 years versus age 10 – 19, age 20 – 29, age 30 – 34 years
- Age 10 – 19 years versus age 20 – 29, Age 30 – 34 years
- Age 20 – 29 years versus age 30 – 34 years

For each cause of death analysis, three Poisson log-linear models were developed, with each model denoting a different age reference level: 0-9 years, 10-19 years, and 20-29 years. This enabled us to compare the six comparisons mentioned above and identify age groups that are at increased risk of death from specific causes. Overall, statistically significant differences were observed between causes of death in different age ranges (table 22).

Table 22: Statistical comparisons using Poisson log-linear model and count data relating to mortality numbers according to age groups. Statistical significance deemed as a p value of <0.05.

Category	Age 0-9 vs Age 10 - 19	Age 0-9 vs Age 20 - 29	Age 0-9 vs Age 30 - 34	Age 10 – 19 vs Age 20 - 29	Age 10 – 19 vs Age 30 - 34	Age 20 – 29 vs Age 30 - 34
A1 (SADS)	<0.001	<0.001	<0.001	0.151	<0.001	<0.001
IHD	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Cardiomyopathies	<0.001	<0.001	0.0143	<0.001	<0.001	0.0646
Myocarditis	0.00211	<0.001	0.49531	0.00219	<0.001	0.02259
Aortopathy	<0.001	<0.001	<0.001	0.0108	<0.001	0.00523
Other ill-defined and unspecified causes	<0.001	<0.001	<0.001	<0.001	<0.001	0.0923
Epilepsy	<0.001	<0.001	<0.001	0.137	<0.001	<0.001

Drowning	0.000113	<0.001	0.000318	<0.001	<0.001	<0.001
Other causes	<0.001	<0.001	<0.001	<0.001	<0.001	0.639

3.7 **Discussion**

Our present study spanned nationally collected data over two decades and employed similar methodology to Papadakis M et al., which utilised ONS mortality data for a four-year period from 2002 to 2005.[13] Overall our findings build on this seminal study by contributing to temporal trends in mortality as well as demonstrating similarity in disease epidemiology across various age groups and gender as previously observed.

Our study revealed a mean number of 414.19 definite cardiac deaths at per annum, translating to approximately 7.96 deaths per week and an annual incidence of 1.68 per 100,000 individuals. Our incidence figure may be an underestimate in comparison to data from other studies including those from within the United Kingdom. Nevertheless, it broadly fits within an established incidence from contemporary studies globally and work from our group previously.[11,13,17,23,25,66,67]

We must consider that certain conditions may manifest as a result of an underlying arrhythmogenic substrate, but the death may be labelled as an ill-defined cause, epilepsy or drowning. For instance, within a significant cohort of individuals with

SADS, 7% reportedly suffered from epilepsy.[68] This underscores the diagnostic challenges, potentially leading to misclassifications of deaths into class B, which may represent definite cardiac deaths. Therefore, considering a conservative estimate that at least 20% of deaths categorized into class B may be misclassifications, it implies that there are at least nine cardiac and sudden cardiac deaths occurring in England and Wales on a weekly basis.

Ischaemic heart disease (IHD) emerges as the predominant cause of mortality among the young, with its impact increasing with age, particularly in the 30 to 34 age group. Followed closely by cardiomyopathies and SADS. This finding aligns with historical data and contemporary studies, emphasizing the significant role of primary myocardial disease and structurally normal hearts indicative of SADS in the context of cardiac deaths in young individuals.[7,22,23,26,69]

The observation that mortality from cardiomyopathies and SADS peak in the 10 to 19 and 20 to 29 year age groups are particularly relevant from a prevention perspective as strategies to identify individuals harbouring often quiescent electrical and structural abnormalities may be identified through measures such as cardiac screening in the general population. Whilst at the same time, measures to identify individuals with atherosclerotic risk factors become particularly relevant in individuals with advancing age, as mortality from ischaemic heart disease clearly demonstrates a rising trend with advancing age and peaks in the 30 to 34 age group.

Our study encompassed individuals under the age of 1, a demographic not previously explored in the original study by Papadakis et al.[13] Twinned with this, a

notable finding from our analysis was that 24% of possible cardiac deaths (class B) were attributed to sudden infant death syndrome (SIDS). Historically, environmental factors have predominantly been implicated in SIDS mortality. However, emerging literature indicates genetic variants in cardiac genes such as SCN5A and KCNQ1 may also be identified in SIDS cohorts.[70,71] This suggests the presence of potentially lethal arrhythmogenic substrates in certain infants at risk of SIDS and holds significant implications, particularly for surviving family members. Epidemiologically, it is worth noting the substantial progress made since the implementation of the Back to Sleep Campaign in England and Wales in 1991, which has led to an over 81% decrease in SIDS mortality.[72,73] Current estimates from the Lullaby Trust in the UK suggest approximately 182 SIDS deaths occur annually, equating to roughly 3 babies per week.[72] Overall, our findings underscore the enduring prevalence of SIDS as a significant cause of mortality in young individuals.

Whilst single-centre studies, including from large registries such as our CRY-CCP, may carry inherent referral biases, they still provide significant insights into the aetiology of young sudden cardiac death.[7,69,74] Our study includes data from across England and Wales through a national reporting process, and therefore helps mitigate potential biases associated with single-centre or registry data. The ranking of cardiomyopathies higher than SADS in our dataset may be an important reflection that not all cardiomyopathy deaths are referred to expert pathology registries such as the CRY-CCP, as the cause of death may be elucidated locally or at other regional centres and in essence our study offers unique insights into the distribution of causes of cardiac mortality in the young in England and Wales.

It is also worth conceding that in the two-decade study period, SADS lacked a dedicated ICD-10 code. Instead, the codes we have utilized have been selected by experts in the field of ICCs, who are involved at the forefront of genetic heart diseases including cardiac autopsy, thus likely representing deaths from this entity. Other conditions that did not identify with a designated ICD-10 code include LQTS, short QT syndrome (SQTS), and brugada syndrome, where deaths are likely being reflected in our class A and a significant proportion in class B. Furthermore, arrhythmogenic cardiomyopathy (AC), which is regarded as having a prevalence of 1:2000 to 1:5000 in adults[75] did not have a designated ICD-10 code, and deaths were typically coded as cardiomyopathy other (I42.8) or cardiomyopathy unspecified (I42.9). The inaccurate coding of deaths and subsequent epidemiological analysis poses challenges to clinicians and surviving family members in terms of assessing for the inheritability of these conditions.

Turning to temporal trends, our study reveals an upward trend in SADS cases, particularly up until 2010. This trend may reflect increased awareness of the condition, improved recognition of post-mortem findings of uncertain significance, and subsequent reclassification of the cause of death. Such reclassifications are often driven by access and referral pathways to expert cardiac histopathologists who have specific expertise in the field.[76,77] Accurate diagnosis is of paramount importance, and conditions such as myocarditis should not be hastily diagnosed in the presence of scattered inflammatory cells without fibrosis or myocyte necrosis.[78] Similarly, mild ventricular dilatation in the absence of inflammation or fibrosis should not be equated to dilated cardiomyopathy. In fact, as many as one in two deaths with

autopsy findings of uncertain significance could be attributed to an arrhythmogenic syndrome following familial evaluation.[78]

Recently a prospective observational study by de Noronha et al. found that structurally normal hearts at autopsy tended to be underdiagnosed by general pathologists, who were more inclined to diagnose cardiomyopathy compared to formal examination conducted by expert cardiac pathologists.[77] Disagreements between general and expert pathologists regarding the cause of death occurred more than 40% of the time, with 37% of normal hearts incorrectly reported as diseased, reflecting structural findings sufficient to initially label them with a pathological entity.[77] This underscores the critical role of specialist pathological services in accurately identifying pathology. Misclassified causes of death could have far-reaching consequences, such as the failure to carry out familial investigations for potentially lethal cardiac conditions, ultimately leading to preventable sudden cardiac deaths within the same family. Our findings are overall consistent with contemporary cohorts in Canada and Denmark, where a significant proportion of sudden cardiac deaths in young individuals were classified as SADS.[66,79]

If novel considerations are given to mortality attributed to SADS at the CRY-CCP in comparison to deaths coded into class A1 utilising ONS data, during our study period from 2001 to 2021 (figure 20), similar observations in the increment in SADS numbers from 2001 to 2010 can be observed, with a more gradual incline from 2010 to 2019 and a subsequent drop in 2020 and 2021. Furthermore, it can be observed that from 2007 to date, the deaths attributed to SADS from the CRYCCP exceed

those reported by ONS, with significant variation in the past decade. Based on our estimates, between 2001 to 2021, there have been 2137 total deaths from SADS reported by the CRY-CCP. This is in comparison to 1891 deaths attributed to conditions in class A based on our analysis. This striking finding, with at least 12% of deaths not accounted in ICD-10 codes consistent with SADS on a population level in comparison to a single-centre national registry, extenuates variability in mortality coding on a national level, following autopsy, whereby deaths are perhaps being coded into mortality codes in class B. Data presented from the CRY-CCP is also for individuals including and up to the age of 35-years. This is also happens to be the upper limit of the CRY nationwide screening programme. However, ONS datasets particularly for the over 30 years of age group, ends at 34 years of age (30-34 years of age). So, it is also plausible that the additional 1-year worth of data included in Figure 20 may account for some mortality in the 34 to 35 age group, though from a SADS perspective, this effect is likely to be small, as the entity appears to peak in the earlier years, particularly in the 21 to 30 year age group. Further discussion relating to the CRY CCP is reserved for subsequent chapters.[74]

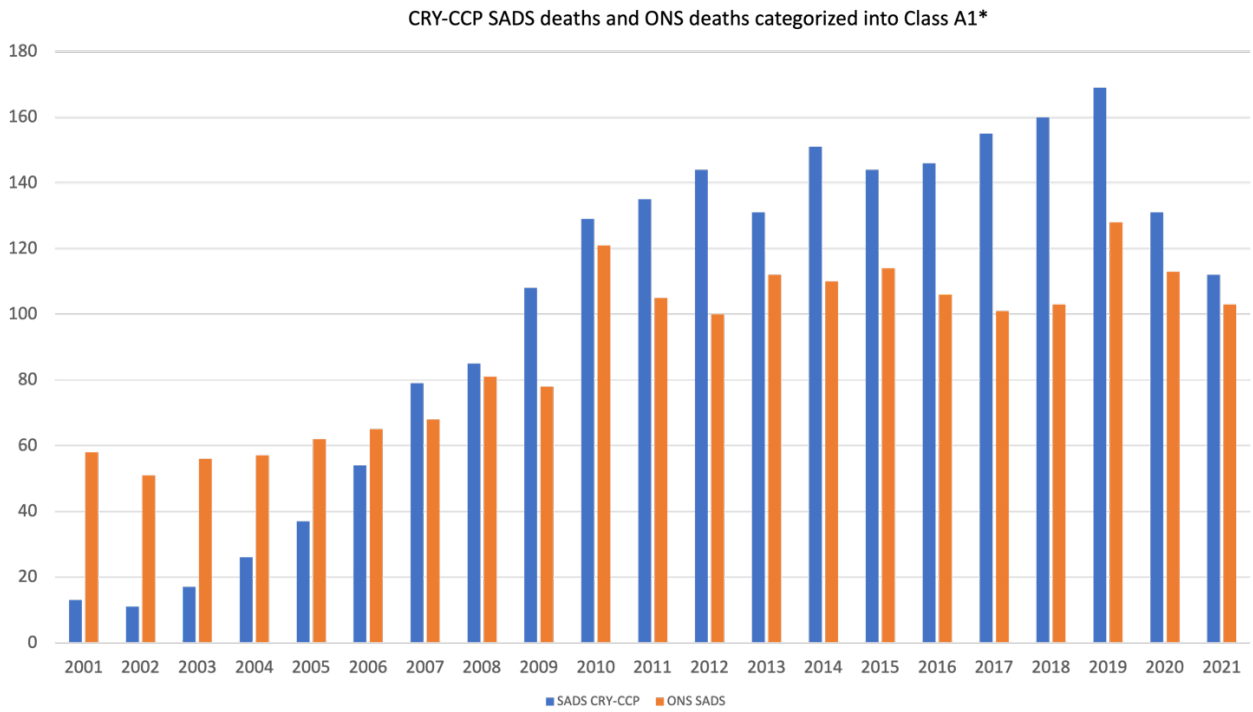


Figure 20: Deaths coded as sudden arrhythmic death syndrome (SADS) at the Cardiac Risk in the Young Centre for Cardiac Pathology (CRY-CCP) in comparison to mortality coded into class A1 utilising Office for National Statistics (ONS) data. *Figures from ONS do not take into account deaths that may have been coded or registered into alternative categories. Mortality from the CRY-CCY specifically related to individuals under the age of 35 years. Overall CRY-CCP data provided by Professor Mary Sheppard and Dr Joseph Westaby. Analysed by RTB.

A unique contribution of our study is the demonstration of an overall downward trend in definite and possible cardiac mortality over a span of 21 years in England and Wales. In particular deaths from structural heart disease, which represents 75% of all definite cardiac deaths demonstrated a significant downward trend in incidence rates over 21-years. The estimated rate ratio of the downwards trend was 0.975 (95% CI: 0.971 - 0.979) per year, indicating a 2.5% (95% CI: 2.1% - 2.9%) incidence rate reduction per year over the time period; p value <0.001. Such findings are similar to

those reported in general epidemiological trends in CV disease in the United Kingdom on an annual basis, whereby it is now well established that CVD mortality has consistently declined over recent decades.[80] In young individuals, this decline may be attributed, in part, to improvements in preventative strategies. This includes earlier diagnosis and appropriate disease specific management such as those discussed in chapter one (table 2), broadly encompassing lifestyle advice, medical and device therapy, as well as sophisticated interventional and surgical techniques. In terms of earlier diagnosis, accessibility to cardiac screening initiatives in the community or in expert ICC centres may have contributed to the observed trends. Furthermore, increased awareness around CPR training, and the availability of AEDs may have also contributed to improved survival following SCA.

From a cardiac screening perspective, although not currently mandated by UK government, laudable initiatives such as those by the charity CRY, have facilitated the identification of numerous young individuals in the UK with quiescent cardiac conditions associated with young sudden cardiac death. Recent large-scale population level data from MacLachlan et al., suggests that 104,369 consecutive individuals aged 14 to 35 years were screened by CRY between 2007 to 2018 with a health questionnaire and a 12-lead ECG followed by onsite echocardiography. 280 (0.3%) were identified with a cardiac condition associated with SCA or SCD and at least 115 received life-saving therapies, which included individuals who underwent catheter ablation, permanent pacemaker insertion, implantable cardioverter defibrillators and individuals who underwent cardiac transplantation.[81] Similar findings have been reported by Dhutia et al.,[40] in 26,900 screened individuals between 2012 and 2014, where again 0.3% were identified with diseases implicated

in young SCD. Certainly, such findings are undoubtedly contributing to preventing young SCD as well as reducing cardiac morbidity by early disease recognition and timely, appropriate medical therapy where indicated. Furthermore, in the context of CV screening, the evolution of contemporary ECG interpretation criteria in the athletic population has translated into improved cost-effectiveness for screening and may serve as a reference for similar standards in the young general population.[82]

3.7.1 **Limitations**

Our study has several notable limitations that merit consideration. Firstly, our study lacks conclusive evidence regarding whether individuals included in the ONS mortality datasets died of known cardiac conditions. We did not have access to individual death certificates or post-mortem reports. However, at a systematic population level, we meticulously examined formally reported causes of death to the ONS, which serves as the official source of validated data in England and Wales and serves as the only official source of mortality data. Additionally, existing research, including work from our group, indicates that as many as 80% of sudden cardiac deaths in young individuals occur due to quiescent conditions without antemortem diagnosis.[7,41,69,83] Therefore, it is reasonable to assume that a substantial proportion of deaths in our study are likely a result of sudden cardiac deaths in otherwise healthy apparent young individuals. However, to remain cautious, we report on cardiac deaths as a collective entity. Secondly, our dataset lacks information on important demographic factors, such as ethnicity, physical activity, or athletic status, all of which are recognized risk factors for sudden death in young individuals. However, in contrast to numerous studies focusing on elite athletes, our findings

encompass a broader spectrum of young individuals, and provides valuable insights into population-level data. Thirdly, our study did not include mortality attributed to congenital heart disease (CHD), specifically, ICD-10 codes q20-28. Based on current estimates, CHD is diagnosed in at least 1% of births with cardiac defects representing the most common congenital anomaly in babies born in the United Kingdom.[84] In an attempt to ensure consistency with methods utilised in the study by Papadakis et al.[13], which formed the foundations for our study and establish temporal trends in ICD-10 codes which were scrutinised by senior authors (M.P., S.S., E.R.B. and M.N.S.), these specific CHD ICD-10 codes were not utilised; but lends itself for future work. Finally, due to the methodology of our study, we are unable to provide detailed explanations for the observed downward trends in mortality. Nevertheless, this finding is hypothesis generating and based on our own experience, it is plausible that preventative strategies and advancements in medical therapy are contributing factors to these observations.

3.8 **Conclusion**

Our study demonstrates that the incidence of cardiac and sudden cardiac death in young individuals in England and Wales is 1.68/100,000 individuals/per. Ischaemic heart disease, cardiomyopathies and SADS are the main causes of mortality. Despite the challenges that persist in epidemiological analyses, our research reveals a promising downward trend in definite and possible cardiac mortality in the young.

Funding: RTB is funded by a research grant from the charity Cardiac Risk in the Young (CRY). CRY prevents young SCD through raising awareness, supporting affected families, a voluntary screening programme and funding clinical research.

Contributions: All authors contributed to study design conception, data acquisition, analysis, interpretation; drafting of manuscript; critically revising the manuscript. SS, SC and MP gave final approval. RTB, SS, SC and MP agree to be accountable for all aspects of work ensuring integrity and accuracy.

3.9 Clinical implications

Over a 21-year period the ONS dataset demonstrates a small but significant downward trend in cardiac mortality in young individuals. Despite this based on a conservative estimate, at least 9-young individuals continue to die on a weekly basis in England and Wales from cardiac causes. In addition, the significant life years lost and impact to society as a whole supports conceited efforts to address this public health issue. We have demonstrated an increase in expert cardiac post-mortems which correlates with an increase in deaths attributed to SADS. However, inaccurate coding of deaths particularly in the absence of dedicated ICD codes for conditions such as SADS, long QT syndrome, Brugada syndrome and arrhythmogenic cardiomyopathy continue to impact on understanding the true burden of cardiac mortality in the young. The advent of ICD-11 codes as highlighted in our discussion will hopefully ameliorate some of these issues in the future. Accurate diagnosis is central to appropriate evaluation of first-degree family members particularly when an ICC is suspected.

Chapter 4: Setting the scene: the Cardiac Risk in the Young Centre for Cardiac Pathology

4.1 Introduction

The autopsy examination is an essential diagnostic step which steers the clinical evaluation of surviving relatives toward inherited structural diseases or primary arrhythmogenic syndromes. The interpretation of the postmortem results, however, is a complex task and uncertainty may exist about the exact significance of certain pathological findings and their causal relationship with SCD. For example, the significance of myxoid degeneration of the mitral valve with prolapse, stable atherosclerotic coronary plaque with limited (<50%) luminal stenosis and focal myocarditis, which are relatively common in the general population, may be erroneously overestimated.

Similarly, the postmortem diagnosis of HCM may be solely based on the presence of LVH in the absence of pathognomonic histological changes such as myocyte disarray. However, LVH is a recognized feature of physiological adaptation to exercise and may be present in obese individuals. In a recent study tertiary centre prospective observational study by de Noronha et al.,[77] a disparity in diagnosis between referring pathologists and expert cardiac histopathologists was noted in 41% of cases of SCD. Referring pathologists were more inclined to diagnose cardiomyopathy than normality with only 50 out of 80 (63%) normal hearts being described correctly.[77] General pathologists were more inclined to describe a heart as

pathological, typically cardiomyopathic, with only 63% of normal hearts being described correctly, following expert cardiac histopathology review.[77] Despite a recognition of the multiple benefits from cardiac autopsy, variations in uptake exist globally. Egger F et al., recently reported on sudden death in worldwide football between 2014 to 2018, as part of the FIFA Sudden Death Registry.[85] Strikingly, across 67 countries, autopsy was only performed in 34% of cases of sudden deaths. Similarly, a recent survey which captured data from European countries disseminated by the European Heart Rhythm Association (EHRA), highlighted that autopsy was performed in only 43% of sudden unexpected deaths in the young.[86] In certain European countries, factors hindering autopsy uptake include, costs, logistic factors, and a lack of mandate from regulatory bodies to encourage such practice.[86]

In the UK, however, as has been alluded to in the previous chapter, all deaths, particularly sudden deaths need to be reported to the coroners who will provide guidance on whether an autopsy is indicated. Such practice has led to higher rates of autopsy in the UK. Based on recent figures from the Ministry of Justice and national statistics from the coroners in England and Wales (2022), post-mortem examinations were performed in 43% of all deaths reported, which represents a 7% increment from the previous year.[87]

4.2 The Cardiac Risk in the Young Centre for Cardiac Pathology

The Cardiac Risk in the Young Centre for Cardiac Pathology (CRY-CCP) based at St. George's, University of London is now regarded as the largest global registry of autopsy findings in the context of sudden unexpected cardiac deaths. Since its

inception in 1994 to date the CRY-CCP has performed over 7000 consecutive post-mortems. The centre is funded through donations from supporters of the charity CRY which largely includes bereaved families of individuals who have succumbed to SCD. Referral into the service is largely governed by local coroners and based on current estimates the service receives in excess of 400 whole hearts per annum. As a centre of excellence for a fast-track expert cardiac pathology service for bereaved families, this is free of charge when the cause of death is unascertained, and the person is aged 35 years or under. The overall process aims to return the heart in two weeks to facilitate burial. It is encouraged that the coroner requests permission for the whole heart to be sent to the CRY-CCP as this facilitates accuracy of diagnosis. Individuals over the age of 35 years can of course be referred in as well, but the cost is not free. Guidance criteria has been created for referrers (table 23)

Table 23: Cardiac Risk in the Young Centre for Cardiac Pathology (CRY-CCP) United Kingdom (UK) National Sudden Cardiac Death (SCD) database entry criteria. Criteria is open to individuals over the age of 1, with no upper limit; both sexes; and all racial groups.
Circumstances of death
• Found dead in bed or community with no previous significant heart disease history. • Found collapsed in community either brought in dead or died shortly after admission to accident and emergency department of local Hospital. • Witnessed collapse with failure to resuscitate at home or in the community.

• Collapse during or after sport event. • Death Following impact to chest in sport. • Cardiac arrest with resuscitation and survival to hospital admission but died with hypoxic brain damage. • Drowning where circumstances are no clear. Found dead at bottom of pool with no struggle. • Road traffic accident where circumstances indicate driver collapsed before accident or car veered off road before impact. Found dead at wheel of car that is stationary. • Toxicology is negative or non-toxic levels of drugs are found.
Local autopsy findings
• Normal heart and no cause identified after full autopsy and toxicology. • Dilation/ fatty appearance/ scarring in right or left ventricle with normal coronary arteries. • Mitral valve prolapse. • Ventricular hypertrophy with no reported history of hypertension or aortic valve disease. • Anomalous coronary arteries/ coronary artery dissection/ vasculitis /aneurysm. • Coronary arteries with obstruction/dilatation not due to atheroma. • Coronary artery atheroma in under 40 age group.

• Aortic dissection in under 40 years with no history of hypertension. • Congenital heart abnormality with or without surgery.

Clinical information is prospectively provided by the respective coroners and a detailed completed questionnaire is obtained from all cases which provides relevant information relating to the deceased's, demographics, lifestyle, past medical history, family history, cardiovascular symptoms, medication history, physical activity, circumstances of death and if available antemortem cardiac investigations e.g., 12-lead ECG and cardiac imaging findings. This information is electronically recorded and stored by the CRY-CCP in accordance with strict governance policies.

4.3 **The expert post-mortem examination**

Following referral to the CRY-CCP, all post-mortems are performed by expert cardiac histopathologists (MNS and JW), in accordance with standardised guidelines with a report issued within 14-days of initial referral. A pre-requisite prior to referral to the CRY-CCP is a negative full body autopsy and toxicology before being referred and subsequently undergoing detailed cardiac evaluation including histological analysis by expert cardiac pathologists (figure 21).

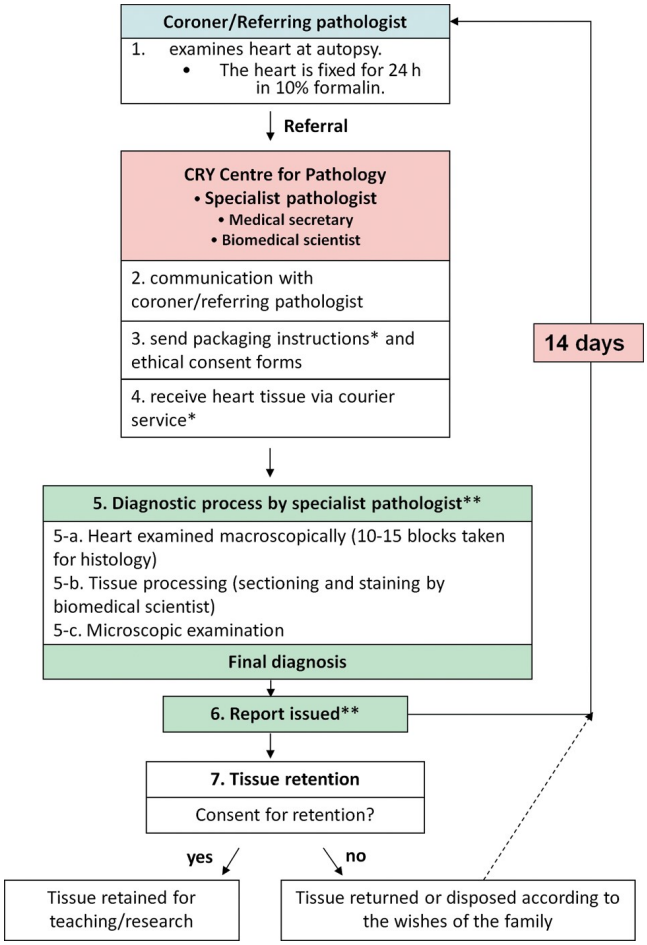


Figure 21: Flow chart showing the cardiac referral procedure at CRY CCP. *According to national guidelines for transporting biological material. **Free service. Courtesy of Professor Michael Papadakis.

Sections of myocardium are fixed in formalin which is a technique developed over time by MNS. All cardiac structures are systematically examined, with a particular emphasis on the coronary arteries, myocardium, cardiac valves, conduction tissues, aorta and pericardium. In addition, the heart weight is recorded in grams and ventricular wall thickness and internal cavity dimensions are measured at mid-ventricular level excluding the papillary muscles and fat. A minimum of 10 blocks of tissue are taken for

histological analysis (Figure 22). The criteria for defining specific cardiac pathologies is summarised in Table 24. Importantly, photographic documentation is often made and stored in the laboratory information system to facilitate indefinite storage of findings.

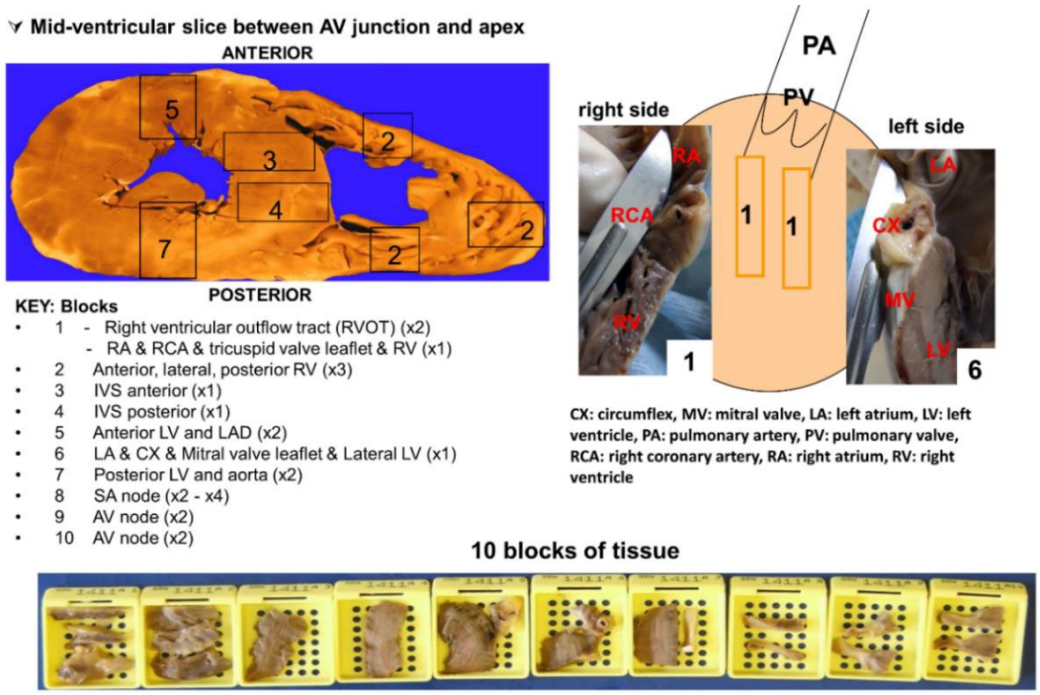


Figure 22. Blocking protocol for the post-mortem examination from the CRY-CCP laboratories. For each case at least 10 blocks of tissue are retained for histology as standard. **Abbreviations:** AV: atrio- ventricular; CX: circumflex; IVS: interventricular septum; LA: left atrium; LAD: left anterior descending; LV: left ventricle; RA: right atrium; RCA: right coronary artery; SA: sinus-atrial. Courtesy of Prof MN Sheppard.

Table 24. Pathological macroscopic and microscopic criteria defining main underlying diseases. Note, increase in heart weight defined as heart weight >500 g in men and > 400 g in women. Developed in conjunction with Professor MN Sheppard and published literature from CRYCCP.

	Macroscopic	**Microscopic**
Hypertrophic cardiomyopathy	• Left ventricular wall thickness ≥15 mm circumferentially or focally. • Right ventricular wall thickness >5 mm. • Heart weight >500 g in men and >400 g in women. • Macroscopic criteria may be normal. • Absence of coronary artery disease.	• Myocyte hypertrophy and myocyte disarray (> 20% of myocardial disarray in at least two tissue blocks of 4 cm2) with or without interstitial or replacement fibrosis and thick-walled blood vessels.
Idiopathic left ventricular hypertrophy	• Left ventricular wall thickness >15 mm and increased heart weight in the absence of abnormal loading conditions.	• Myocyte hypertrophy +/- fibrosis **in the absence of myocyte disarray.**
Idiopathic left ventricular fibrosis	• Normal heart weight and wall thickness with/without scarring macroscopically. • Absence of coronary artery	• Fibrosis (> 20% in at least two tissue blocks of 4 cm2) with no myocyte disarray.

	disease.	
Arrhythmogenic cardiomyopathy	• Normal or increased heart weight. • Right or left ventricular thinning, fatty replacement, fibrosis on the epicardial surface. • Macroscopic criteria may be normal. • Absence of coronary artery disease.	• Fat and fibrosis (> 20% in at least two tissue blocks of 4 cm2) in the wall of the right and/or left ventricle, particularly in outer wall, with degenerative changes in the myocytes.
Myocarditis *Please refer to Myocarditis chapter 8 for specific details and subclassification*	• Normal or dilated ventricles with irregular streak like appearances. • Fibrinous pericarditis. • Can be normal macroscopically.	• Inflammation (> 20% in at least two tissue blocks of 4 cm2) with associated myocyte necrosis.
Anomalous coronary artery	• Anomalous origin and/or course of the coronary artery. • Interarterial course.	• Fibrosis/acute/chronic infarction in the left or right ventricle. • May be no evidence of infarction.
Coronary	• Atherosclerosis with	• Acute or chronic

atherosclerosis	estimated luminal narrowing >75% or lumen <1 mm or unable to insert 2 mm probe. • Evidence of infarction or scarring in myocardium in a coronary artery territory/ distribution. • Normal myocardium. • Rupture with haemopericardium. • Thrombosis in coronary artery.	infarction in the left or right ventricle. • May be no evidence of infarction.
Dilated cardiomyopathy	• Increase in heart weight with dilated left ventricle (>4cm) and thin compact wall (<1cm). • Mural thrombi in ventricles. • Dilated atria with thrombi in appendages. • Absence of coronary artery disease.	• Diffuse interstitial and replacement fibrosis (>20% in at least two tissue blocks of 4 cm2) in the left ventricle with degenerative changes in the myocytes.
Mitral valve prolapse	• Prolapse of mitral valve above the atrio-ventricular junction with ballooning	• Myxoid degeneration with expansion in spongiosa of leaflets and destruction of

	between chordae in one or both leaflets. • Diffuse thickening of leaflets. • Mitral annual dilatation. • Cordal thinning and/or rupture.	fibrosa layer.
Bicuspid aortic valve	• Fusion of two aortic cusps, with or without presence of a raphe often with significant valve stenosis.	
Hypertensive heart disease	• Increase in heart weight. • Left ventricular wall thickness >15 mm. • History of established hypertension antemortem. • No coronary artery disease.	• Myocyte hypertrophy with fine interstitial fibrosis in subendocardium. • Absence of myocyte disarray.
Morphologically normal heart	Normal	Normal

4.4 **Rationale for onward clinical research utilising histopathological dataset**

Several gaps exist in our knowledge in the setting of SCD and in our experience the post-mortem if performed by expert histopathologists offers unique insights into potential aetiologies and facilitates downstream investigations in surviving members of the family. Furthermore, clinical parallels may be able to be drawn with antemortem clinical states, demographics and imaging findings to prevent the occurrence of young SCD.

In an attempt to utilise the robust histopathological dataset from the CRYCCP, four focussed areas of clinical interest were developed and studied, as summarised in figure 23 below and subsequent chapters to follow (chapter 5 to chapter 8)

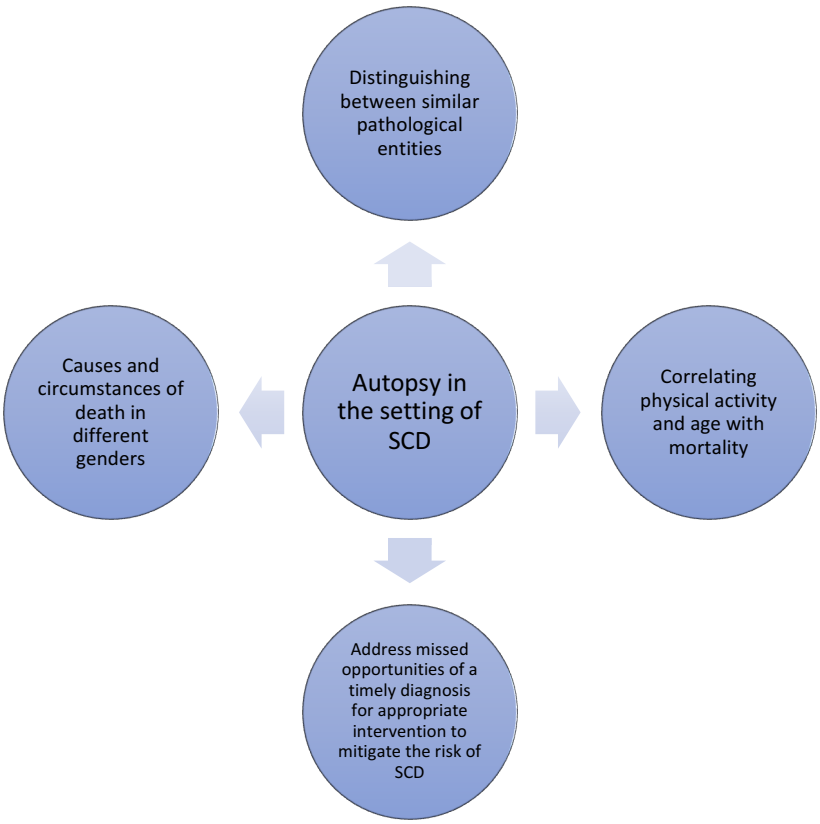


Figure 23: Four focussed areas of research identified in the context of the CRY-CCP and SCD.

Chapter 5: Sudden Death in Female Athletes: Insights from a Large Regional Registry in the United Kingdom

(Publication attached in appendix 1)

5.1 Abstract

Background: Existing literature suggests that sudden cardiac death (SCD) in female athletes is less frequent than in male athletes and the precise reasons for this observation remain elusive.

Aim: This study aimed to investigate the causes and circumstances of SCD in female athletes from a large nationwide SCD registry.

Methods: Between 1994 and 2020, 748 consecutive cases of athletes succumbing to SCD underwent detailed autopsy evaluation including histological analysis by expert cardiac histopathologists (MNS and JW). Clinical information was obtained from referring coroners and a comprehensive family questionnaire.

Results: Females constituted 98 (13%) of all athlete deaths. The average age of the decedents was 31 ± 15 years. Death during intensive exertion occurred in 57 (58%) female athletes compared with 538 (83%) male athletes ($p<0.001$). Sudden arrhythmic death syndrome (SADS) was the most prevalent cause of death in both sexes but was more common in females than males (57% vs 43% respectively; $p=0.008$). Furthermore, primary myocardial disease was less common in female than male athletes (23% vs 37%; $p=0.006$). SADS was the most prevalent cause of death

in female athletes irrespective of age whereas myocardial disease became the leading cause of death with advancing age in males.

Conclusions: Sudden cardiac death occurs less frequently in female athletes than their male counterparts. SADS appears to be the predominant cause in female athletes. Death during rest affects over 40% of female athletes and occurs more commonly than in male athletes, reinforcing the need for preventative strategies aimed at facilitating earlier diagnosis of potentially fatal quiescent electrical and structural cardiac conditions.

5.2 Introduction

Existing literature consistently suggests that females exhibit a lower susceptibility to exercise related SCD than their male counterparts.[7,21,22] Maron et el., reported that 11% of SCDs in 1866 athletes over a 27-year period, occurred in female athletes, with the proportion of deaths attributed to females increasing over the study period with no apparent temporal trends in the age at death in female athletes.[22] The disparity in sex distribution in the context of SCD, was also demonstrated in a seminal study by Finocchiaro et al., where between 119 and 2014, from 357 consecutive cases of athletes who died suddenly, only 27 (7%) occurred in females.[7] In terms of incidence estimates, Corrado et al. assessed the risk of SCD in male and female athletes aged between 12 to 35 years, over a 21-year period in the Veneto Region of Italy.[21] They reported an incidence of SCD at 2.6 per 100,000 person-years among male athletes, while the rate among female athletes was notably lower at 1.1 per 100,000 person-years.[21] Interestingly, in non-athletes' similar trends were observed, whereby mortality rates in males was 1.3 and females 0.5 per 100,000 person-years.[21]

The precise underlying reasons for this sex-based disparity remain elusive. Nevertheless, several factors have been postulated as potential contributors. These factors include historical differences in participation rates between males and females in sports, variations in the prevalence of risk factors relevant to specific cardiac diseases, the impact of sex hormones, environmental influences on pathological substrates, and the possibility of differing rates of performance-enhancing drug usage among the sexes. Coupled with historical challenges in obtaining comprehensive post-mortems, our understanding of the causes and precipitating factors for SCD in female athletes remains limited. The burgeoning

increase in the number of women participating in high-level sports competitions, including sports historically dominated by males, calls for more focused studies on the causes and circumstances of SCD in female athletes.

5.3 **Aim**

We aimed to investigate the causes and circumstances of SCD in a large cohort of female athletes where expert cardiac pathologists performed the cardiac autopsy.

5.4 **Personal contribution**

RTB reviewed comprehensive data relevant to the project and assisted with analysis of data and preparation of the published manuscript. RTB was not involved with the post-mortem evaluation or toxicology screen of any of the subjects that was performed by JW and MNS.

5.5 **Methods**

We reviewed a database of 6847 cases of SCD that were referred to the CRY-CCP at St George's, University of London, between 1994 and 2020. SCD was defined as death occurring within 12 hours of apparent well-being. We retrieved a subgroup of 748 (10.9%) decedents who engaged in sport activities, defined as >3 hours of organized physical training per week. Clinical information was obtained from referring coroners. Competitive athletes were defined as those who were involved in organized sport requiring participation in regular, formal competition. Circumstances

of death were subdivided broadly into death occurring during exercise and death during rest or sleep.

As described earlier, all cases at the CRY-CCP underwent detailed autopsy evaluation of the heart, including histologic analysis, by expert cardiac pathologists (MNS and JW). A minimum of 10 blocks of tissue were taken for histologic analysis.[74] The criteria for defining specific cardiac pathologies have been previously described (table 24). Importantly, SADS was defined as a structurally normal heart with no evident abnormality on macroscopic and histological evaluation, and a negative toxicology screen.[74]

5.5.1 Ethical approval

Ethical and research governance approval has been granted for this study (10/H0724/38). The next of kin consented to material retention for anonymized research in each case. Data will be made available upon reasonable request to the corresponding author.

5.5.2 Statistical analysis

Statistical analysis was performed using the PASW software (PASW 18.0 Inc, Chicago, IL). Results are expressed as mean ± standard deviation (SD) for continuous variables or as number of cases and percentage for categorical variables. Comparison of groups was performed using Student's T-test for

continuous variables with correction for unequal variance when necessary and Chi-square test or Fisher Exact Test, as appropriate for categorical variables.

5.6 **Results**

5.6.1 Clinical characteristics

Females constituted 98 (13%) of the 748 SCDs among individuals who engage in regular sports activities. There were no differences in the mean age at death between males and females (31 ± 15 in female athletes and 32 ± 14 in male athletes; p=0.573) (Table 25). The average body mass index (BMI) and body surface area (BSA) were 26 ± 5.4 Kg/m2 and 2.0 ± 0.3 m^2, respectively. BMI was similar in males and females (25.8 ± 5.8 vs 26.1 ± 5.3; p=0.673).

Table 25. Aetiology of SCD in male and female athletes

	Total denominator (n=748)	**Female athletes (n=98)**	**Male athletes (n=650)**	**P**
Age (years)	32 ± 14 [8 - 86]	31 ± 15 [8 - 82]	32 ± 14 [8 - 86]	0.573
BMI	26 ± 5.4	25.8 ± 5.8	26.1 ± 5.3	0.673
Death during exercise n (%)	595 (79)	57 (58)	538 (83)	<0.001
SADS n (%)	335 (45)	56 (57)	279 (43)	0.008
Myocardial disease n (%)	262 (35)	23 (23)	239 (37%)	0.006
HCM n (%)	47 (6)	4 (4)	43 (7)	0.265
ARVC n (%)	115 (15)	7 (7)	108 (17)	0.011
DCM n (%)	10 (1)	4 (4)	6 (0.9)	0.012
ILVH n (%)	48 (6)	2 (2)	46 (7)	0.058
ILVF n (%)	29 (4)	6 (6)	23 (3)	0.126
Myocarditis n (%)	5 (0.6)	/	5 (0.8)	0.023
Coronary anomalies n (%)	25 (3)	4 (4)	21 (3)	0.596
Coronary atheroma n (%)	46 (6)	1 (1)	45 (7)	0.022
VHD/CHD n (%)	24 (3)	6 (6)	18 (3)	0.126
Aortic dissection n (%)	6 (0.8)	2 (2)	4 (0.6)	0.143
Commotio cordis n (%)	13 (2)	1 (1)	12 (2)	0.495

ARVC: arrhythmogenic right ventricular cardiomyopathy; CHD: congenital heart disease; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; ILVH: idiopathic left ventricular hypertrophy; ILVF: idiopathic left ventricular fibrosis; SADS: sudden arrhythmic death syndrome; VHD: valvular heart disease. * ARVC includes also cases of arrhythmogenic cardiomyopathy with biventricular or mainly LV involvement.

A significant proportion of the 98 female athletes were competitive athletes (n=41, 42%), participating in team (n=20) or individual (n=21) sports. The remainder (n=57, 58%) participated in recreational sport. Sporting disciplines included: running (n=16, 16%), gym activities (n=14, 14%), regular physical exercise/athletics (n=13, 13%), swimming (n=10, 10%); several individuals engaged in a series of different sports during their life.

The majority of athletes were asymptomatic (n=85, 87%) and only 5 (5%) had a family history of premature sudden death (defined as death of a first-degree relative <50 years). Of the 13 (13%) symptomatic athletes, 5 had syncope, 4 had palpitations, 3 had chest pain, and 1 complained of decreased exercise tolerance. Of the 4 athletes with palpitations, 3 underwent further investigations that resulted in the diagnosis of atrial flutter, and one was diagnosed with right ventricular outflow tract tachycardia (RVOT) non-sustained ventricular tachycardia (NSVT) in the absence structural disease. Five athletes suffered from one or multiple syncopal episodes: 3 were cleared after a normal ECG and echocardiogram, 1 athlete revealed multiple premature ventricular beats and ventricular bigeminy and was treated with an anti-arrhythmic agent, and 1 athlete with normal investigations received an implantable loop recorder (ILR) which did not reveal any sinister arrhythmias prior to death.

5.6.2 Comorbidities

Three athletes had a previous diagnosis of congenital heart disease or coronary artery anomaly, of which 1 had surgical correction of a patent ductus arteriosus at a young age, 1 had a small ventricular septal defect and 1 was diagnosed with anomalous left coronary artery from the pulmonary artery (ALCAPA) and surgically corrected shortly after birth.

One athlete was diagnosed prior to death with dilated cardiomyopathy (DCM), 1 with hypertrophic cardiomyopathy (HCM), 1 with mitral valve prolapse (MVP), 1 had complete heart block (CHB) following childbirth which was treated with a permanent pacemaker (PPM); all of these individuals engaged in recreational sport.

Non cardiac comorbidities included asthma 10 (10%) and thyroid dysfunction (n=6, 6%). Of note, 2 individuals died during the post-partum period, and one was pregnant (24 weeks) at time of death.

5.6.3 Autopsy findings

The mean heart weight in female decedents was 333 ± 89 g, compared with 434 ± 122 g in males; $p<0.001$. The mean heart weight/body weight ratio in female decedents was 0.48% ± 0.12 compared with 0.54% ± 0.13 in males; $p=0.003$. Fifteen (15%) athletes exhibited an absolute value of > 400 g. Eight (53%) of these individuals were overweight or obese according to body mass index. Left ventricular fibrosis was found in 24 (24%) female athletes, compared with 205 (31%) male athletes, $p=0.159$.

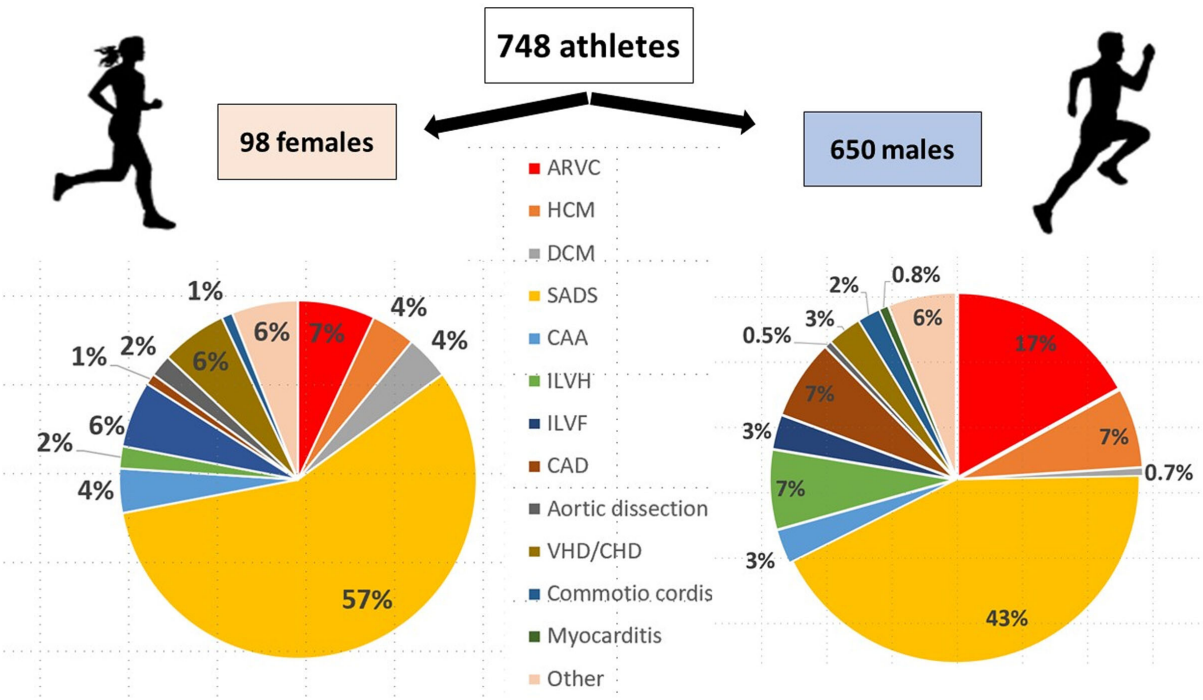


Figure 24 Causes of sudden cardiac death in male and female athletes. In the female athletes population, the subgroup classified as “other” (n=6) comprised cardiac tumor (n=1), Kawasaki syndrome (n=1), microinfarcts of unknown origin (n=1), and hypertensive disease (n=3). ARVC indicates arrhythmogenic right ventricular cardiomyopathy; CAA, coronary artery anomaly; CAD, coronary artery disease; CHD, coronary heart disease; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; ILVF, idiopathic left ventricular fibrosis; ILVH, idiopathic left ventricular hypertrophy; SADS, sudden arrhythmic death syndrome; and VHD, valvular heart disease.

The main causes of death are illustrated in Figure 24. A normal autopsy indicative of SADS was the most common finding and accounted for 56 (57%) deaths. Myocardial

disease was present in 23 (23%) cases. Among these, ARVC accounted for 7 (7%) deaths, followed by idiopathic fibrosis (n=6, 6%), HCM (n=4, 4%), DCM (n=4, 4%) and idiopathic left ventricular hypertrophy (ILVH) (n=2, 4%). Valvular heart disease/ congenital heart disease accounted for 6 (6%) deaths, including mitral valve abnormalities in 3 cases; prolapse of the mitral valve in all cases.

SADS was the most prevalent cause of death in both sexes but was more common in females (57% vs 43%; p=0.008). Myocardial disease was less common in females compared with males (23% vs 37%; p=0.006) (Table 25). Similarly, atherosclerotic coronary artery disease was less common in female than male athletes (1% vs 7%; p=0.022).

5.6.4 Causes of death by age

The prevalence of specific cardiac pathologies varied with age (Figure 25). SADS was most common in younger cases and showed a reducing trend with increasing age. A normal heart was reported in 60% of children and adolescents (<18 years), 62% of young adults (18-35 years) and 43% of older (>35 years) individuals.

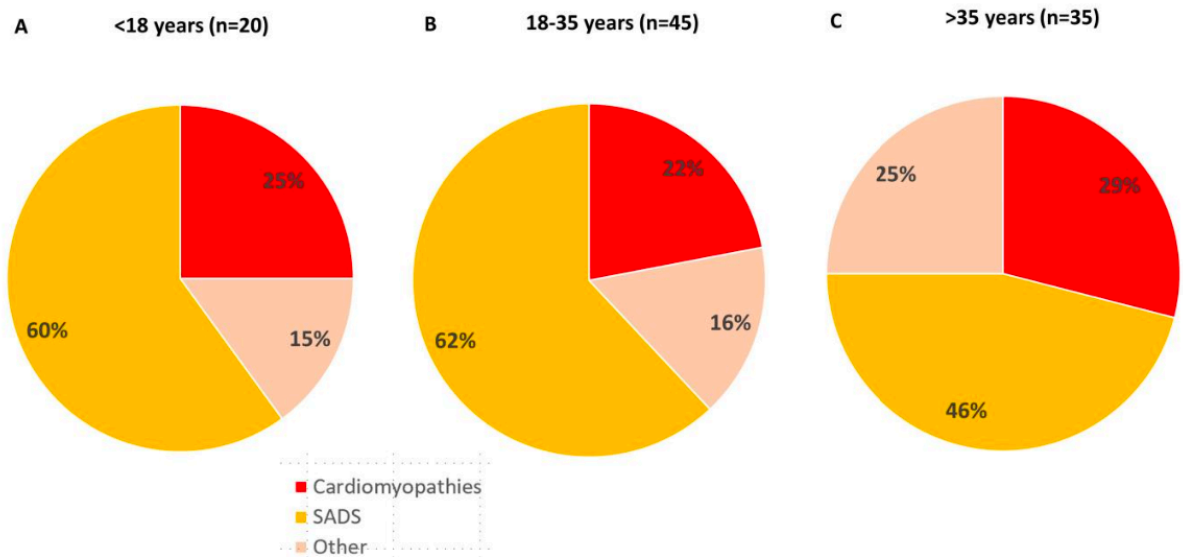


Figure 25: Cause of death by age. SADS: sudden arrhythmic death syndrome

5.6.5 Circumstances of death

Death during intense exertion occurred in 57 (58%) cases and was less common than male counterparts (n=538 (83%); p<0.001). The age and distribution between athletes who died during exertion and those dying at rest was similar (Table 26). In females, most commonly SCD occurred during swimming (n=14), followed by running (n=13), gym-based exercise (n=11) and dancing (n=4). Of the 41 individuals who died at rest, 1 died during sleep and the remaining individuals died during daily activities. There was no significant difference between the 2 subgroups in terms of underlying aetiologies or features at autopsy.

Table 26. Characteristics of the population according to circumstances of death.

	Total (n=98)	**Died on exertion (n=57)**	**Died at rest (n=41)**	**P**
Age (years)	31 ± 15	31 ± 16	31 ± 13	0.81
FH of SD n (%)	5 (5)	3 (5)	2 (5)	1
Heart weight (g)	333 ± 89	341 ± 94	324 ± 83	0.373
LV fibrosis n (%)	24 (24)	14 (24)	10 (24)	1
SADS n (%)	56 (57)	34 (60)	22 (54)	0.555
Myocardial disease n (%)	23 (23)	14 (24)	9 (22)	0.818
HCM n (%)	4 (4)	2 (3)	2 (5)	0.613
ARVC n (%)	7 (7)	4 (7)	3 (7)	1
DCM n (%)	4 (4)	4 (7)	/	0.08
ILVH n (%)	2 (2)	1 (2)	1 (2)	1
ILVF n (%)	6 (6)	3 (5)	3 (7)	0.678
Coronary anomalies n (%)	4 (4)	2 (3)	2 (5)	0.613
Coronary atheroma n (%)	1 (1)	1 (2)	/	0.365

ARVC: arrhythmogenic right ventricular cardiomyopathy; CHD: congenital heart disease; DCM: dilated cardiomyopathy; FH: family history; HCM: hypertrophic cardiomyopathy; ILVH: idiopathic left ventricular hypertrophy; ILVF: idiopathic left ventricular fibrosis; SADS: sudden arrhythmic death syndrome; VHD: valvular heart disease.

5.7 **Discussion**

Whereas previous studies relating to SCD in sport have focussed on male athletes, this study reports on SCD in largely young (≤ 35 years old) female athletes in the UK and provides novel findings on pathologies and circumstances of SCD in female athletes.

It is worth acknowledging, that since a previous study[7] reporting on data from the CRY-CCP where only 27 deaths were in female athletes, the present study reported on a larger cohort of female athletes from a national SCD registry spanning 26 years, where it is noteworthy that the number of athletes in this registry, particularly over the past 6-years has doubled. This offers a unique insight into aetiology and circumstances of SCD across various demographics. In agreement with previous studies[7,22,23], SCD was less prevalent in female athletes than in male athletes.

A structurally normal heart, suggestive of SADS, was the most common cause of SCD in females and accounted for 57% of all deaths, compared with 43% in male counterparts. The high prevalence of SADS in this cohort may be partly explained by a referral bias, but such cases are also similarly prevalent in collegiate athletes from the United States (US)[23] young military personnel[20]. Our own experience suggests that 42% of such cases have a familial basis and are usually secondary to ion channel disorders.[53] SADS was the most common finding across all age spectrums in females. A recent study in a large (n=1,710) cohort of patients with long QT syndrome showed that female sex was a predictor of life-threatening arrhythmia events during follow up.[88] Observational studies in human subjects and animal models show that the sex hormones account for most of the gender differences observed in cardiac repolarization and susceptibility to sympathetic triggered activity.

Oestradiol prolongs the QT interval, is associated with a higher risk for drug-induced QT prolongation and has a pro-arrhythmic effect, whereas testosterone and progesterone shorten QT duration and exert an anti- arrhythmic effect.[89–91]

Myocardial disease accounted for 23% of cases and was less common than in male counterparts. Although ARVC or AC was the predominant diagnosis among cardiomyopathies, it accounted for only 7% of cases compared with 17% in male athletes. Recent studies have shown an association between adverse arrhythmic outcomes in ARVC and higher levels of plasma testosterone in males and decreased oestradiol levels in females, supporting the hypothesis that sex hormones may have a role in prognosis.[92,93]

Idiopathic LVH was rare in females. The significance of idiopathic LVH is still uncertain, however our experience indicates that is a different entity to familial HCM.[94] Possible mechanisms underlying the higher prevalence of idiopathic LVH in males include higher circulating concentration of testosterone and a higher density of myocardial testosterone receptors in males[95,96] and higher peak exercise related systolic blood pressure[97]. Moreover, the use of exogeneous steroids or other performance enhancing drugs is more common in males[98] and it is also possible that there are both quantitative and qualitative differences to the pattern of training among men that may promote increased hypertrophy.

There was a low prevalence of HCM in female decedents. As our population of SCD victims mostly comprised young and asymptomatic individuals, it is possible that HCM was underrepresented in our cohort because women with HCM are older at diagnosis than men.[99,100] Population studies show no differences in overall mortality of appropriate discharge rates from implantable cardioverter defibrillators[101],

however male sex appears to be a risk factor for SCD in athletes and exercising individuals.

Idiopathic fibrosis was detected in 6% of cases. The clinical significance of idiopathic fibrosis is uncertain, however healed myocarditis[102], incomplete expressions of cardiomyopathy or cardiac response to intensive exercise may explain some cases. Studies in masters athletes have shown that fibrosis, detected by late gadolinium enhancement on cardiovascular magnetic resonance (CMR) imaging is generally confined to males and that long-standing intense exercise may be a causal factor with demonstration of an increased prevalence of myocardial fibrosis on CMR mainly in male endurance veteran athletes.[103,104] A relationship between dose and years of exercise and most importantly peak exercise blood pressure and presence of myocardial fibrosis have been shown, raising the possibility that females may be less affected because blood pressure is lower during exercise.

None of female decedents were diagnosed with myocarditis compared with 5 males. It is recognised that males are more commonly affected with myocarditis.[105] Murine studies have revealed that daily exercise in mice infected with Coxackievirus is associated with an increased risk of fulminant myocarditis and testosterone promotes increased inflammation, fibrosis and heart failure.[106] It is possible that male athletes may be more inclined to ignore coryzal symptoms enhancing the likelihood of fatal arrhythmias in the context of acute myocarditis and use exogeneous anabolic steroids more frequently which may induce myocarditis.[107]

5.7.1 Relation of sudden cardiac death to exercise

There was a greater prevalence of SCD during exercise in males and females, however 42% of all deaths in females occurred at rest compared with 17% in males. Most of exercise-induced deaths occurred during swimming (14/57) and SADS accounted for 10 of these deaths. The deleterious effect of swimming in long QT syndrome has been previously described. In a study of 35 cases affected by long QT syndrome, six had a personal or family history of drowning or near drowning.[108] Swimming may trigger cardiac events in nearly 15% of children and young adults with long QT syndrome, especially LQT1. It is postulated that activation of the sympathetic nervous system during cold water immersion and simultaneous activation of the parasympathetic nervous system during voluntary apnoea whilst diving introduces an autonomic conflict that predisposes to a fatal ventricular arrhythmia.[109,110]

5.7.2 Limitations

Our study does have some noteworthy limitations. Firstly, in our cohort 13% of SCD occurred in female athletes compared to 87% in men. As this is a registry based post-mortem study, we are unable to provide precise reasons for this sex-based difference in mortality and this lends itself to future work. Secondly, our center usually receives cases of SCD in young individuals, including athletes with ambiguous autopsy or where an inherited cardiac condition is suspected. This referral bias means that overt pathologies that are predominant in middle aged and older athletes such as coronary artery atherosclerosis are underrepresented in our cohort, therefore the results of our study generally pertain to young (<35 years old) athletes and furthermore we are unable to provide any estimates to general

population level incidence rates. Thirdly, it is possible that subtle or incomplete expressions of cardiomyopathy may have been misclassified as SADS, however, considering our thorough laboratory protocol, it is highly unlikely that such cases accounted for a significant proportion of deaths attributed to SADS. Fourthly, our study is a pathology series, therefore we do not have any data pertaining to survivors of sudden cardiac arrest (SCA). As such it is possible that the results are biased towards lethal causes of SCA such as cardiomyopathies and primary arrhythmia syndromes, while diseases more amenable to survival following cardiac arrest are under-represented. Finally, a limitation of our study is the absence of genetic testing data, from a molecular autopsy, in our cohort and the lack of antemortem 12-lead ECGs.

5.8 **Conclusions**

Sudden cardiac death occurs less frequently in female athletes than male counterparts. Sudden arrhythmic death syndrome accounts for the majority of deaths in female athletes in all age groups. More than 40% of female athletes die at rest or during daily activities, underscoring the need for preventative strategies, such as pre-participation screening which can be complementary to the widespread use of AEDs in public places. Furthermore, the wider inclusion of female sex in SCD registries will continue to enhance our understanding of sex differences which in tandem may provide unique insights from a preventative perspective.

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Disclosures:

No author has any relevant conflicts of interest to declare.

5.9 Clinical implications

The prevalence of SADS among victims of SCD in our study highlights the importance of preventive measures, particularly pre-participation screening. It is noteworthy that only a minority of athletes exhibited warning symptoms or had a family history of cardiac issues. This underscores the potential limitations of relying solely on medical health questionnaires and physical examinations as screening tools.[102]

Since SADS often results from channelopathies, which can be detected with an ECG even in individuals without symptoms, advocating for ECG-based screening policies becomes pivotal in early identification and management of at-risk individuals. Additionally, the widespread deployment and education around the use of Automatic

External Defibrillators (AEDs) in sporting venues proves invaluable across various ages and demographics. However, it is crucial to acknowledge that nearly half of the female athletes in our study experienced cardiac events during their daily activities, where timely access to an AED may have been limited, potentially preventing some of these tragic deaths.

Moreover, the past two decades have witnessed significant growth and infrastructure development in female sports, such as football. Our findings may lend support to the implementation of similar pre-participation screening initiatives in women's sports, mirroring what has been widely practiced in men's sports.

5.9.1 Clinical parallels: case in point. Female sex and persistent inequalities in the care of patients with hypertrophic cardiomyopathy.

(Publication attached in appendix 1)

Inequalities in healthcare have existed for decades and have been exemplified by the COVID-19 pandemic. Specific characteristics such as sex, ethnicity, age and disability, social, cultural and economic factors, and geography have all been implicated. Cardiovascular disease (CVD) has historically been viewed as a "*man's disease*". Although campaigns have helped to increase awareness, CVD in females remains understudied, under-recognised, underdiagnosed, and undertreated.[111] While biological differences between females and males likely contribute to differences in outcomes, disparities in preventive strategies, diagnosis and appropriate treatment also play a role. Scientific societies and the World Health Organisation (WHO), recognise the complex interplay between sex and gender as

important factors, in addition to the biological science, which when addressed holistically, may reduce the burden of CVD.[111–113]

Similar to other cardiovascular diseases, sex related differences have been reported in hypertrophic cardiomyopathy (HCM). As acknowledged, in our study there was a low prevalence of HCM in female decedents of SCD, in what was overall a young cohort of athletic individuals. However, this observation touches on interesting findings from other studies in the non-athletic population which warrant mention.

Olivotto et al.[99] studied 969 consecutive HCM patients in Italy and North America, with a follow up period over 6.1±6.1 years. The authors reported that at initial evaluation in a tertiary referral setting, female patients were older (47±23 vs. 38±18 years; $p<0.001$), more likely to exhibit left ventricular outflow tract obstruction and in a worse New York Heart Association (NYHA) functional class. Although HCM related mortality was similar between sexes, females were more likely to progress to NYHA functional class III/IV and had higher mortality due to heart failure and stroke. A recent meta-analysis on sex-related differences in HCM with a total of 9,427 patients, including 3,719 females, reported that females were at increased risk of all-cause mortality (OR:1.63, 95% CI:1.26–2.10, $p\leq0.001$), HCM-related mortality (OR:1.47, 95% CI:1.08–2.01, $p=0.015$), and worsening HF or HF hospitalization (OR:2.05, 95% CI:1.76–2.39, $p\leq0.001$).[114]

Recently, Javidgonbadi et al[115] performed a seminal retrospective analysis of a non-selected cohort of patients with obstructive HCM (oHCM) to identify factors that account for excess mortality in female patients. The authors interrogated databases

in all ten hospitals in the West Götaland Region in Sweden which yielded 250 patients with oHCM, 123 (49%) females. Clinical information was systematically recorded at baseline and last assessment. To facilitate comparison on the effect of therapy, the authors converted beta-blocker doses to an equivalent dose of metoprolol. For survival analysis, the cohort was further divided into 83 pairs matched for age at diagnosis, degree of LVH, LVOT gradient and treatment strategy, which included, medical therapy only, pacing, or myectomy. The authors should be commended on collecting follow up data for the entire cohort for a mean of 18.1 years.

There are three pertinent findings from this study. Firstly, females were on average 11 years older than males at the time of diagnosis with oHCM and had a more severe disease phenotype, as evident by greater BSA adjusted left ventricular septal hypertrophy and greater proportion with severe symptoms, NYHA class-III. These findings are consistent with previous studies. Unlike ischaemic heart disease where biological factors may explain clinical expression of the disease at a later stage in females, more plausible reasons in oHCM include delayed recognition, reluctance of females to seek medical attention until symptoms are severe and physician bias. It is well established that females exhibit 1-2mm lower absolute wall thickness to males.[116] The lack of sex-specific diagnostic criteria in HCM and the widespread use of absolute wall thickness in clinical practice, means that females need to exhibit proportionally greater wall thickness than males to satisfy a diagnosis of HCM. Females with CVD may present at a later stage due to a combination of false perceptions, atypical symptoms but also social, cultural, and economic barriers. Physicians may misinterpret symptoms in females and evidence suggests that even

guideline recommended investigations may be delayed or performed less frequently in females.[117] This notion is further reinforced in the study by Javidgonbadi et al,[115] where 51% of males underwent genetic testing compared to only 28% of females, despite the fact that HCM is largely inherited in an autosomal dominant pattern and genetic testing in an affected individual has an integral role in familial cascade screening.

Secondly, females had excess disease-related mortality compared to males (2.8% versus 1.4% per annum). The excess female mortality stemmed from the older age groups (≥50 years) and was due to heart failure (HF) and myocardial infarction (MI) related deaths. Although at first glance excess female mortality may be attributed to delayed diagnosis and treatment and worse clinical profile at baseline compared to males, the mortality differences persisted even in groups matched for age and established risk factors, such as LVOT gradient and NYHA class at diagnosis. Most studies in the literature demonstrate excess female morbidity and mortality, with some reporting higher all-cause mortality among female patients, while other studies showing an excess of female death from heart failure or stroke but no difference in overall mortality. In a large multicenter report of 4893 patients (36.1% females) with HCM presenting at 7 European referral centers, the investigators found excess mortality in females compared with males that persisted throughout the age spectrum.[118] Such findings suggest that biological factors and postmenopausal endocrine changes may impact the clinical course of females with HCM, although accrued myocardial injury and resultant fibrosis due to delayed recognition and treatment is also plausible. Unfortunately, the study by Javidgonbadi et al [115] did not include data from CMR imaging, which is increasingly being incorporated into contemporary risk stratification by clinicians globally.

From a therapeutic perspective higher beta-blocker dose, above the cohort-median, was associated with reduced disease-related mortality, irrespective of sex, with survival curves separating 5 years after diagnosis.[115] Betablocker therapy was well tolerated as more than 85% of the cohort were established on treatment at follow-up and only 3.2% discontinued treatment during the course of the study. However, fewer females received betablocker therapy after diagnosis (64%) compared to males (78%) and in smaller doses, which is surprising considering females were more symptomatic and with similar prevalence of LVOT obstruction at diagnosis. Female patients were prescribed more frequently calcium channel antagonists which in this study was associated with increased disease-related mortality. The reason for the different prescribing approach was unclear and could not be justified based on the clinical information available.

By nature of the study design and cohort size, these results should be viewed with caution but provide invaluable insights into sex disparities in conditions such as HCM. Further research in the form of prospective randomised trials is required to evaluate disease-modifying effects of drug therapy. In the context of the relative low prevalence of the condition and the low mortality rates, such studies will require large numbers of patients and prolonged follow-up, suggesting that they are unlikely to materialise outside the context of publicly funded, multinational collaboration.

Recently, Dybro et al[119] investigated the effects of metoprolol on LVOT obstruction, symptoms, and exercise capacity in oHCM in a double-blind, placebo-controlled randomised crossover study. Compared to placebo, metoprolol therapy reduced LVOT obstruction at rest and during exercise, provided symptom relief and improved

quality of life. However, maximal exercise capacity was unchanged, and the trial was not designed to look at survival benefit.

In agreement with cumulative evidence, the seminal study by Javidgonbadi et al[115] suggests considerable sex-related differences in oHCM. It is evident that there is room for significant improvement in the management of females with oHCM. This must start with improved awareness and recognition of the condition in females to reduce time to diagnosis, followed by appropriate, evidence-based management (central illustration). Potential solutions include (figure 26), addressing sex and gender specific challenges posed by social, cultural and economic aspects in the delivery of care to patients with HCM; broadening the diagnostic criteria, whereby an absolute maximal wall thickness of 13-14mm in a female may facilitate early disease surveillance and diagnosis; use of normalised wall thickness measurements in everyday clinical practice; developing sex-specific risk stratification models which go beyond the risk of SCD and address the broader HCM-related mortality and progression of HF; and promote appropriate genetic testing to facilitate early familial screening. Above all, similar to the study of Javidgonbadi et al,[115] females must be well represented in HCM studies and also studies in general, particularly in the context of SCD, which in tandem can facilitate a sex-specific evidence base and ensure that females benefit from the survival and quality of life improvements conferred by the refinement of HCM treatments.

Importantly, drawing parallels to post-mortem datasets as initially described in this chapter, it is worth acknowledging that taking into consideration data from the aforementioned studies, perhaps more gender specific cut off values need to

be explored in the setting of the autopsy and SCD. This again, emphasises the importance of the expert histopathologist in distinguishing between similar pathologies such as HCM and ILVH.

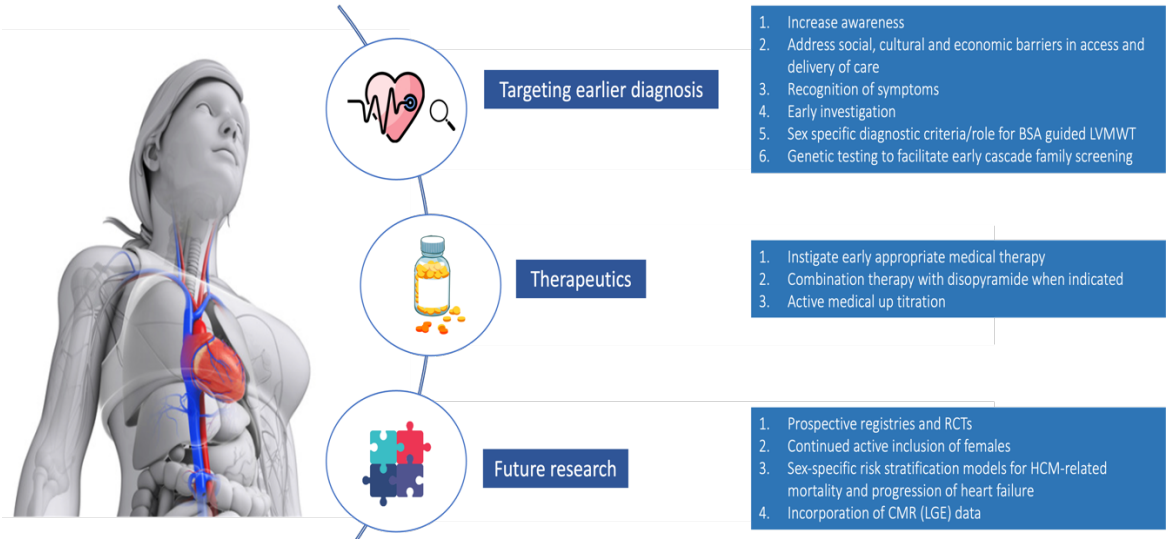


Figure 26: Case in point. Clinical pointers that deserve considerable attention in the management of female patients with hypertrophic cardiomyopathy. BSA, body surface area; CMR, cardiac MRI; HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement; LVMWT, left ventricular maximal wall thickness; RCTs, randomized control trials.

Chapter 6: Mitral Valve Abnormalities in Decedents of Sudden Cardiac Death due to Hypertrophic Cardiomyopathy and Idiopathic Left Ventricular Hypertrophy

(Publication attached in appendix 1)

6.1 Abstract:

Background: The sole identification of left ventricular hypertrophy (LVH) in a young individual that died suddenly may often lead to an erroneous diagnosis of hypertrophic cardiomyopathy (HCM). Emerging data suggests that idiopathic LVH (ILVH) and HCM may be separate entities.

Aim: We aimed to report on the prevalence and nature of mitral valve (MV) abnormalities, in a cohort of sudden cardiac death (SCD) victims with a post-mortem examination consistent with HCM and ILVH.

Methods We reviewed 6860 consecutive cases of SCD referred to our specialist cardiac pathology centre between 1994 and 2020. SCD was defined as death from a cardiovascular cause within 12 hours of apparent well-being. HCM was defined by the presence of LVH, in the absence of abnormal loading conditions and characterised by myocyte disarray at histology. ILVH was defined as unexplained LVH (heart weight >500 g in males and >400 g in females) and left ventricular (LV) wall thickness >15 mm, in the absence of myocardial disarray or secondary causes of LVH. The MV was examined for patency, circumference, thickening, nodularity, ballooning, bulging between cords, perforation, and the presence of impact lesions in the LV outflow tract (LVOT) and aortic outlet.

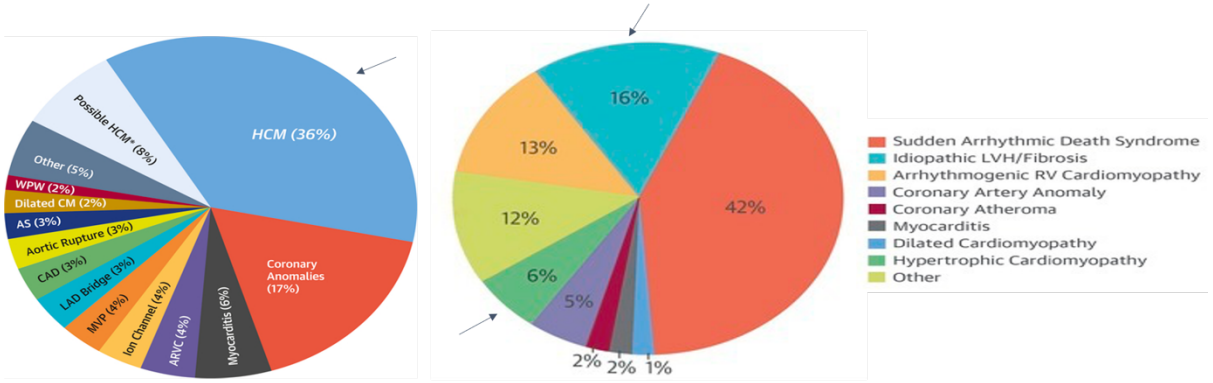
Results Of the total cases of SCD, 264 (4%) were due to HCM (mean age 41±18 years, 78% males, LV maximal wall thickness 19±6 mm). Ante-mortem symptoms were reported in 44 (17%) cases and for the majority (n=217, 82%) HCM was established at post-mortem. Death was attributed to ILVH in 253 (3%) cases (mean age 43±16 years, 80% males, LV maximal wall thickness 18±4 mm). MV abnormalities were found in 58 (22%) decedents with HCM (mean age 38±17 years; 72% males) and in 13 (5%) decedents with ILVH (mean age 55±15 years; 77% male), $p<0.001$. Amongst the 58 (22%) cases with HCM and MV abnormalities, 15 (6%) cases had multiple MV abnormalities. These included impact lesions associated with thickening of the anterior leaflet of the MV (n=39) and degenerative changes (n=34) such as bulging and ballooning; and thickening and nodularity. Decedents with HCM exhibiting MV abnormalities were younger than decedents with a normal MV (38±17 versus 45±19 years; $p=0.08$). Among the 253 decedents with ILVH, 13 (5%) cases exhibited MV abnormalities, which largely included degenerative changes (n=12). Among decedents with HCM and ILVH exhibiting MV abnormalities, the former was significantly younger (38±17 versus 55±15; $p=0.001$). Myocardial fibrosis was observed in 162 (61%) cases of HCM and 99 (39%) cases of ILVH, $p<0.001$.

Conclusion This is the first histopathological study to demonstrate that MV abnormalities are over four-fold more common in individuals with HCM than those with ILVH and may be considered as additional macroscopic features to differentiate between these two entities. Furthermore, the inherent descriptive terminologies used

when assessing the MV, support a greater emphasis on the standardisation and quantification of MV abnormalities as part of the autopsy in victims of SCD.

6.2 **Introduction:**

Sudden cardiac death (SCD) in apparently healthy individuals is commonly due to a diverse spectrum of inherited cardiac diseases (ICCs). Historically, hypertrophic cardiomyopathy (HCM) has been regarded to account for approximately 1/3rd cases of non-traumatic related SCDs. This data has largely stemmed from North America[26], whilst contemporary studies, identify myocardial disease in 40% of cases of SCD victims – from which HCM represents 6% of the overall cohort and in fact an entity known as idiopathic left ventricular hypertrophy accounts for 16% of mortality (figure 27). [7] This perhaps also raises concerns around historical categorization of cases as hypertrophic cardiomyopathy and again emphasizes the importance of expert cardiac histopathologists.



Maron, Barry J. Historical perspectives on sudden deaths in young athletes with evolution over 35 years. *The American Journal of Cardiology* 116.9 (2015): 1461-1468.

Finocchiaro, Gherardo et al. "Etiology of Sudden Death in Sports: Insights From a United Kingdom Regional Registry." *Journal of the American College of Cardiology* vol. 67,18 (2016): 2108-2115.

Figure 27 Aetiology of sudden cardiac death in athletes. Insights from North America and the United Kingdom.

Overall HCM in the general population is quoted to have a prevalence of 1:200 to 1:500 with the pathognomonic finding of unexplained LV hypertrophy of ≥15 mm and

on histology is characterised by the presence of myocyte disarray.[59] However, in living individuals, a wall thickness of ≥13 mm in the context of a family history of positive genetic test may also be regarded to demonstrate a phenotype for HCM.[59] Furthermore, at autopsy, the heart may in fact be macroscopically normal, emphasising the importance of detailed microscopic examination, which may reveal evidence of LV myocyte disarray (>20% disarray in at least two cardiac sections) with or without interstitial or replacement fibrosis and thick-walled blood vessels.[74]

The interpretation of autopsy findings in the context of SCD is complex and the sole identification of significant LVH in a young individual that died suddenly may often lead to an erroneous diagnosis of HCM. A recent study from our group suggests that idiopathic LVH (ILVH), which is an increasingly common entity identified at autopsy is a separate entity from HCM.[120]

6.3 **Aim**

We aimed to report on the prevalence and nature of MV abnormalities, in a cohort of SCD victims with a post-mortem examination consistent with HCM and ILVH. We hypothesised that MV abnormalities are more common in individuals with HCM than those with ILVH and considered as additional macroscopic features to differentiate between these two entities in the setting of SCD.

6.4 **Personal contribution**

I formulated the study hypothesis, reviewed and analysed the St George's University and CRY sudden death database, performed quality control, statistical analysis, manuscript preparation and subsequent manuscript revisions. I specifically reviewed

all post-mortem reports and the clinical and histopathological features of each individual included in the database. I was not directly involved with the post-mortem evaluation or toxicology screen of any of the subjects which was performed by our cardiac pathology team (MNS and JW). RTB presented the findings from this work at national and international meetings.

6.5 **Methods**

In the United Kingdom (UK) where there is a sudden unexpected death, the case is referred to the attention of the coroner and local pathologist (figure 28). Where the cause of death remains uncertain, the case is often referred to the Cardiac Risk in the Young Centre for Cardiac Pathology (CRY-CCP). Over the past 26-years, we have managed to assess 6860 consecutive cases of SCD. For the purpose of this study, we reviewed all 6860 consecutive cases of SCD referred to our specialist cardiac pathology centre between 1994 and 2020. SCD was defined as death from a cardiovascular cause within 12 hours of apparent well-being. Comprehensive clinical information from the coroner was collected. This included, age, sex, body weight, clinical information, family history, previous electrocardiograms (ECGs), previous cardiac imaging, histology, cause of death and letter to the pathologist. All cases underwent detailed autopsy evaluation and a minimum of 10 tissue blocks underwent histological analysis.[76]

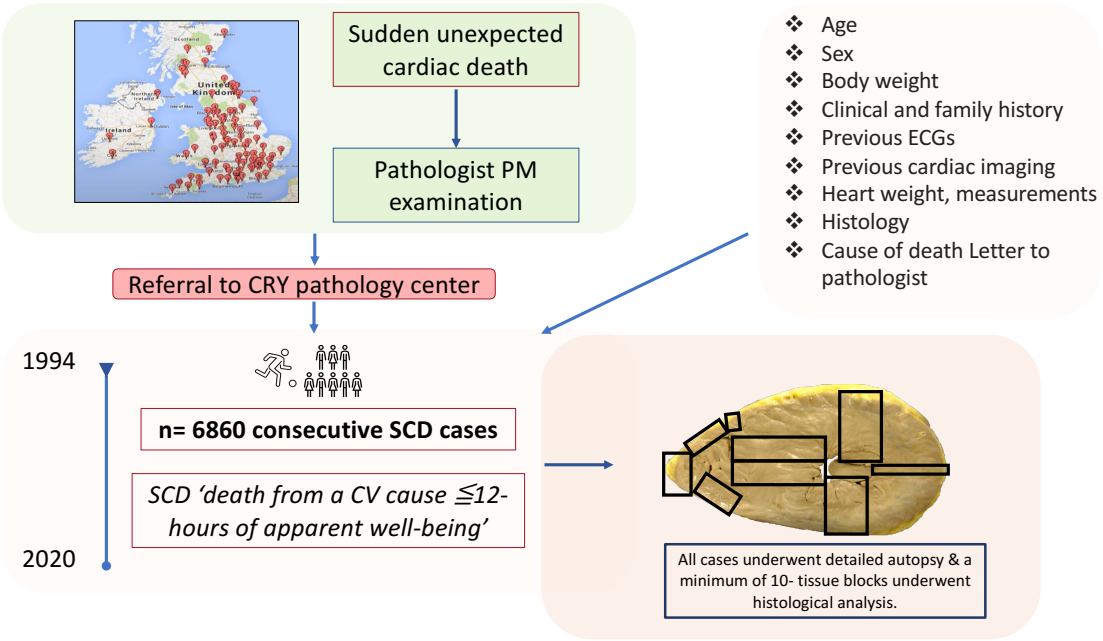


Figure 28: study overview.

ILVH was defined as unexplained LVH (heart weight >500 g in males and >400 g in females) and left ventricular (LV) wall thickness >15mm, in the absence of myocardial disarray or secondary causes of LVH such as hypertension or coronary artery disease.[120] The MV was examined for patency, valvular circumference, thickening, nodularity, ballooning, bulging between cords, perforation, endocarditis, and the presence of impact lesions in the LV outflow tract (LVOT) and aortic outlet. The integrity of the papillary muscles and chordae tendineae were also noted. The following qualitative standardised definitions were utilised to facilitate data analysis of MV abnormalities:

Ballooning of leaflets: prominent saccular bulging of the scallop's inwards and upwards into the atria.

Bulging of leaflets: saccular extension of the scallop's inwards and upwards into the atria.

Fibrosis of leaflets: replacement or infiltration of myocytes by collagenous tissue in an abnormal distribution.

Nodularity of leaflets: uneven thickening of the leaflets with multiple foci of calcification.

Thickening of leaflets: an increase in the measurement between the atrial and ventricular surfaces of the leaflet with some allowance made with increasing age.

The MV annular circumferences of between 5 to 10 cm was regarded as normal. In the closed position as a floor to the left atrium, the anterior MV leaflet is regarded make up one third of the annual circumference.

LV wall thickness measurements have been made in systole, which is not comparable with measurements from imaging studies. In addition, appreciably this poses challenges in conclusively commenting on the presence of LV outflow tract obstruction (LVOT obstruction). However, we have described the presence of impact lesions in the cohort, which could be regarded as a surrogate marker for individuals that may have had LVOT obstruction.

To assist our analysis, we utilised the following classification system of LV hypertrophy:

1. Asymmetrical septal hypertrophy
2. Asymmetrical non septal hypertrophy
3. Symmetrical hypertrophy
4. Myocyte disarray and myocyte hypertrophy, with no evidence of left ventricular hypertrophy

6.5.1 Ethical approval

Ethical and research governance approval has been granted for this study (10/H0724/38). The next of kin consented to material retention for anonymized research in each case. Data will be made available upon reasonable request to the corresponding author.

6.5.2 Statistical analysis

Statistical analysis was performed using Microsoft Excel 365 (2021). Results are expressed as mean ± standard deviation (SD) for continuous variables or as number of cases and percentage for categorical variables. Comparison of groups was performed using Student's T-test for continuous variables with correction for unequal variance when necessary and Chi-square test or Fisher Exact Test, as appropriate for categorical variables.

6.6 **Results**

From 6860 total cases of SCD (mean age 38 ± 18 years), 264 (4%) were attributed to HCM (figure 29). The mean age was 41 ± 18 years, 78% were males, and 72% Caucasian. The LV maximal wall thickness was 19 ± 6 mm and the mean heart weight was 549 ± 182 g. The mean MV circumference was 80 ± 15 mm and the mean LV cavity size was 32 ± 9 mm. Overall, ante-mortem symptoms were reported in 44 (17%) cases, and for the majority (n=217, 82%) a diagnosis of HCM was established at post-mortem, without any availability of antemortem cardiac imaging. Death was attributed to ILVH in 253 (3%) cases. The mean age was 43 ± 16 years, 80% were males, and 80% were Caucasian. The LV maximal wall thickness was 18 ± 4 mm, and the mean heart weight was 543 ± 137 g. The mean MV circumference was 81 ± 17 mm, and the mean LV cavity size was 35 ± 8 mm.

MV abnormalities were found in 58 (22%) decedents with HCM (mean age 38 ± 17 years; 72% males) and in 13 (5%) decedents with ILVH (mean age 55 ± 15 years; 77% male), $p < 0.001$. Myocardial fibrosis was observed in 162 (61%) cases of HCM and 99 (39%) cases of ILVH, $p < 0.001$.

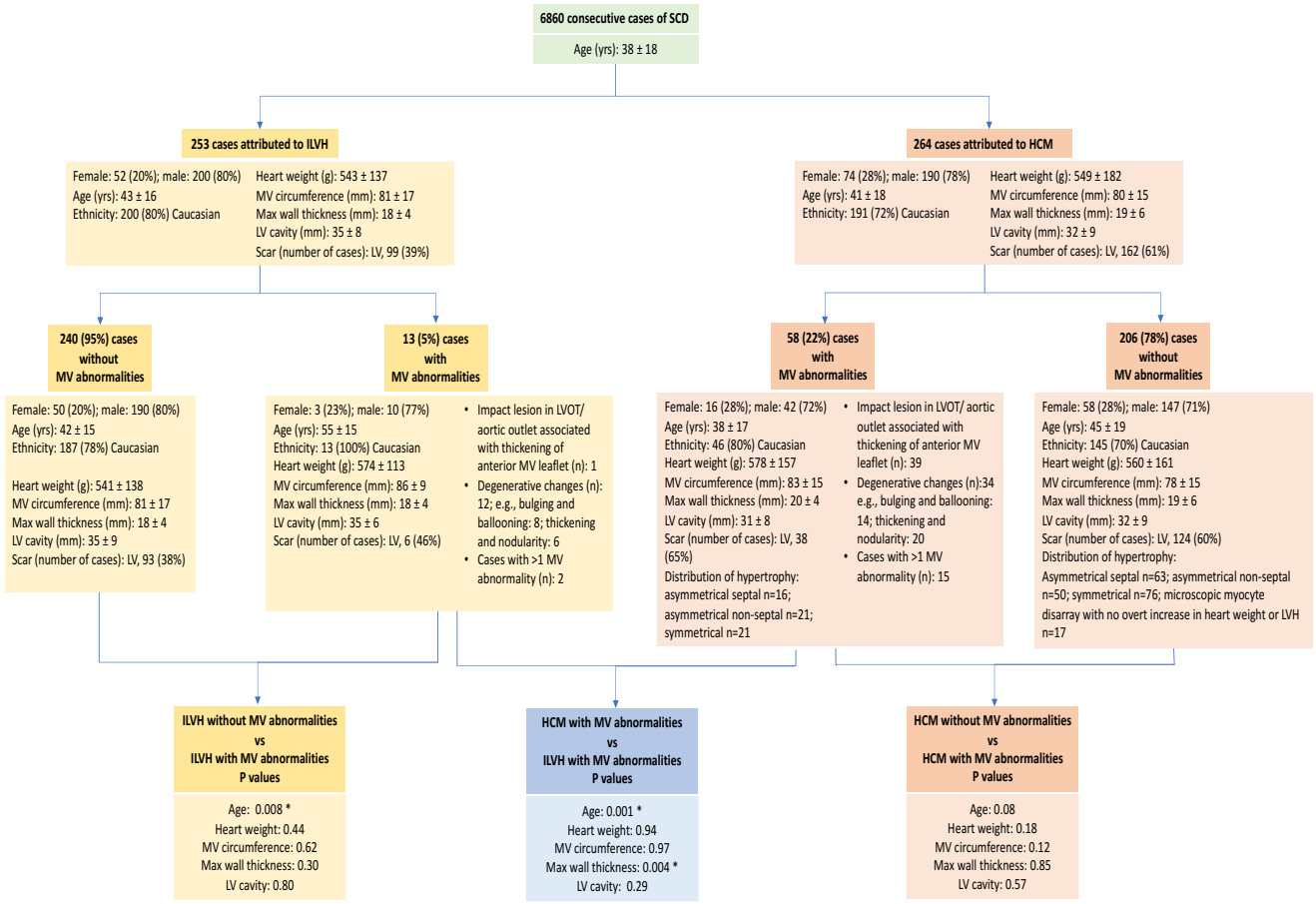


Figure 29 Overall results. HCM, hypertrophic cardiomyopathy; ILVH, idiopathic left-ventricular hypertrophy; LV, left ventricle; MV, mitral valve; RV, right ventricle; SCD, sudden cardiac death. * Statistically significant (P<0.05). MV terminology; Bulging and ballooning: an increase in the area of each leaflet between the attached cords which extend up beyond the atrioventricular junction into the left atrium. Thickening and nodularity: an increased in collagen and expansion of the spongiosa in each leaflet.

Based on our classification system of LV hypertrophy, the following observations were made:

HCM with MV abnormalities n=58 (22%)

- Max wall thickness (mm) 20 ± 4
- Asymmetrical septal hypertrophy n=16
- Asymmetrical non septal, hypertrophy n=21
- Symmetrical hypertrophy n=21

HCM with no MV abnormalities n=206 (78%)

- Max wall thickness (mm) 19 ± 6
- Asymmetrical septal hypertrophy n=63
- Asymmetrical non septal, hypertrophy n=50
- Symmetrical hypertrophy n=76
- Myocyte disarray and myocyte hypertrophy, with no evidence of left ventricular hypertrophy n=17

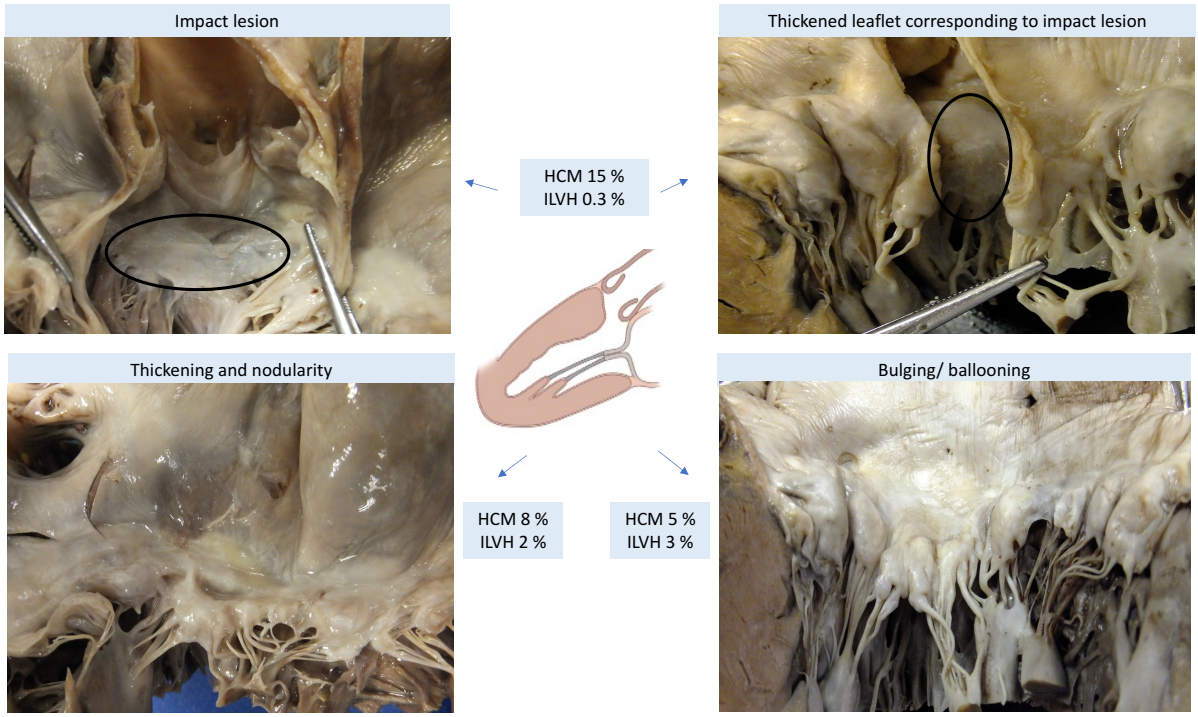
Amongst the 58 (22%) cases with HCM and MV abnormalities, 15 (6%) cases had multiple MV abnormalities. These included impact lesions associated with thickening of the anterior leaflet of the MV (n= 39) and degenerative changes (n=34) such as bulging and ballooning; and thickening and nodularity. Decedents with HCM exhibiting MV abnormalities were younger than decedents with a normal MV (38 ± 17 years versus 45 ± 19 years; p=0.08).

Among the 253 decedents with ILVH, 13 (5%) cases exhibited MV abnormalities, which largely included degenerative changes (n=12). Among decedents with HCM and ILVH exhibiting MV abnormalities, the former was significantly younger (38 ± 17 versus 55 ± 15; p= 0.001) and had a higher degree of LVH (20± 4 mm versus 18 ± 4 mm).

Intriguingly, individuals with ILVH that demonstrated MV abnormalities, compared to those with ILVH who did not demonstrate MV abnormalities were significantly older

(55±15 years versus 42±15 years; p <0.008) and tended to demonstrate a higher proportion of degenerative changes as opposed to the HCM cohort (figure 29 and figure 30).

Figure 30: Mitral valve abnormalities in decedents of sudden cardiac death due to hypertrophic cardiomyopathy (HCM) and idiopathic left ventricular hypertrophy (ILVH). Histopathological specimens from cases included in study. Images courtesy of Professor Mary Sheppard (MNS) and Dr Joseph Westaby (JW), CRY-CCP, St. George's, University of London.



6.7 Discussion

MV abnormalities were identified in 22% and 5% of decedents of SCD attributed to HCM and ILVH, respectively. Imaging studies, predominantly on cohorts with dynamic LVOT obstruction have reported mitral malformations in up to 70% of HCM

patients.[121,122] Kaple et al., demonstrated that 14% of patients undergoing surgery for HCM, following transthoracic and transoesophageal echocardiogram required a concomitant MV procedure, which included 58% undergoing a MV repair and 43% a MV replacement.[121] Similarly, Maron et al., utlised cardiovascular magnetic resonsance imaging to demonstrate that anterior and posterior MV leaflet lengths are greater in HCM patients than in control individuals, with no overt relationship between leaflet length and maximal LV wall thickness.[122] Whereas the same information in decedents of SCD with HCM and ILVH, prior to our study was largely unknown.

We speculate that the lower prevalence of significant MV abnormalities in our cohort may be due to a lower proportion of obstructive cases, since most decedents did not have any pre-existing cardiovascular symptoms and SCD was the first manifestation of the disease. As has been noted in analysis of our ONS data, the CRY-CCP does not receive all cases of sudden death that are attributed to cardiomyopathies in the UK. Although LV outflow tract obstruction is regarded as a risk factor for fatal arrhythmias, an impact lesion was observed only in 39 out of 264 cases of HCM (15%), suggesting that systolic anterior motion of the MV (SAM) and possible dynamic obstruction were relatively rare in this population.

MV abnormalities were rare in ILVH and were found in older individuals, suggesting an underlying mechanism that is un-related to a sarcomeric disease. A recent study by Finocchiaro et al., further supports this observation in that 125 first-degree relatives underwent comprehensive clinical and genetic assessment by experts in inherited cardiac conditions.[120] The diagnostic yield in first degree relatives for a

cardiac condition was 30% and this primarily included individuals with inherited arrhythmia syndromes and cardiomyopathy. However, strikingly, no family member was diagnosed with HCM, and genetic evaluation did not yield any pathogenic variants in genes encoding sarcomeric proteins.[120]

It is worth acknowledging that in addition to overt mitral valve abnormalities in individuals with cardiomyopathies such as HCM and ILVH, additional abnormalities, particular those relating to the sub mitral apparatus also exist. These include abnormalities of the papillary muscles and the insertion into the MV leaflets, significant hypertrophy of the papillary muscles, fusion of the anterior papillary muscle with the ventricular septum or left ventricular (LV) free wall, abnormal chordae tendineae arrangements and accessory papillary muscles. Mechanistically, all of the above geometrical arrangements can contribute to bowing of the MV leaflets towards the septum and accentuating a left ventricular outflow tract gradient. However, historically even in living individuals the variety of permutations of the sub-MV apparatus, can be challenging to appreciate using traditional imaging modalities such as 2- dimensional echocardiograph. Based on our clinical expertise, and in vivo studies, the clinical consequences of mitral valve abnormalities including those listed above, largely also depend on the functional status of the LV and modulators of the haemodynamic status of an individual, which may include, age, sex, ethnicity, baseline physical activity level, co-existing anaemia, infection and electrolyte disturbances.

Antemortem information for example, from imaging studies was not available due to 82% of cases of sudden cardiac death (SCD) being the first manifestation of

hypertrophic cardiomyopathy (HCM). Furthermore, our study is purely addressing autopsy findings in decedents of SCD and pathologists historically, do not routinely describe the papillary muscles other than in the context of abnormalities such as rupture, infarction or infection. Our expert histopathologists (JW and MNS), appreciate that post-mortem measurements do not necessarily correlate with imaging studies due to the inanimation of the heart. Furthermore, the papillary muscles demonstrate great heterogeneity even within a structurally normal heart, with further variations even between different ethnicities. In our opinion, this lends itself for future work in the form a detailed anatomical study, in which the first step would be to characterise the papillary muscles in the normal heart at autopsy across a broad range of ethnicities, prior to assessing any changes within a cohort of individuals with mitral valve abnormalities. A limitation of our current study is the absence of findings from molecular autopsy. Furthermore, the inherent descriptive terminologies used when assessing the MV, support a greater emphasis on the standardisation and quantification of MV abnormalities as part of the autopsy.

6.8 **Conclusion**

From a histopathological perspective, our study is the first to report that the prevalence of MV abnormalities is over four-fold more common in individuals with HCM than those with ILVH and may be considered as additional macroscopic features to differentiate between these two entities. MV abnormalities were rare in ILVH and were found in older individuals, which suggests an underlying mechanism that is unrelated to sarcomeric disease and continues to support ILVH as a separate entity. Sudden cardiac death was the first manifestation of HCM in 82% of cases. From a clinical perspective, these findings may facilitate onward risk-stratification

from a preventative perspective in family members of SCD victims and encourage the utilisation of broader diagnostic criteria. This includes individuals and athletes who may undergo cardiac imaging as part of primary preventative screening initiatives.

Acknowledgements:

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Funding sources:

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Disclosures:

No author has any relevant conflicts of interest to declare.

6.9 Clinical implications

From a clinical perspective, this histopathological study describes the relationship between MV abnormalities in SCD cases associated with HCM and ILVH. All cases underwent examination by expert cardiac histopathologists using stringent criteria to ameliorate any ambiguity in the cause of death, particularly in the setting of SCD with

the presence of left ventricular hypertrophy, which in other series may been categorised as probable HCM deaths.[22]

In situations of diagnostic uncertainty following SCD, paying attention to MV abnormalities may aid in distinguishing between underlying pathologies which historically have been regarded as similar entities. Notably, MV abnormalities are observed to be more than four times as prevalent in individuals with HCM, suggesting their potential utility not only in post-mortem diagnosis but also as subtle indicators of underlying pathology in cases where cardiac imaging has been conducted for specific reasons antemortem. This finding has important implications, especially when considering follow-up care for young individuals, particularly adolescents, where age-related penetrance of overt cardiomyopathy phenotypes is often observed. Additional supportive features may help guide clinicians in assessing the level of suspicion and the need for ongoing surveillance, as our findings indicate a high index of suspicion and expansion of historical morphological definitions of HCM, beyond a disease specifically of the myocardium. Whilst our study identified systolic anterior motion of the MV and dynamic obstruction as relatively rare occurrences in the studied population, it remains crucial for clinicians to remain vigilant regarding dynamic outflow tract obstruction in HCM patients, especially those experiencing symptoms. Timely and appropriate management may help alleviate symptoms and reduce mortality.

Chapter 7: Sudden Cardiac Death During Exercise in Young Individuals With Hypertrophic Cardiomyopathy

(Publication attached in appendix 1)

7.1 Abstract

Background: Sudden cardiac death (SCD) in young individuals and athletes is generally caused by hereditary cardiac conditions, including cardiomyopathies such as hypertrophic cardiomyopathy (HCM). Although historically HCM has been reported as the predominant cause of SCD in young athletes, it is unclear as to what degree exercise is a trigger for possible fatal arrhythmias.

Aim: We aimed to report on the circumstances of SCD in a cohort of young individuals aged ≥10 and <30 whose autopsy was consistent with HCM.

Methods: We reviewed 6860 consecutive cases of SCD referred to our specialist cardiac pathology centre 1994 and 2020. SCD was defined as death from a cardiovascular cause within 12 hours of apparent well-being. All cases underwent detailed autopsy evaluation of the heart, including histological analysis, by expert cardiac pathologists (MNS and JW). A minimum of 10 blocks of tissue were taken for histological analysis. HCM was defined by the presence of increased heart weight or increased wall thickness and significant myocyte disarray at histological examination.

Results: Of the total cases of SCD, 264 (4%) were due to HCM. Our cohort of young decedents comprised of 66 individuals (average age 21±5 years, males 76%). For the majority (n=52, 79%) SCD was the first manifestation of HCM. The average heart weight was 507±152 grams and left ventricular (LV) fibrosis was found in 36 (54%) cases. Death was more common between 16 and 20 years of age (n=24). Death occurred during exertion in 25 (38%) individuals and at rest or during daily activities in the remaining 41 (62%), including 5 individuals who died during sleep. Male sex was more represented among decedents who died during exertion (88% compared with 68% in the group that died at rest, p=0.07); LV fibrosis was more commonly observed in individuals who died during exertion (56% compared with 34% in the group who died at rest, p=0.08). Younger individuals between 10–15 years of age died mostly during exercise (80%), in other age groups death occurred mainly at rest (33% in age group 16–20 years, 30% in age group 21–25 years, 33% in age group 26–30 years).

Conclusions We observed a high age-related variability in terms of circumstances of death. In the context of HCM, our findings suggest that individuals aged 10–15 years are the most vulnerable in terms of exercise-related-SCD. This exemplifies the importance of preventative cardiac screening in young individuals who might be harbouring quiescent cardiac conditions associated with young SCD.

7.2 Introduction

Hypertrophic cardiomyopathy (HCM) is a heterogenous disease entity with varied phenotypic expression, symptom burden and natural history.[59,99,100,123] As has been noted, in adults a LV wall thickness of ≥15mm in any myocardial segment that is not explained by abnormal loading conditions, is suggestive of a diagnosis of HCM. However, this is generally the case in adults. In children, the diagnosis is often challenging in view of continued growth and age related penetrance of the condition, and usually a diagnosis requires a LV wall thickness ≥ 2 standard deviations than the predicted mean (z-score > 2).[123,124] In children and adolescents, SCD is the most common mode of death in individuals with HCM and whilst our understanding of risk evolves, it is generally felt that there is a >50% higher risk in children and adolescents compared to adults[123].[59] To this end, Norrish et al., recently published novel clinical findings and survival data in children with HCM, and found that 80% of patients who died suddenly were under the age of 18 at the time of death and patients with more severe disease phenotypes presented at a younger age.[125]

Although the benefits of exercise on individuals of all ages are irrefutable[126], historically, a diagnosis of HCM in athletes, was automatically met with precautionary disqualification or strict advice to athletes to abstain from high intensity training and competitive sport due to the risk of exercise related fatal arrhythmia. Pellicia et al., challenged this notion and explored outcome data in athletes with a median age of 31 years (IQR: 19-44 years) and a low-risk HCM phenotype who engaged in competitive sport and demonstrated no difference in the risk of sudden cardiac arrest (SCA) after 7-years of follow-up.[127] Similarly, Basu et al., recently reported the

absence of a negative impact on cardiac phenotype, in 53 asymptomatic athletes with a morphologically mild HCM phenotype[128], however, it is important to note that the mean age was 39 ± 12 years (range 19 to 65 years). Seminal work by Malhotra et al., with a well-defined denominator of adolescent footballers (mean age 16.4 ± 1.2 years) affiliated with the English Football Association (FA) cardiac screening program demonstrated that HCM was the most common cardiomyopathy identified and accounted for 38% of the SCDs during a mean time of between screening and the occurrence of SCD of 6.8-years.[25] As such, an important observation from most studies with HCM is that data from the adult population, particularly in athletes is far from uniform and may not be extrapolated to children or adolescent individuals where there appears to be a heightened susceptibility to SCD and this likely involves a complex interplay of genetic predispositions, ethnicity and lifestyle factors.

7.3 **Aim**

It is unclear to what degree exercise is a trigger for possible fatal arrhythmias in individuals with HCM. The aim of our study was to build on emerging literature and report on the circumstances of SCD in young individuals whose autopsy was consistent with HCM and performed by expert cardiac histopathologists, taking into account age and physical activity.

7.4 **Personal contribution**

RTB reviewed comprehensive data relevant to the project and assisted with analysis of data and preparation of the published manuscript. RTB was not involved with the

post-mortem evaluation or toxicology screen of any of the subjects that was performed by JW, MNS. RTB presented the findings from this work at national and international meetings.

7.5 **Methods**

We reviewed a database of 6,860 consecutive cases of SCD referred to the Cardiac Risk in the Young (CRY) center for cardiac pathology which is based at St. George's University of London, between 1994 and 2020. SCD was defined as death from a cardiovascular cause within 12 hours of apparent well-being. Clinical information was obtained from referring coroners who were asked to complete a detailed health questionnaire that was filled at the time of the post- mortem examination. All cases underwent detailed autopsy evaluation of the heart, including histological analysis, by expert cardiac pathologists (M.N.S., J.W.). A minimum of 10 blocks of tissue were taken for histological analysis, and HCM was defined as reported previously.

The current study focused on young individuals aged ≥10 and ≦30 years of age (figure 31). Based on our dataset, four age brackets were chosen a priori (10-15 years of age, 16-20 years of age, 21-25 years of age and 26-30 years of age) with the scope to analyse differences in terms of circumstances of death. Death during exercise was defined as occurring while the individual was engaging in exercise, as opposed to death during daily activities, rest or sleep. Particular attention was given to retrieve any information relating to cardiopulmonary resuscitation (CPR) and use of automatic external defibrillators (AED) if performed in the community.

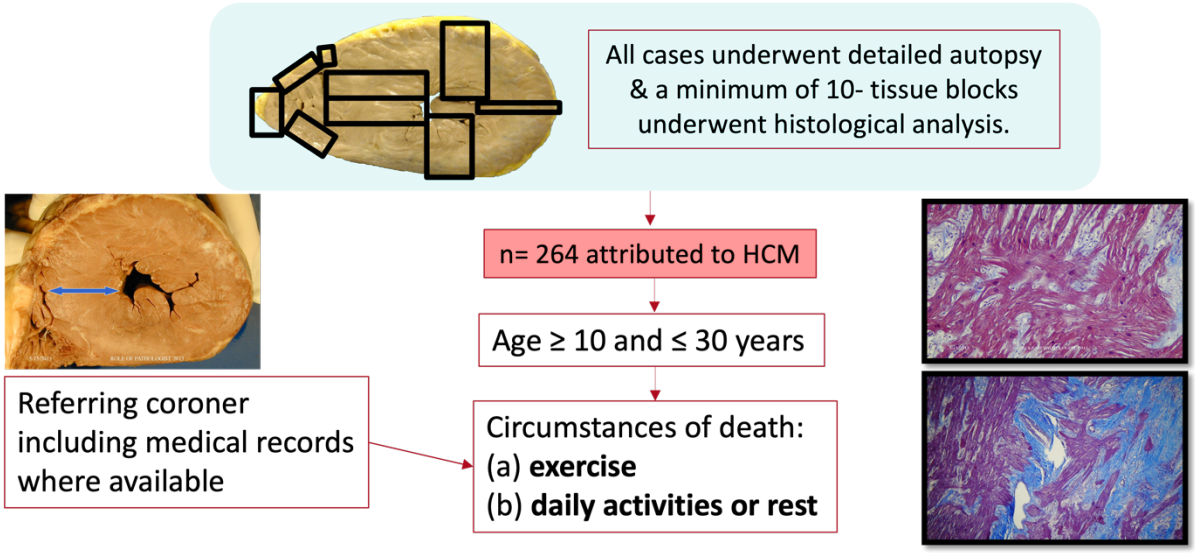

Figure 31: Study overview. HCM: hypertrophic cardiomyopathy.

7.5.1 Ethical approval

Ethical and research governance approval has been granted for this study (10/H0724/38). The next of kin consented to material retention for anonymized research in each case. Data will be made available upon reasonable request to the corresponding author.

7.5.2 Statistical analysis

Statistical analysis was performed using Microsoft Excel 365 (2021). Results are expressed as mean ± standard deviation (SD) for continuous variables or as number of cases and percentage for categorical variables. Comparison of groups was performed using Student's T-test for continuous variables with correction for unequal

variance when necessary and Chi-square test, as appropriate for categorical variables.

7.6 **Results**

Of the total cases of SCD, 264 (4%) were due to HCM. Our cohort of young decedents comprised 66 individuals, with an average age of 21 ± 5 years, 76% were males and 91% were white Caucasian. The mean heart weight was 507 ± 152 g, the LV maximal wall thickness 21 ± 7 mm and fibrosis in the LV was noted in 54% of cases. For the majority (n=52 [79%]), the diagnosis was made only following the autopsy examination. There was no significant difference in baseline characteristics, which included, age, sex, heart weight, LV fibrosis and LV maximal wall thickness, between individuals who died at rest compared to those that died during exercise (table 27). Bystander CPR was performed in 70% of cases, and 23% of cases received automatic external defibrillation AED.

Table 27: Differences between individuals in whom SCD occurred at rest and during exercise. LV: left ventricle.

	Total (n=66)	SCD at rest (n=40)	SCD during exercise (n=26)	p value (<0.05 deemed significant)
Age (years)	21 ± 5	21 ± 5	21 ± 5	0.913
Males n (%)	50 (76)	28 (70)	22 (85)	0.167
Heart weight (grams)	507 ± 152	499 ± 165	519 ± 131	0.620

LV fibrosis n (%)	36 (54)	20 (50)	16 (61)	0.384
Maximal wall thickness (mm)	21 ± 7	22 ± 7	21 ± 6	0.822

The age bracket in which SCD was more common was between 16 and 20 years of age (n=24) (Figure 32). Death occurred during exercise in 26 (39%) individuals (most commonly during football and running activities) (table 28) and at rest or during daily activities in the remaining 40 (62%), including 5 individuals who died during sleep. LV fibrosis was slightly more common in individuals who died during exercise. While younger (age bracket 10-15 years) died mostly during exercise (80%), in other age brackets death occurred mainly at rest (33% in the age bracket 16-20 years, 30% in the age bracket 21-25 years, 33% in the age bracket 26-30 years) (Figure 32).

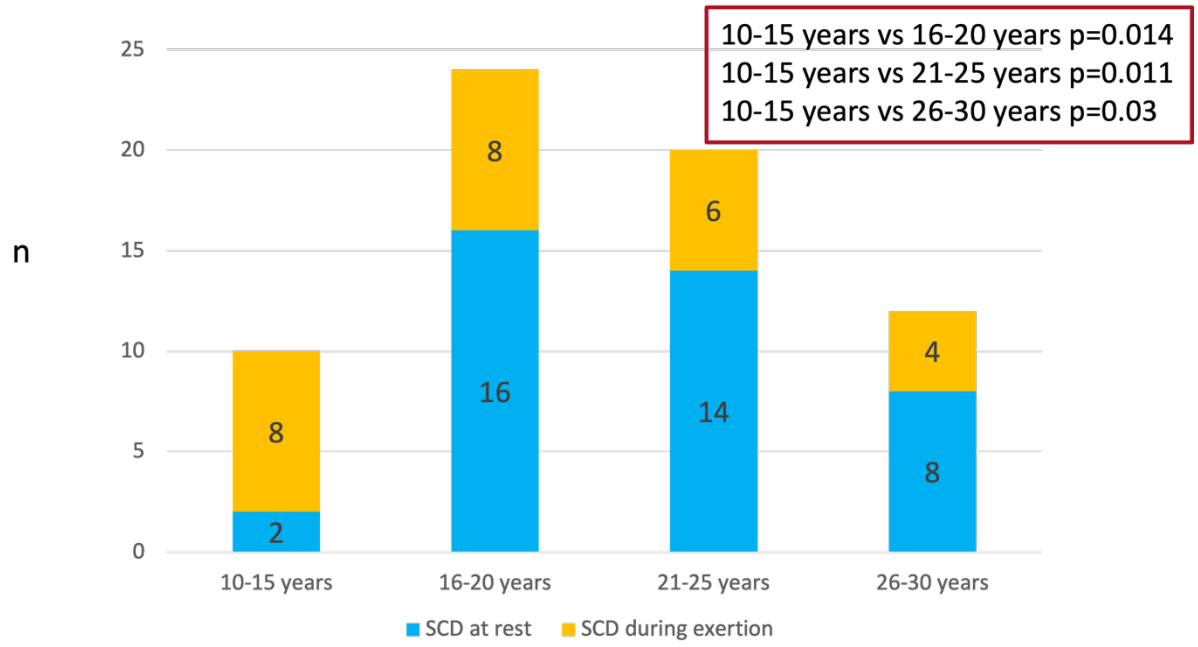

Figure 32: Age brackets and circumstances of SCD. n=total number of individuals; SCD: sudden cardiac death. Differences in proportion of SCD during exercise among age brackets; specifically, we compared the age bracket 10 to 15 years with the other age brackets.

Table 28: Type of exercise activity that triggered SCD. SCD: sudden cardiac death.

Age (years)	Type of activity if death during exercise
10 to 15 Death during exercise n=8	4 running, 3 football, 1 rugby
16 to 20 Death during exercise n=8	3 football, 2 running, 1 sexual intercourse, 1 golf, 1 general exercise
21 to 25 Death during exercise n=6	3 running, 1 football, 1 rugby, 1 general exercise
26 to 30 Death during exercise n=4	1 football, 1 running, 2 general exercise

7.7 **Discussion**

Although HCM is historically reported as the predominant cause of SCD in young athletes,[22] it is unclear to what degree exercise is a trigger for possible fatal arrhythmias in these patients. When a diagnosis of HCM is made, current international guidelines recommend against competitive sport in most cases.[129] In

our cohort of SCD victims with HCM, death occurred during exercise in 39% of the cases. Interestingly, we observed that younger individuals (10-15 years of age) died suddenly mostly during exercise (in 80% of the cases), in comparison to slightly older (>16 years of age) individuals in whom death occurred more at rest (in 70% of the cases). All deaths occurred in the community and/or on arrival into the accident and emergency department following paramedic arrival. In young individuals who died during exertion, there was a correlation with physical activity associated with an increasing dynamic component: 31% were playing football, 39% running and 15% engaging in sports which include Rugby.

Overall, the findings from our focussed study are consistent with studies which consistently demonstrate that young athletes with HCM represent a vulnerable substrate for SCD during exercise, where based on the recent critical appraisal of the evidence by experts, antemortem the risk of HCM related SCD in young athletes is felt to range from 0.1% to 6.6% per annum, with higher mortality rates in male athletes and high-risk sports for example, basketball, soccer and American football.[130]

Some may speculate that this difference is explained by younger children being more physically active than their adult counterparts. However, a sedentary lifestyle appears increasingly common among adolescents.[131] Our current study is a descriptive study and is not meant to assess causality, but we speculate that since phenotypic conversion often occurs during prepuberal and puberal age, myofibers may be particularly susceptible to exercise-induced arrhythmias at this early stage.

Our findings emphasise the importance of earlier disease identification in younger individuals through preventative strategies such as cardiac screening, this applies to

athletes as well as individuals in the general population. In tandem, this may facilitate individualised safe-exercise prescriptions which take into account risk-stratification and surveillance, particularly in adolescent individuals who appear to demonstrate a greater propensity to exercise related SCD.

In our study, by-stander cardiopulmonary resuscitation (CPR) was performed in 70% of cases and only 23% of cases received automatic external defibrillation (AED). Furthermore, 81% of mortality during exercise occurred outdoors and outside of an individual's place of residence. Such findings highlight room for improvement in educating the public around basic and advanced life support (BLS and ALS) measures and public health institutions to widen the availability of AEDs in a variety of settings such as public places, schools, colleges and sporting venues.

Our study does have some limitations. This includes a relatively small sample size, especially in the younger group, the retrospective assessment of clinical data, and the absence of genetic testing i.e., molecular autopsy, which lends itself to future work. In addition, our cohort predominantly included white individuals. However, we hope the findings contribute to our growing understanding of HCM and risk of SCD in individuals partaking in physical activity and proves hypothesis generating for future work.

7.8 **Conclusion**

In conclusion, SCD occurs during exercise in approximately 40% of young patients with HCM. While younger individuals (10 to 15 years of age) die mostly during exercise, death occurs more frequently at rest after 16 years of age. An early diagnosis of HCM even in asymptomatic patients appears relevant especially in

individuals <15 years of age, as exercise prescription tailored to the individual condition and risk profile may have the potential to prevent exercise induced SCD.

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Funding sources:

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Disclosures:

No author has any relevant conflicts of interest to declare.

7.9 Clinical implications

Significant limitations exist with current risk stratification tools in the setting of HCM. Specifically, the ESC HCM 5-year risk score, has been derived from non-athletic cohorts. Whilst current guidelines[31] supports vigorous exercise in individuals with HCM in the absence of conventional high-risk markers, our study indicates in the young population a more cautious approach is warranted. The clinical correlations from this study emphasize the need for tailored risk assessment, early detection,

individualized management strategies and the importance of public awareness and education in improving outcomes in cases of SCD. Furthermore, our findings are relevant as part of a shared decision-making approach which is often a complex discussion with young patients, families, and sporting organisations. Further research is warranted in individuals of different ethnicities and more severe phenotypes.

Chapter 8: Myocarditis and Sudden Cardiac Death in the Community: Clinical and Pathological Insights From a National Registry in the United Kingdom

(Publication attached in appendix 1)

8.1 Abstract

Background: Myocarditis is an inflammatory condition which has received considerable attention in recent years, especially in the context of sudden cardiac death (SCD), raising questions about missed opportunities of a timely diagnosis.

Aim: We aimed to examine the presenting features, and circumstances of death in a large cohort of decedents who experienced SCD in the community and were subsequently diagnosed with myocarditis at autopsy. In addition, we aimed to investigate for any temporal trends in myocarditis mortality over the study period, which intersected with the COVID-19 pandemic.

Methods: 7702 consecutive cases of SCD referred to our specialist cardiac pathology centre between 1994 and 2022 were reviewed. SCD was defined as death from a cardiovascular (CV) cause within 12-hours of apparent well-being. Clinical information was obtained from referring coroners, and included, demographic characteristics of the deceased, medical history, family history and circumstances of death. Cases underwent comprehensive autopsy evaluation of the heart, including histological analysis of a minimum of 10-tissue blocks, by expert cardiac pathologists. The diagnosis of myocarditis was based upon published histological

criteria. We only included deaths attributed to myocarditis in non-hospitalised individuals.

Results: 1.1% cases of non-hospitalised SCD were attributed to myocarditis. The majority of decedents were male (65%) with a mean age of death 32 ± 15 years. Most individuals died at rest (89%) and the vast majority of individuals (61%) were reportedly asymptomatic prior to SCD. 16% reported symptoms consistent with an infective process in the 6-months prior to death. CV symptoms were reported in 15 18% decedents and 5% reported co-existing CV symptoms in the context of ongoing infective symptoms. Lymphocytic myocarditis was the most common form (56%). There were no significant differences in the clinical or histopathological findings between individuals who died at rest compared with individuals who died during activity. No clear increment in mortality trend was attributed to myocarditis during the COVID-19 pandemic.

Conclusion: Myocarditis is a relatively rare cause of SCD in non-hospitalised individuals and the majority of decedents die at rest. Almost 1 in 5 individuals had prodromal cardiac symptoms and our findings overall highlight significant challenges in identifying non acute cases of an arrhythmogenic substrate in the community and emphasise the need for early diagnosis which may be facilitated by a high index of suspicion of the disease and instigating rapid assessment and risk-stratification to reduce morbidity and mortality.

8.2 Introduction

Myocarditis is an inflammatory cardiac disorder with variable clinical presentations and outcomes.[132–134] Whereas some patients present with transient symptoms followed by rapid resolution, others may develop cardiogenic shock or fatal arrhythmias. Diagnosis is often challenging and is typically based on the findings from histologic, immunologic and immunohistochemical criteria, typically in the context of an endomyocardial biopsy where clinically indicated.[134] With the advent of sophisticated non-invasive imaging techniques such as cardiovascular magnetic resonance imaging and high sensitivity biomarkers, diagnosis is increasingly being made without invasive assessment.[135]

The estimated incidence of myocarditis ranges from 1 to 10 cases per 100,000 persons per year with the highest being attributed to males and in those aged between 20 to 40 years of age.[136] The aetiology may be broad and includes infectious agents, medications, systemic disease and toxins.[132] In North America and Europe, molecular techniques utilising reverse transcriptase polymeracase chain reaction (PCR) amplication, demonstrate that the majority of cases are due to viral infections such as enterovirus, adenovirus and influenza viruses amongst others.[132] Histological classification systems have also been devised based on the predominant inflammatory infiltrate.[132,137]

Harris et al., recently interrogated two large registries and reported that 47% of young individuals which included athletes in the cohort prior to death reported viral prodromal symptoms or cardiovascular symptoms, including 9% of individuals who had been reviewed by a cardiologist prior to death, but a diagnosis of myocarditis was not established in any individual antemortem.[133]

Certainly, data from global registries have consistently reported myocarditis as a common cause of SCD in young individuals.[7,23,138,139] Furthermore, the absence of an antemortem diagnosis and deaths occurring in the community without warning, raises questions about missed opportunities of a timely diagnosis for appropriate intervention to mitigate the risk of sudden cardiac death (SCD).

8.3 Aim

We aimed to examine the presenting features, and circumstances of death in a large cohort of decedents who experienced SCD in the community and were subsequently diagnosed with myocarditis at autopsy. In addition, we aimed to investigate for any temporal trends in myocarditis mortality over the study period at the CRY-CCP, which intersected with the COVID-19 pandemic.

8.4 Personal contribution

RTB reviewed data relevant to the project, performed analysis of data, drafting of the published manuscript including rebuttals. The author was not involved with the post-mortem evaluation or toxicology screen of any of the subjects or the initial raw data collection that was performed by our expert histopathology team (MNS and JW).

8.5 Methods

We reviewed 7702 consecutive cases of SCD referred to our specialist cardiac pathology centre between 1994 and 2022. SCD was defined as death from a cardiovascular (CV) cause within 12-hours of apparent well-being. Clinical information was obtained from referring coroners, and included, demographic

characteristics of the deceased, medical history, family history and circumstances of death. Cases underwent comprehensive autopsy evaluation of the heart, including histological analysis of a minimum of 10-tissue blocks, by expert cardiac pathologists (JW and MNS).[50] The diagnosis of myocarditis was based upon published histological criteria, which included the predominant cell type, and specific macro and microscopic criteria (table 29).[137] Importantly, we only included deaths attributed to myocarditis in non-hospitalised individuals.

Table 29: Autopsy myocarditis diagnostic criteria utilised in study. LA: left atrium, LV: left ventricle, RV: right ventricle. Courtesy of Professor Mary N. Sheppard. Practical Cardiovascular Pathology. 3rd ed. CRC Press; 2022.

Pathology	**Macroscopic criteria**	**Microscopic criteria**
Lymphocytic myocarditis	Normal heart Increase in heart weight with dilated LV and normal/thin wall Irregular colour variation throughout RV /LV May be pericarditis May be apical thrombi in RV /LV	Diffuse lymphocytic/macrophage inflammation (>20% in at least 2 tissue blocks of 4 cm^2) in the left ventricle with myocyte necrosis ± myocardial fibrosis
Eosinophilic myocarditis	Normal heart /increased heart weight. Dilated LV. Normal/ increased wall thickness circumferentially or focally LA dilatation May be pericarditis/subendocardial thrombus Normal coronary arteries/vasculitis	Diffuse eosinophilic infiltrate in (>20% in at least 2 tissue blocks of 4 cm^2) ± myocardial fibrosis with ± vasculitis
Neutrophilic myocarditis	Normal heart /increased heart weight. Dilated LV. Normal/ increased wall thickness circumferentially or focally LA dilatation	Diffuse neutrophilic infiltrate in (>20% in at least 2 tissue blocks of 4 cm^2)

	May be purulent pericarditis/myocardial abscess	
Granulomatous/ sarcoid myocarditis	Normal heart /increased heart weight. Dilated LV. Normal/ increased wall thickness circumferentially or focally with white firm pale areas in free wall of RV and LV and septum.	Perivascular well formed epithelioid granulomas with giant cells and lymphocytic infiltrate in (>20% in at least 2 tissue blocks of 4 cm^2) with usually extensive myocardial fibrosis. Granulomas extend into epicardial fat
Giant cell myocarditis	Normal heart /increased heart weight. Normal /dilated LV. Normal/increased LV wall thickness circumferentially or focally with white soft pale or haemorrhagic areas in free wall of RV /LV.	Diffuse mixed giant cell, macrophage, lymphocytic and eosinophilic infiltrate with extensive myocyte necrosis in (at least 2 tissue blocks of 4 cm^2). Inflammation does not extend into epicardial fat ± myocardial fibrosis
Toxic myocarditis	Normal heart/increase in heart weight/dilated LV Normal wall	Diffuse interstitial Mixed infiltrate, macrophages,

	thickness/thin LV wall RVPLV myocardium Normal appearance	neutrophils, eosinophils, lymphocytes Interstitial oedema Little myocyte necrosis Contraction band necrosis

8.5.1 Ethical approval

Ethical and research governance approval has been granted for this study (10/H0724/38). The next of kin consented to material retention for anonymized research in each case. Data will be made available upon reasonable request to the corresponding author.

8.5.2 Statistical analysis

Statistical analysis was performed using Microsoft Excel 365 (2021). Results are expressed as mean ± standard deviation (SD) for continuous variables or as number of cases and percentage for categorical variables. Comparison of groups was performed using Student's T-test for continuous variables with correction for unequal variance when necessary and Chi-square test, as appropriate for categorical variables.

8.6 **Results**

Of the total cases of SCD, 82 (1.1%) were attributed to myocarditis (table 30). The majority of decedents were male (n=53 [65%]) with a mean age of death 33 ± 16 years (range 1-68 years) and 81% were white. The mean heart weight was 378 ± 129 g. Most individuals died at rest (n=73 [89%]), including during sleep (n=16 [19%]) whilst the remainder died during exertion (n=9 [11%]). Our cohort comprised 5 athletes, (3 of whom died at rest, and 2 during exertion). Only 1 individual who was serving a prison sentence was diagnosed with viral myocarditis, antemortem, following a 3-day inpatient stay, prior to SCD in his cell 2-weeks post discharge.

Table 30: SCD attributed to myocarditis in non-hospitalized individuals from the CRY-CCP. Baseline characteristics of cohort. IQR: interquartile range; SD: standard deviation. p value <0.05 deemed statistically significant.

Characteristic	**Overall**, N = 82[1]	**Exertion**, N = 9[1]	**Rest**, N = 73[1]	**p-value**[2]
Age				0.74
Mean (SD)	33 (16)	34 (15)	32 (16)	
Median (IQR)	32 (26)	40 (27)	32 (25)	
Range	1 - 68	16 - 51	1 - 68	
Sex				0.48
Male	53 (65%)	7 (78%)	46 (63%)	
Female	29 (35%)	2 (22%)	27 (37%)	
Ethnicity				0.34
White	48 (81%)	3 (75%)	45 (82%)	

Table 30: SCD attributed to myocarditis in non-hospitalized individuals from the CRY-CCP. Baseline characteristics of cohort. IQR: interquartile range; SD: standard deviation. p value <0.05 deemed statistically significant.

Characteristic	**Overall**, N = 82[1]	**Exertion**, N = 9[1]	**Rest**, N = 73[1]	**p-value**[2]
Indian	4 (6.8%)	0 (0%)	4 (7.3%)	
Chinese	2 (3.4%)	0 (0%)	2 (3.6%)	
Asian	1 (1.7%)	0 (0%)	1 (1.8%)	
Black	1 (1.7%)	1 (25%)	0 (0%)	
Black Other	1 (1.7%)	0 (0%)	1 (1.8%)	
Mixed	1 (1.7%)	0 (0%)	1 (1.8%)	
Pakistani	1 (1.7%)	0 (0%)	1 (1.8%)	
Missing	23	5	18	
BMI				0.74
Mean (SD)	24.1 (5.3)	23.1 (5.7)	24.2 (5.4)	
Median (IQR)	24.0 (7.5)	23.1 (5.5)	24.0 (7.5)	
Range	15.6 - 37.0	16.3 - 30.0	15.6 - 37.0	
Missing	39	5	34	
Symptoms				0.083
No	50 (61%)	8 (89%)	42 (58%)	
Yes	32 (39%)	1 (11%)	31 (42%)	
Infective symptoms prior				>0.99

Table 30: SCD attributed to myocarditis in non-hospitalized individuals from the CRY-CCP. Baseline characteristics of cohort. IQR: interquartile range; SD: standard deviation. p value <0.05 deemed statistically significant.

Characteristic	**Overall**, N = 82[1]	**Exertion**, N = 9[1]	**Rest**, N = 73[1]	**p-value**[2]
No	69 (84%)	8 (89%)	61 (84%)	
Yes	13 (16%)	1 (11%)	12 (16%)	
Resuscitation attempted				>0.99
Yes	30 (65%)	1 (100%)	29 (64%)	
No	16 (35%)	0 (0%)	16 (36%)	
Missing	36	8	28	

Heart weight				0.93
Mean (SD)	378 (129)	375 (91)	379 (133)	
Median (IQR)	386 (125)	385 (127)	387 (122)	
Range	86 - 789	250 - 490	86 - 789	
Missing	8	2	6	
LV scar				0.29
No	40 (68%)	4 (100%)	36 (65%)	
Yes	19 (32%)	0 (0%)	19 (35%)	
Missing	23	5	18	

[1] n (%)

[2] Two Sample t-test; Fisher's exact test

Most individuals (n=50 [61%]) were reportedly asymptomatic prior to SCD. Thirteen (16%) individuals reported symptoms consistent with an infective process in the 6-months prior to death. CV symptoms were reported in 15 (18%) decedents, including dyspnoea n=6 [7%]), chest pain (n=5 [6%]), syncope (n=3 [4%]) and palpitation (n=1 [1%]). Four decedents (5%) reported co-existing CV symptoms in the context of ongoing infective symptoms. Lymphocytic myocarditis was the most common form, n=46 (56%) (figure 33); followed by, neutrophilic, n=14 (17%), eosinophilic, n=13 (16%), toxic, n=6 (7%), and giant cell myocarditis, n=3 (4%). There were no significant differences in the clinical or histopathological findings between individuals who died at rest compared with individuals who died during activity.

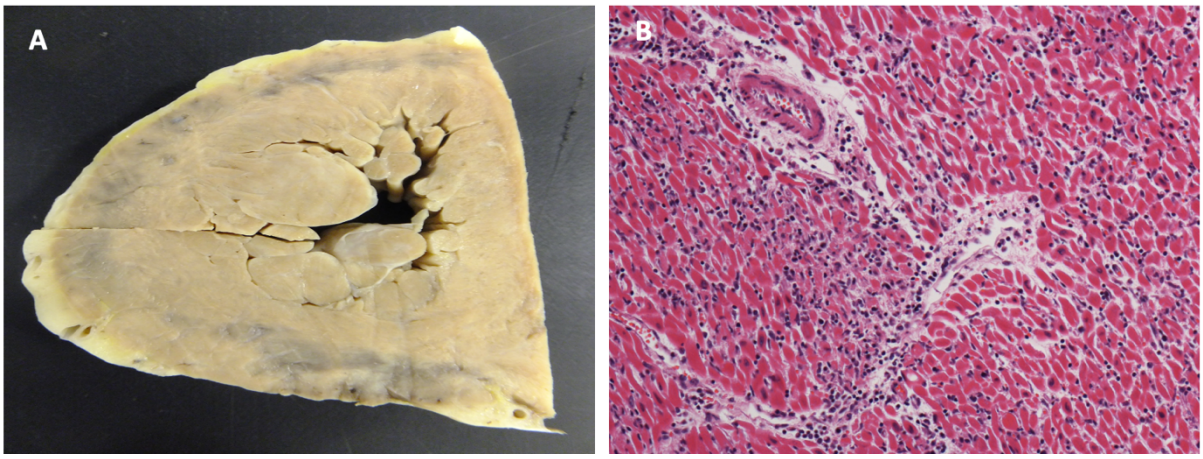

Figure 33: Macroscopic (A) and microscopic appearances (B) of myocardium with lymphocytic myocarditis. The myocardium demonstrates mottling with dark discolouration (A) and evidence of a diffuse lymphoid infiltrate with corresponding myocyte necrosis (B).

The dataset was also interrogated to establish any temporal trends in the occurrence of myocarditis over the 29-year study period at the CRY-CCP (Figure 34).

When absolute SCD morality numbers from myocarditis in non-hospitalized individuals during the study period of 1994 to 2022 were examined (Figure X), no clear pattern emerged. However, specifically, no increments were seen during 2020 to 2022 which intersected with the COVID-19 pandemic.

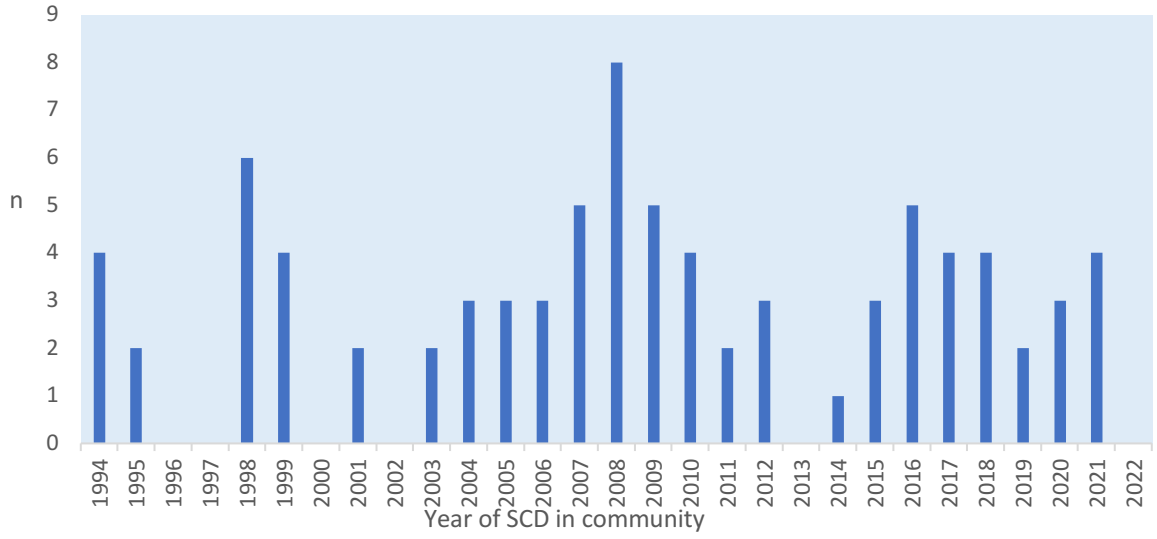

Figure 34: Absolute SCD mortality numbers from myocarditis in non-hospitalised individuals during study period, 1994-2022. n=number of cases.

Temporal trends were further assessed between 1994 to 2022. Incidence rate was modelled using Poisson log-linear models considering the number of cases as the response variable and the total deaths from myocarditis in non-hospitalized individuals as an offset. Time since 1994 was considered the independent variable. The piece-wise function of time was considered when cases showed non-linear

trends. Analysis was conducted using R programming language version 4.2.2. A significant downward trend in the rate of myocarditis cases over the study period was observed ($p<0.001$). The estimated rate ratio since 1994 was 0.90 (95% CI 0.87 – 0.92) per year, indicating a reduction of 2.0% (95% CI: 0.08% - 1.3%) per year in the incidence over the study period (table 31 and figure 35). No increment in mortality trends were observed during 2020 to 2021 or after 2021.

Table 31: Fitted model – deaths attributed to myocarditis in non-hospitalized individuals from the CRY-CCP.

	Estimate	Std. Error	z value	Pr(>|z|)
Intercept	-2.6052	0.2444	-10.661	<0001
Time since 1994	-0.1119	0.0159	-7.037	<0001
Time during 2020 to 2021	0.3576	0.2737	1.307	0.191
Time after 2021	-17.8170	2103.3627	-0.008	0.993

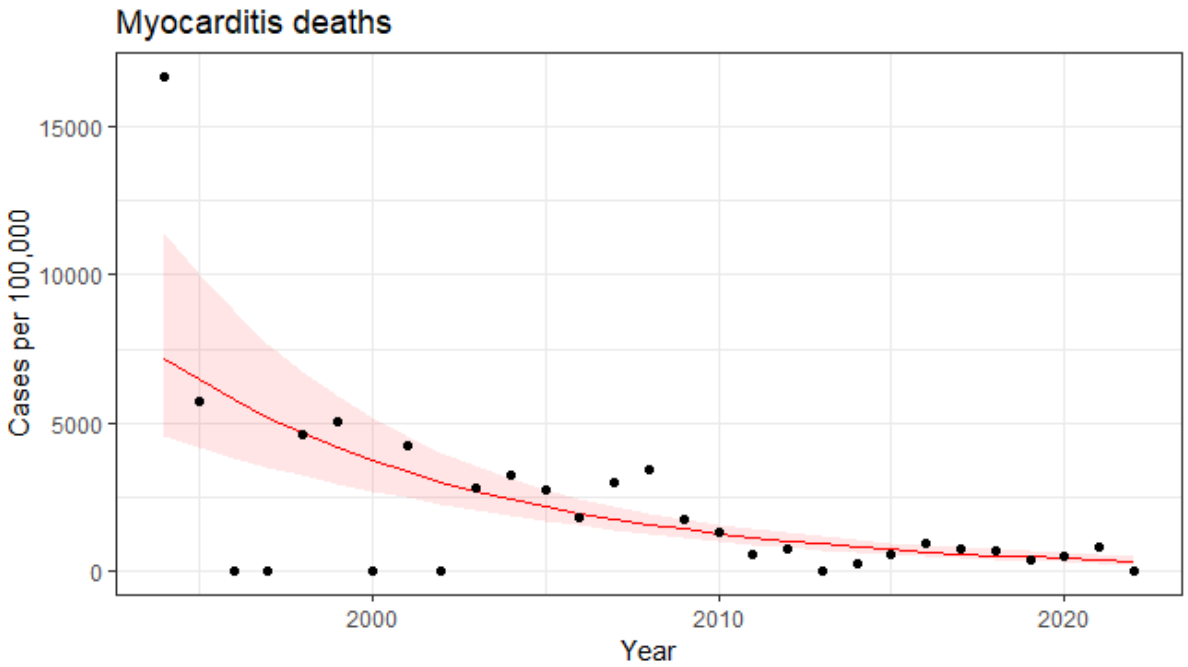

Figure 35: Temporal trends in myocarditis deaths in non-hospitalized individuals at the CRY-CCP. Incidence rates modelled using Poisson log-linear model. The solid red line represents the model output, and the respective 95% confidence intervals either side demonstrated by the shaded area. The black dots correlate with absolute mortality counts.

8.7 Discussion

Our observations from a large histopathological dataset demonstrates that myocarditis is a relatively rare cause of SCD in non-hospitalised individuals (1.1%). In terms of aetiology, lymphocytic myocarditis was the most common form, which is consistent with data from studies based on living individuals assessed with endomyocardial biopsies (EMB).[132,133,137] Almost 1 in 5 individuals had prodromal cardiac symptoms, however only 26% of these occurred in the context of an infective process. According to our results, only 5% of the decedents would have had a suspected diagnosis of myocarditis on the basis of cardiac symptoms in conjunction with an infective process, prior to SCD.

The majority of individuals died at rest, which may challenge the historical notion that sudden death risk in myocarditis is greater during physical activity and strenuous exercise.

Our findings highlight the challenges in identifying non acute cases of an arrhythmogenic substrate in the community and emphasise the need for early diagnosis which may be facilitated by a high index of suspicion of the disease and instigating rapid assessment and risk-stratification to reduce morbidity and mortality.

This is particularly relevant in the modern era with high sensitivity biomarkers and widely accessible non-invasive cardiac imaging studies.

It is worth acknowledging that based on our data, no causal relationship may be inferred between myocarditis cases during the COVID-19 pandemic and SCD. Possible cases of COVID-19 myocarditis may not have been referred to our centre and furthermore, public health measures to curtail viral spread, including social distancing and isolation, during the pandemic may have resulted in a reduction of the transmission of other infections. Despite these considerations, as highlighted in our results, our nationwide registry did not see an increment in SCD cases attributed to myocarditis.

Our study has some limitations. Our referral centre for cardiac pathology is more likely to receive hearts from subjects where the clinical history is suggestive of an inherited cardiac disease, or the autopsy findings are normal or equivocal, hence our data may have underestimated the prevalence of SCD from myocarditis in non-hospitalised individuals. Nevertheless, we receive a high volume of unexpected SCD referrals (>400/year) and the large number of examinations performed in our unit suggests that the results are likely to represent the type and frequency of cardiac diseases implicated in SCD, especially in young individuals.

8.8 Conclusion

In conclusion, myocarditis accounts for 1% of all SCDs in non-hospitalised individuals. Cardiac symptoms preceding a fatality are noted in approximately one in

five individuals although only 5% express cardiac symptoms in conjunction with infective symptoms.

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Disclosures:

No author has any relevant conflicts of interest to declare.

8.9 Clinical implications

Despite significant challenges in identifying individuals with myocarditis in the community, our study highlights the importance of comprehensive evaluations, that include clinical assessments, biomarkers, ECGs, cardiac imaging particularly timely CMR imaging with appropriate mapping and tissue characterisation sequences, and a high index of suspicion. Whilst the number of athletes in the cohort were small and is likely an underestimate of physically active individuals based on age and BMI, the

propensity for ventricular arrhythmias during physical activity and SCD supports tailored risk-stratification strategies and periodic surveillance.

The rapidly expanding practices of routine screening of high-risk populations, such as athletes and a high index of suspicion in symptomatic individuals, particularly with a history of a recent or historical evidence of a debilitating viral illness or infective processes, may identify those at increased risk of SCD. Furthermore, appropriate guideline directed medical therapy, which includes timely escalation of care to specialised centres[140], and periodic surveillance in the convalesce period particularly in the context of haemodynamic instability, ventricular arrhythmia, LV-systolic dysfunction and myocardial scar may reduce morbidity and mortality.

Further research is needed to elucidate the genetic and molecular mechanisms underlying myocarditis and its progression to SCD. Such knowledge could inform the development of targeted therapies to prevent or mitigate the potentially devastating consequences of this disease.

Chapter 9 COVID-19, physical activity and the athletic heart

(Publication attached in appendix 1)

9.1 Introduction

Regular exercise curbs risk factors for atherosclerosis. Compared with sedentary individuals, those who exercise regularly reveal a better blood pressure and serum lipid profile, normal body mass index (BMI) and a lower prevalence of metabolic syndrome and type 2 diabetes mellitus.[126,141] Middle aged and older individuals who exercise regularly show a 50% reduction in the incidence of death from atherosclerotic coronary artery disease (CAD).[142] The relative benefits of exercise in individuals with established cardiovascular disease (CVD) are 2-fold greater than in individuals without CVD.[143] Whereas the greatest benefits in individuals without CVD are observed in those who progress from a sedentary state to performing 500 metabolic equivalent of task (MET) minutes per week,[144] individuals with CVD continue to show significant benefits up to 1000 MET mins/week.

Apart from curtailing risk factors for atherosclerosis, exercise has several central, peripheral and autonomic benefits associated with a reduced incidence of several CVDs and all-cause mortality (Figure 1).[145] The World Health Organisation (WHO), European Society of Cardiology (ESC) and American Heart Association (AHA) recommend that all able individuals, including the elderly should partake in at least 150 minutes of moderate intensity or 75 minutes of vigorous intensity per week and may double this duration for additional benefits.[35,144,146]

9.2 Early concepts during 2020 and 2021

SARS-CoV-2 is a highly infectious virus and is responsible for the COVID-19 infection pandemic, which has been associated with a critical illness rate of 4% and mortality rate up to 2%. Deaths are most common in the elderly, individuals with cardiac or respiratory comorbidities and individuals with established risk factors for CVD such as obesity, hypertension and type 2 diabetes mellitus.[147–149] Public health guidance to curtail viral spread and protect the most vulnerable included mandatory self-isolation periods and avoidance of populated areas. However, these measures have resulted in sedentary behaviours especially among cohorts that reap the greatest benefits from exercise.[150,151] Obesity, hypertension, dyslipidemia and diabetes mellitus are associated with a pro-inflammatory state, which is attenuated by regular moderate intensive exercise.[126,141,152] Furthermore, contemporary studies have demonstrated the benefits of moderate intensity exercise for up to 60 minutes, 3-4 times per week on cellular and humoral immunity.[152–155] More recently, data has demonstrated that patients with COVID-19 who were consistently inactive, during 2 years preceding the pandemic, had a greater risk of hospitalisation, escalation of care to the intensive care unit and subsequent mortality, in comparison to patients who were consistently meeting physical activity guidelines.[151] At the other end of the fitness spectrum, the pandemic had enforced the postponement or cancellation of major elite sporting events and mass endurance events, although social and economic pressure eventually resulted in the gradual resurgence of many spectator free elite sports.

COVID-19 infection is transmitted via droplets from the respiratory tract. Common symptoms include fever (89%), a dry cough (68%), fatigue (38%), sore throat,

myalgia and headache.[148] Most affected individuals (80%) experience a mild illness although a significant proportion (15%) will develop a severe illness and become debilitated for several days, or even require hospital admission. Critical illness occurs in 4.7%, which necessitates hospital admission, often for advanced life support.[156]

9.3 The impact of SARS-CoV-2 virus on the heart

The effect of SARS-CoV-2 virus on the cardiovascular system is still evolving (figure 36). Reports from China initially revealed that between 12% and 30% of patients admitted to hospital with SARS-CoV-2 had a raised troponin above the 99th percentile.[148] Patients with raised troponin experienced more severe disease and were more likely to require mechanical ventilation and die.[157,158] The precise cause of the raised troponin concentrations is unclear and likely multifactorial. Amongst non-survivors serum troponin concentrations continued to rise beyond day 4, suggesting that elevated serum troponin concentration may be a consequence of the systemic inflammatory response or cytokine storm.[158] Myocyte necrosis could be a consequence of right ventricular strain resulting from profound hypoxaemia secondary to the respiratory illness and/or pulmonary embolism.[159] Among individuals with chronic coronary syndromes or subclinical coronary artery disease, plaque rupture, acute thrombosis and distal embolisation may complicate the acute inflammatory and hypercoagulable state. In the context of a severe systemic reaction the possibility of a stress induced cardiomyopathy cannot be excluded.[160]

Figure 36: Possible mechanisms of cardiac involvement in COVID-19 infection. Bhatia RT, Marwaha S, Malhotra A, et al. Exercise in the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) era: A Question and Answer session with the experts Endorsed by the section of Sports Cardiology & Exercise of the European Association of Preventive Cardiology (EAPC). *Eur J Prev Cardiol*. 2020;27(12):1242-1251.

Although a diagnosis of myocarditis cannot be confirmed in the absence of endomyocardial biopsies or cardiovascular magnetic resonance (CMR) imaging

scans, several case reports emerged early on in pandemic implicating myocarditis as an additional cause of cardiac damage.[160,161] SARS-CoV-2 virus binds to angiotensin converting enzyme 2 (ACE2) in the upper airways and lungs after the protein spike on the virus is activated by transmembrane protease serine.[162,163] The myocardium also contains a high concentration of ACE2 receptors, activation of which may exert direct toxic effects within the myocardium.[163] Certainly early observations reported a proportion of patients diagnosed with COVID-19 infection have presented with chest pain and palpitations rather than symptoms due to the respiratory tract involvement.[164]

9.4 Myocarditis and Exercise

As has been mentioned in the previous chapter, myocarditis is an inflammatory disease of the myocardium itself and often has a variable presentation, which might be acute, subacute, or chronic. In young individuals it often follows a self-limiting course, however, cardiogenic shock, fatal arrhythmias, permanent left ventricular dysfunction and myocardial scar are recognized complications. Murine models have demonstrated that intensive exercise is associated with a greater burden of myocyte necrosis, and an exaggerated inflammatory response phase with subsequent myocardial scar which serves as a substrate for arrhythmic events.[165,166] Myocarditis is implicated in 5-15% of all sudden cardiac deaths in young competitive athletes and up to 20% of sudden cardiac death in US military recruits.[7,167,168] The diagnosis of myocarditis is an indication for a mandatory resting period of 3-6 months depending on the severity of the illness.[129] Individuals who exhibit persistent severe left ventricular systolic dysfunction or exercise induced complex ventricular arrhythmias

should abstain from intensive exercise in the future whereas those with ventricular scar would require surveillance for future arrhythmias.[35]

9.5 Diagnosing myocarditis

The clinical manifestations of myocarditis are variable, ranging from minimal coryzal symptoms to rapidly progressive cardiogenic shock. Physical examination may be predominated by systemic features of viral infection such as pyrexia, tachycardia, rash, lymphadenopathy, and arthralgia. Overt cardiac involvement is recognized by signs of cardiac decompensation such as added heart sounds or pulmonary oedema. Although endomyocardial biopsy (EMB) is the gold standard investigation for myocarditis, it is reserved for individuals with rapidly progressive heart failure. Furthermore, it may be limited by procedural risk and its overall sensitivity being influenced by sampling technique and biopsy region sampled which might be patchy in view of a heterogenous disease process. In most individuals with suspicion of myocarditis the diagnostic work up usually relies on an armamentarium of non-invasive investigations including biomarkers for cardiac damage, electrocardiography (ECG), transthoracic echocardiography (TTE), viral serology, cardiovascular magnetic resonance imaging (CMR) and prolonged ECG monitoring.[169]

9.6 Challenges in diagnosing myocarditis in athletes with COVID-19 infection

Concerns about subtle myocarditis in athletes galvanized several risk stratification algorithms recommending cardiac investigations in symptomatic athletes or those who have an abnormal nucleic acid test prior to returning to training and competions.[170–173] The diagnosis of myocarditis in athletes without overt cardiac symptoms or signs, however, is problematic.[174]

Recognised electrical manifestations of myocarditis include sinus tachycardia, non-specific ST-T wave changes, bundle branch block, deep-pathological Q waves, supraventricular and ventricular arrhythmias, or variable degrees of heart block. However, the sensitivity of an ECG is less than 50% in myocarditis.[175] The ECG has poor specificity in athletes because repolarization changes compatible with myocarditis, such as J-point, ST segment elevation and tall T waves are common normal variants in highly trained athletes.[46,176] Therefore comparison with previous ECGs is more useful to determine whether an athlete with coryzal symptoms may have myocarditis and it would be reasonable to recommend further investigation in an athlete with new repolarization changes or dynamic changes suspicious of underlying cardiac pathology.

Serum cardiac troponin concentration is often elevated in individuals with acute myocarditis.[174] However, strenuous exercise itself can also cause transient cardiac troponin elevation in healthy individuals.[177–179] It is also noteworthy that the upper limits of troponin assays are derived and validated from a sedentary population rather than athletic individuals and it is possible that athletes may reveal higher levels compared with the general population. Thus, an elevated troponin must be interpreted in the context of clinical presentation. Athletes should abstain from moderate or intensive exercise for 48 hours before assessment to minimize the chance of a false positive result. An athlete with a modestly elevated troponin despite resting should have a repeat assessment after a further 48 hours period of rest; a rising troponin concentration may be suggestive of cardiac pathology and warrants more detailed investigation in the context of COVID-19 infection.

From an imaging standpoint, TTE is a widely accessible modality for investigating myocarditis. Enlarged ventricular dimensions, increased ventricular wall thickness from oedema, regional wall motion abnormalities, impaired cardiac function and the presence of a pericardial effusion are established manifestations of myocarditis.[174] Right ventricular enlargement with impaired systolic function has been recognised following COVID-19 infection.[180] However, enlarged left and right ventricles with a mildly depressed basal left ventricular ejection fraction is also a recognised phenotypic feature of the athletes heart.[181,182]

CMR is regarded as the gold-standard non-invasive imaging modality to provide optimal myocardial tissue characterisation. In the setting of a heightened pre-test probability for myocardial inflammation, the Lake Louise Criteria propose the presence of both myocardial injury, regional or global increase in T1 signal, elevated extra cellular volume (ECV), or the presence of late gadolinium enhancement (LGE) and myocardial oedema (regional or global increase in T2 signal) supportive of a clinical diagnosis of myocarditis.[135] Furthermore, the presence of regional or global ventricular systolic dysfunction and pericardial abnormalities are considered supportive diagnostic criteria.[135] These findings may not be detectable in the very early stages of the illness and ideally the CMR study should be performed after at least 10 days from the initial time of diagnosis of COVID-19 infection.[180] Specific to athletes, there is also a need to obtain more normative CMR data to enable more accurate assessment of athletes with COVID infection and non-athletic control groups. These normative data are required for volumetric assessment, quantification of ejection fraction as well as the indices utilized in the Lake Louise Criteria.

According to current literature ostensibly healthy, highly trained endurance athletes (>12 h training/week at least during the last 5 years) have a significantly higher prevalence of focal fibrosis e.g., at the right ventricle (RV) insertion point, and increased extracellular volume compared with age and gender-matched individuals.[183] In our experience, nearly 11% of middle-aged healthy adults reveal more extensive fibrosis, the significance of which is unclear.[103] In the event of viral symptoms or a positive COVID-19 test, such individuals could be falsely labeled with recent myocarditis. Major fibrosis is unusual in a young athlete but more common in older athletes and can most definitely be attributed to myocarditis in the context of recent COVID-19 illness.

9.7 **Exercise advice during the pandemic – general concepts**

There is evidence that moderate exercise performed for 20–30 min 3–4 times per week may strengthen the immune system and reduce the risk of viral infection.[153,184–186] Studies have also shown that regular moderate exercise prior to developing a potentially serious viral infection such as flu may be associated with better outcomes.[187,188] People who continued to remain active during the 1998 Hong Kong flu were more likely to survive compared with sedentary people.[187,188] During the COVID-19 pandemic, access to gyms and other communal exercising areas or performing team sports was periodically no longer possible, therefore, training regimes needed to be adjusted based on public health advice and restrictions. In some countries one outdoor exercise activity per day was permitted while in others, all outdoor activity has been prohibited.

Individuals who had exercising facilities at home such as treadmills, static bicycles or rowing machines were encouraged to use them to stay physically fit. Callisthenic exercises such as press-ups and sit-ups, yoga, strength training or high intensity exercise were encouraged to be performed indoors or in the garden. There were also many on-line programmes and applications to allow individuals to follow a systematic exercise programme. Furthermore, regular exercise has been shown to have a beneficial psychological impact, which should not be underestimated in times of 'social distancing' and 'self-isolation'.[189] Athletes who are used to regular training may suffer from psychological problems due to sudden withdrawal of a training stimulus and were particularly encouraged to maintain their exercise level.[190,191]

9.8 Testing for COVID-19 infection – general concepts in the early part of the pandemic

Recommendations differed between countries, based predominantly on a balance between the feasibility of testing and its impact on the management of the athlete. Current guidance, in most countries, suggests that COVID-19 testing should be reserved for individuals with symptoms compatible with infection. Testing individuals who have been exposed to somebody that may have had COVID-19 infection was at a stage also advocated by public health authorities. This situation has remained fluid, particularly in the early part of the pandemic (2000-2001) where widespread testing was problematic due to availability of testing. However, in elite sport, organisations considered testing all their players with nucleic acid tests for the presence of viral RNA or check prior exposure through serological tests.

9.9 Cardiac testing post COVID-19 infection

During the pandemic, most countries suggested that such athletes should monitor their symptoms and self-isolate for 7–14 days from the onset of symptoms or until symptoms resolve. Urgent testing was not necessary for the majority of athletes who had improved after a short illness but if there were concerns, then the team doctor may have decided on a case-by-case basis. Tests may have been performed via designated centres or arranging remote individual tests for COVID-19 infection. All athletes who reported symptoms suggestive of a viral infection were considered to suffer from COVID-19 and self-isolate for 7–14 days or until their symptoms have resolved, irrespective of test results, particularly where access to tests was challenging. Coryzal illnesses, however, are common especially in spring; therefore it was possible that the athlete might have had a 'common cold'. It is also possible that the COVID-19 test was falsely negative. Hence it was recommended to repeat the test if possible, in athletes with persistent symptoms. Athletes who had negative tests were supported to continue exercising after resolution of symptoms (Table 32).

Table 32: Recommendations for exercise in athletes based on symptoms and COVID-19 (viral RNA) test result. Based on early recommendations published by Bhatia RT, Marwaha S, Malhotra A, et al. Exercise in the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) era: A Question and Answer session with the experts Endorsed by the section of Sports Cardiology & Exercise of the European Association of Preventive Cardiology. Eur J Prev Cardiol. 2020.

COVID-19 symptoms	**COVID-19 test result**	**Recommendations**
Positive	Positive	• Self-isolate for 7–14 days.

		• Refrain from exercise until symptom free for seven days. • Consider clinical assessment in appropriate environment including blood tests (troponin and CRP). • If troponin positive, consider 12-lead ECG, echocardiogram, CMR and ECG monitor. If evidence of peri/myocarditis treat accordingly. • If no evidence of cardiac involvement reassess after symptom free for seven days and consider graduated return to training for an additional seven days and return to normal training and/or play if asymptomatic and progressing well. • Repeat COVID-19 testing to ensure conversion to negative may be considered prior to return to training.
Negative	Positive	• Refrain from all exercise for seven days from the test result. • If still symptom free after this period, consider graduated return to training and return to normal training and/or play if asymptomatic and progressing well. • Repeat COVID-19 testing to ensure conversion to negative may be considered prior to return to training.
Positive	Negative	• Manage as coryzal illness according to usual policy. • If there is a high index of suspicion, consider repeat COVID-19 testing or adhering to the COVID-19 test

		positive recommendations.
Negative	Negative	• Maintain high standards of hand hygiene and social distancing.

9.10 Early consensus recommendations on the management of an athlete post COVID-19 infection

As alluded to previously, largely due to concerns around myocardial involvement post COVID-19 infection in elite athletes, several consensus groups globally published guidelines on the safe return to play. It is important to acknowledge that at this stage early on in the pandemic, all such protocols were consensus based in a largely evidence free zone.

I initiated and led on the European guidelines, which was endorsed by the European Association of Preventative Cardiology.[173] Following a positive COVID-19 test, athletes were advised to self-isolate for 7–14 days and not to engage in systematic exercise until they have been symptom free for a minimum of seven days. During that period, athletes were supported in engaging in 20–30 minutes of low to moderate physical activity. Professional athletes were advised to monitor symptoms closely through virtual consultations with their team doctor or equivalent.

Athletes with mild symptoms which resolved were advised that they may return to graduated training when they have been symptom free for seven days and can progress gradually to the normal training regime and/or play after an additional seven days. Repeat COVID-19 testing to ensure conversion to negative was considered prior to return to training. Assessment of symptoms by telephone

consultations and monitoring for arrhythmias through a heart rate monitor (if possible) was encouraged, particularly if CV symptoms were experienced to any degree.

For athletes with a debilitating illness and/or symptoms compatible with myocarditis/pericarditis such as chest pain, severe breathlessness or palpitations, were advised to undergo a comprehensive evaluation. This was particularly pertinent for athletes who require a high level of regular training to maintain their fitness. Intensive exercise is associated with raised serum troponin concentration; therefore, we recommended that serum troponin measurements should be performed 48 hours after a rest period to reduce the risk of a false positive result. Athletes with a raised troponin (>99th percentile) were be considered with a high index of suspicion to have myocarditis, until proven otherwise and were advised to undergo a 12-lead electrocardiogram (ECG), echocardiogram, CMR imaging scan and ECG monitor to help confirm the diagnosis and assess risk of arrhythmias.[173] Athletes with convincing features of myocarditis were managed according to established guidelines for myocarditis, which recommend a minimum of three months' rest from intensive exercise.[129]

9.11 Concerns around comprehensive cardiac evaluations for elite athletes prior to return to play

It was recommended that all athletes returning back to competition after prolonged abstinence should undergo a comprehensive clinical assessment including detailed history and examination, which could be performed by the team doctor if applicable. Assuming that sufficient and reliable testing was available, it was deemed

reasonable for sporting organisations to identify players who were silent carriers through throat and nose swabs (nucleic acid tests for the presence of viral RNA) and check for previous exposure to the virus through serological tests. IgM antibodies appear to most likely develop between three and six days after the onset of symptoms and IgG antibodies develop 8–20 days after the onset of symptoms. This was particularly relevant for team sports where players would not be able to observe social distancing during training and games, especially if games resume while the SARS-CoV-2 virus pandemic is beginning to subside but has not resolved. It was also relevant for preventing infection of ancillary personnel working with athletes, including their medical staff.

Our consensus panel (figure 37) believed that for most athletes, who never experienced symptoms of viral infection, an assessment by their team doctor was sufficient. For the minority of athletes who experienced debilitating symptoms (bedridden for several days) or required hospital admission with confirmed COVID-19 infection, comprehensive re-evaluation by a team physician and sports cardiologist was advisable prior to return to play, particularly if there was a documented rise in cardiac troponin and/or ventricular dysfunction and/or arrhythmia noted during the admission.

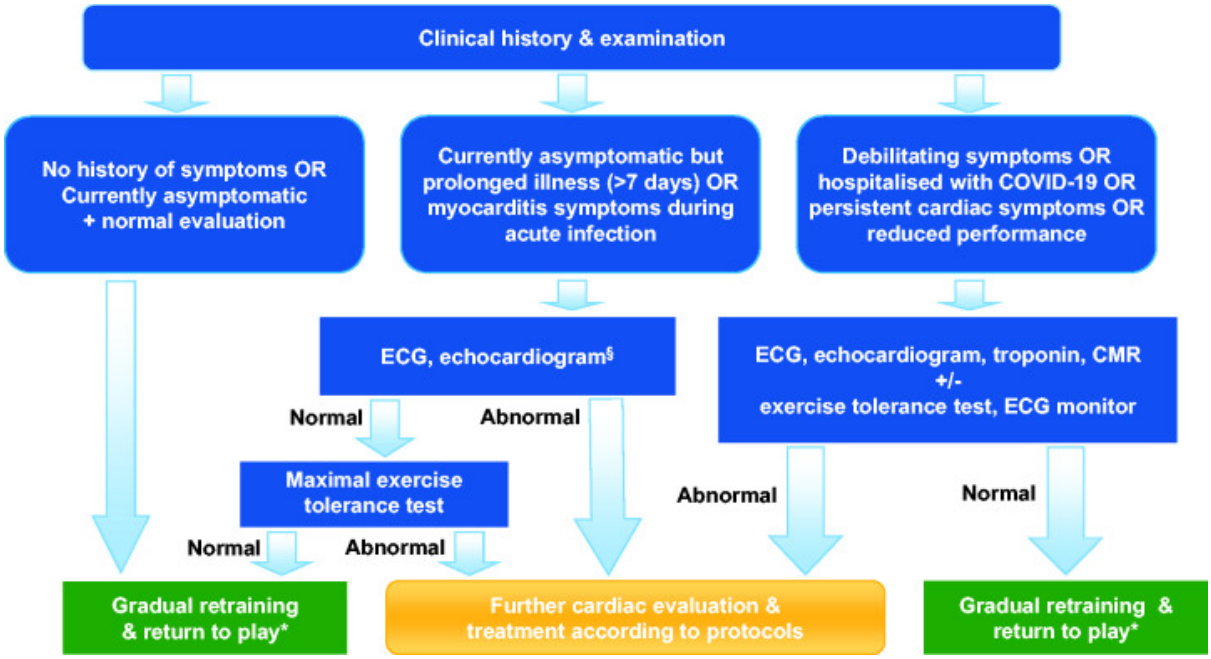

Figure 37: Proposed cardiac evaluation of elite athletes prior to return to competitions. §Depending on the nature of past symptoms a CMR scan may be considered to check for myocardial fibrosis in those with symptoms highly suggestive of myocarditis. *If any cardiac symptoms during re-training assessment by the team doctor and/or sports cardiologist as necessary. ECG: electrocardiogram; CMR: cardiovascular magnetic resonance. Bhatia RT, Marwaha S, Malhotra A, et al. Exercise in the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) era: A Question and Answer session with the experts Endorsed by the section of Sports Cardiology & Exercise of the European Association of Preventive Cardiology (EAPC). *Eur J Prev Cardiol*. 2020;27(12):1242-1251.

Athletes with mild to moderate symptoms who managed their condition at home posed a greater challenge, particularly in the early phase of the pandemic, when access to testing was extremely limited, particularly in the United Kingdom. Few would have been tested for COVID-19 infection and most may have simply

suspected they had the infection. There was a rationale to advise cardiac re-evaluation in some of these athletes from a cardiovascular perspective prior to returning to sport. Our consensus panel broadly felt this was particularly relevant in:

1. Athletes who were currently asymptomatic but had a debilitating illness lasting > 7 days and/or experienced symptoms compatible with myocarditis/pericarditis such as chest pain, breathlessness, palpitations, exertional dizziness or syncope.
2. Athletes who continued to experience persistent cardiac symptoms even after the acute infection had resolved.
3. Athletes with reduced performance despite an appropriate re-training regime.

We advocated that asymptomatic athletes with a prior history of debilitating illness and those who experienced symptoms compatible with myocarditis/pericarditis should have at least a 12-lead ECG and echocardiogram. If these were normal, proceeding to a maximal exercise stress test followed by a clinical review and clearing the athlete to train if normal, was deemed appropriate.

A CMR scan was advised to be considered to check for myocardial odema and fibrosis in those with symptoms highly suggestive of myocarditis. Athletes with on-going symptoms were advised to have additional blood tests, including cardiac troponin, CRP and full blood count and a CMR scan to check for myocardial inflammation or fibrosis. If these preliminary investigations were normal, proceeding to a maximal exercise stress test and ECG monitor was deemed appropriate. Additional investigations and advice relating to return to normal training depended on the symptoms and results of the investigations (Figure X). It was important to

emphasise that personnel performing cardiac investigations were advised to wear personal protective equipment and clean diagnostic tools such as ECG, echocardiography and exercise stress testing machines with a mild detergent or anti-septic wipes after each procedure. In largely an evidence free zone at the time, our protocol[173] may have viewed as very conservative by some or too aggressive by others.

At the time, we believed that this protocol presented a pragmatic approach that safeguards the safety of the athlete and was applicable for most settings. We acknowledged that individual sporting organisations and national societies, however, may decide to implement different protocols depending on availability of testing for the virus as well as cardiovascular testing facilities.

9.12 Initial clinical implications of consensus recommendations

Following publication, our consensus guidelines[173] were widely adopted, endorsed, and put into practice by sporting organizations globally. This included the charity Cardiac Risk in the Young (CRY); several high level clubs affiliated with the English Football Association such as Arsenal FC, Chelsea FC, Crystal Palace FC, Newcastle United FC and Tottenham Hotspur, amongst others; England Rugby; the Rugby Football Union (RFU); and the English Institute of Sport (EIS).

Furthermore, respective sporting organizations worked with us to tailor recommendations for their athletes and infrastructure. Two example protocols are provided below (figure 38 and figure 39); above all, athletes were encouraged to use

these pragmatic protocols as self-assessment tools prior to returning to train following COVID-19 infection in a largely evidence free zone at the time.

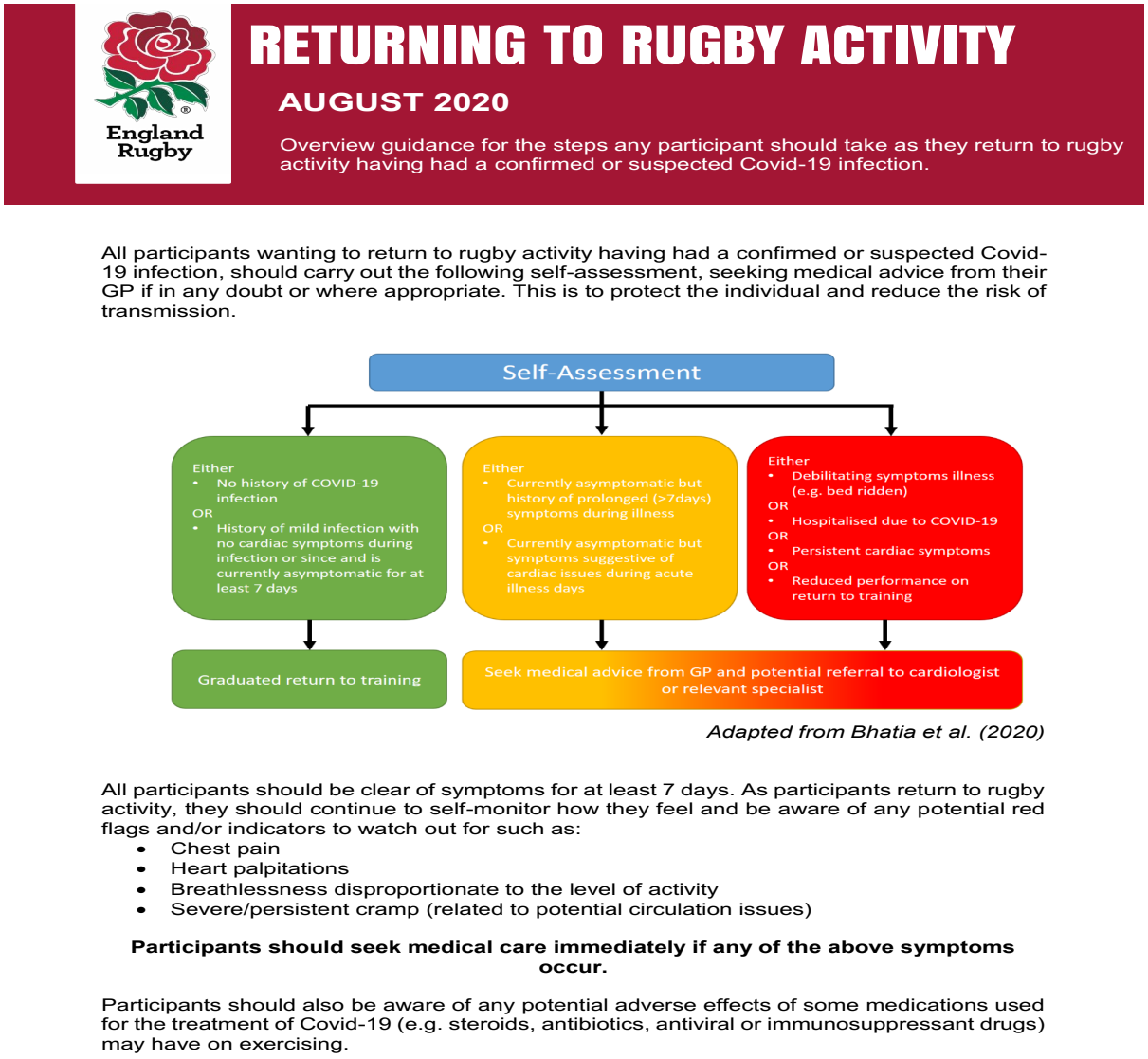

Figure 38: England Rugby returning to rugby activity post COVID-19, August 2020.

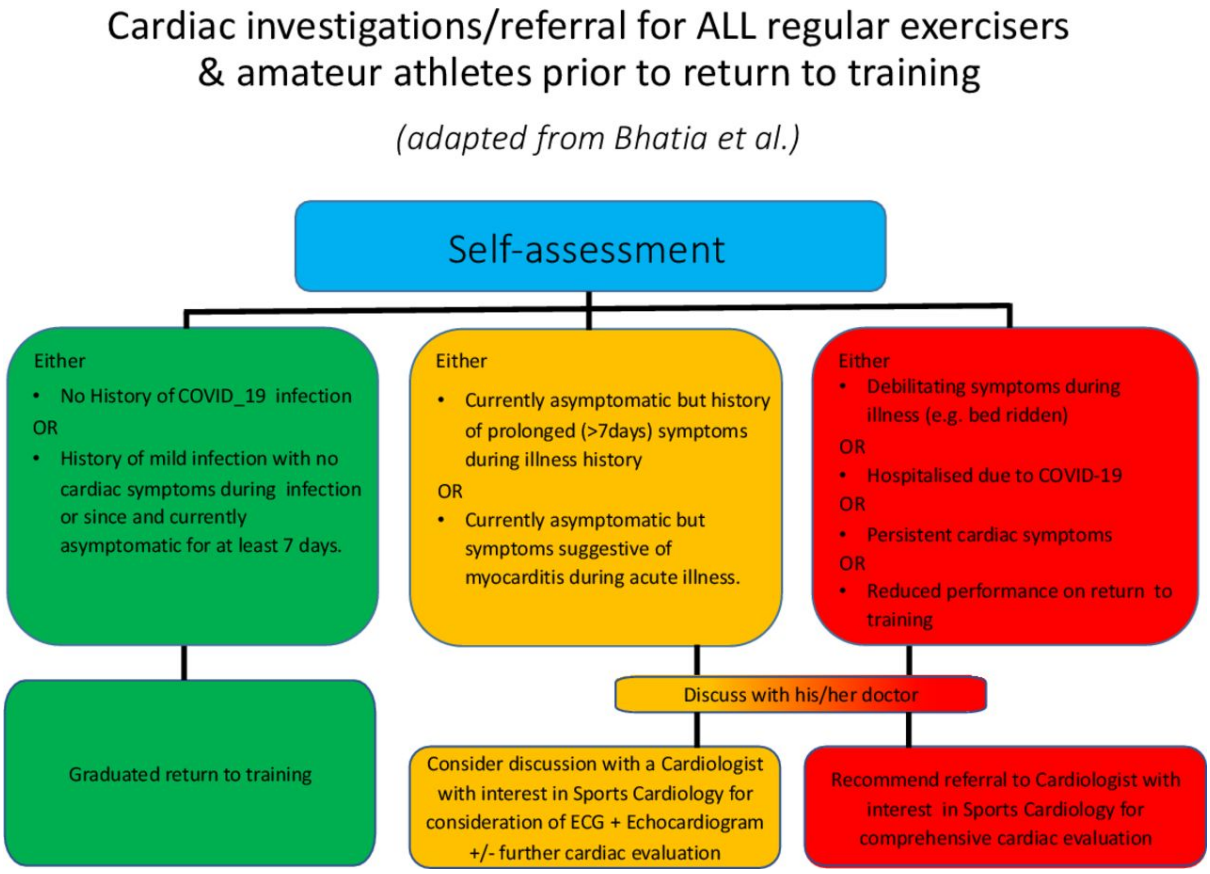

Figure 39: Cardiac investigations/referral for all regular exercisers and amateur athletes prior to returning to training.[192] Utilised by The English Football Association, The English Rugby Football League, The Scottish Football Association, The Lawn Tennis Association, The Welsh Rugby Union and Scottish Rugby, supported by these UK and international Sports and Exercise Medicine bodies: The English Institute of Sport, The Scottish Institute of Sport, Federation Internationale de Football Association, the South African Rugby Union and Wits Sport and Health, University of the Witwatersrand, South Africa.

Our recommendations to date, is one of the most cited papers in its respective discipline. Our Sports Cardiology centre of expertise at St. George's Hospital, London became a clinical hub for onward evaluation of athletes post COVID-19

infection, with referrals coming from across the United Kingdom, which facilitated prospective research to guide clinical practice.

9.13 Temporal knowledge on the prevalence of cardiac involvement following COVID-19 infection in athletes - 2021 to date

In late 2020, small and single-center CMR based studies evaluated athletes with mildly symptomatic or subclinical COVID-19 infection and identified abnormalities on the CMR that could be compatible with recent or previous myocarditis. Rajpal *et al*. investigated 26 collegiate athletes, with mild or asymptomatic COVID-19 infection, 11-53 days after testing positive.[193] It was unclear whether CMR in an individual suffering from influenza, adeno or echo viruses would yield similar findings. None of these athletes had an abnormal cardiac troponin, ECG or transthoracic echocardiogram (TTE), however 4 (15%) fulfilled CMR criteria for myocarditis and 12 (46%) had evidence of scar. This study did not include a control group and the precise details of what constituted an abnormal result were not presented. In another study of 54 young athletes with uncomplicated COVID-19, 1 in 3 showed evidence of resolving pericardial inflammation or pericardial effusion but only 1 revealed evidence of myocardial enhancement and reduced left ventricular systolic function.[194]

Clark *et al.* investigated 59 COVID-19 positive athletes, 60 athletic controls and 27 healthy controls.[195] In addition to a clinical assessment, all COVID-19 positive athletes had ECG, Troponin I, TTE with strain and CMR. The median time from the detection of COVID-19 infection to CMR was 21.5 days. Most athletes had a mild illness (78%) or were asymptomatic (22%). 2 (3%) athletes, both of whom were

asymptomatic with normal preliminary tests were diagnosed with myocarditis. RV insertion point fibrosis was detected in 22% of COVID positive athletes and 24% of control athletes, highlighting the importance of including athletic controls in the context of evaluating CMR findings following COVID-19 infection.

Over 12-months after the outbreak of the pandemic, a commendable large cross-sectional study investigated the prevalence of inflammatory heart disease in over 789 professional athletes with prior, non-severe COVID-19 infection in North America across five professional sport leagues.[196] The mean age was 25 years and 98.5% of the cohort were male. Following a mean of 19 days, the athletes underwent ECG's, serum cardiac troponin assays, and TTEs. Cardiac MRI was only performed where clinically indicated. 30 athletes (3.8% of the cohort) had an abnormality on their initial screen and 5 athletes (0.6%) with moderate symptoms, demonstrated findings consistent with inflammatory heart disease (myocarditis, 3; pericarditis, 2) which required restriction from competitive sport.[196] There were no adverse events in the recovering 25 athletes that returned to play.

Subsequently, a large prospective, multicenter, observational cohort study with data from 42 colleges and universities in North America, reported on the prevalence, clinical characteristics, and outcomes of COVID-19 cardiac involvement in 3018 young competitive athletes who tested positive for COVID-19 infection.[197] 119 athletes had a clinically indicated CMR based on symptoms or abnormalities in 1 or more of (i) cardiac troponin; (ii) ECG or (iii) transthoracic echocardiogram *(triad testing)* and 198 athletes underwent CMR as part of a mandatory assessment irrespectively. None of the athletes had severe illness but 13% had symptoms

consistent with possible cardiac involvement. 2.7% of athletes had an abnormality in the triad of preliminary tests and the prevalence of an abnormal CMR consistent with myocarditis was 0.7% (18% of those referred following an abnormality identified at their initial assessment). The diagnostic yield of CMR for COVID-19 myocardial involvement was 4 times greater for a clinically indicated CMR versus a primary screening CMR.[197] During a median follow-up period of 113 days, there was one (0.03%) adverse cardiac event likely unrelated to COVID-19 infection, amongst the entire cohort.

The studies by Martinez et al.[196] and Moulson et al.[197] highlight the importance of a symptom guided approach to downstream testing. To date, the observed differences in CMR based studies, demonstrates the inherent quandary with utilizing CMR as a routine screening tool in individuals with a self-limiting or mild illness and calls for a more appropriate utilisation based on clinical merit and pre-test probability. These findings were highly relevant in a pandemic, which has resulted in rationing of health-care resources globally, including access to advanced diagnostics such as CMR.

Chapter 10: Prevalence and Diagnostic Significance of De-novo 12-lead ECG Changes After COVID-19 Infection in Elite Soccer Players

(Publication attached in appendix 1)

10.1 Abstract:

Background and aim: The efficacy of pre-COVID-19 and post-COVID-19 infection 12-lead ECGs for identifying athletes with myopericarditis has never been reported. We aimed to assess the prevalence and significance of de-novo ECG changes following COVID-19 infection.

Methods: In this multicentre observational study, between March 2020 and May 2022, we evaluated consecutive athletes with COVID-19 infection. Athletes exhibiting de-novo ECG changes underwent cardiovascular magnetic resonance (CMR) scans. One club mandated CMR scans for all players (n=30) following COVID-19 infection, despite the absence of cardiac symptoms or de-novo ECG changes.

Results: 511 soccer players (median age 21 years, IQR 18-26 years) were included. 17 (3%) athletes demonstrated de-novo ECG changes, which included reduction in T-wave amplitude in the inferior and lateral leads (n=5), inferior leads (n=4) and lateral leads (n=4); inferior T-wave inversion (n=7); and ST-segment depression (n=2). 15 (88%) athletes with de-novo ECG changes revealed evidence of inflammatory cardiac sequelae. All 30 athletes who underwent a mandatory CMR scan had normal findings. Athletes revealing de-novo ECG changes had a higher

prevalence of cardiac symptoms (71% vs 12%, p<0.0001) and longer median symptom duration (5 days, IQR 3-10) compared with athletes without de-novo ECG changes (2 days, IQR 1-3, p<0.001). Among athletes without cardiac symptoms, the additional yield of de-novo ECG changes to detect cardiac inflammation was 20%.

Conclusions: 3% of athletes demonstrated de-novo ECG changes post COVID-19 infection, of which 88% were diagnosed with cardiac inflammation. Most affected athletes exhibited cardiac symptoms; however, de-novo ECG changes contributed to a diagnosis of cardiac inflammation in 20% of athletes without cardiac symptoms.

Introduction

As noted in chapter 10, the novel COVID-19 pandemic, raised global concerns around infection and potential adverse cardiac sequale in athletic individuals. Our pragmatic consensus-based protocol[173] to appraise athletes amidst a largely evidence free zone, was based upon our practical experiences with cardiac screening in the community and expertise with onward evaluations performed in secondary care setting, prior to the pandemic.

Observational studies during the pandemic, revealed that up to 30% of individuals hospitalised for severe COVID-19 infection showed biochemical evidence of myocardial injury.[148,198] Old age, obesity, the presence of multiple risk factors for atherosclerosis and concomitant cardiac comorbidity are recognised risk factors, suggesting that plaque rupture is an important cause of myocardial injury, however it is also well established that COVID-19 infection predisposes to myocarditis.[198,199] Whilst caution must be advised when extrapolating these data to the younger and generally healthier athletic population, a diagnosis of myocarditis, has serious implications in athletes due to its association with fatal arrhythmias during vigorous exercise.[7,129,174]

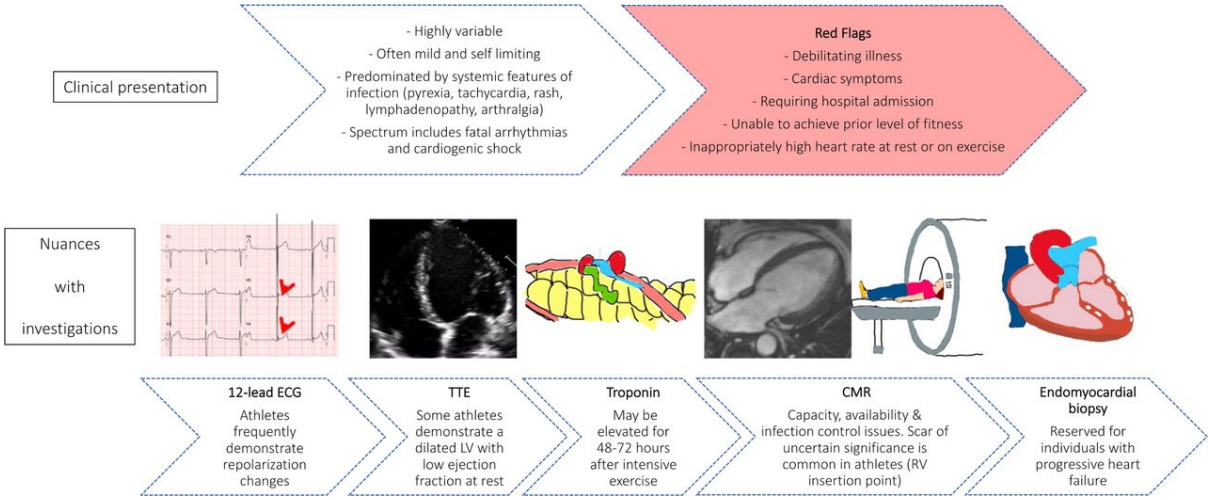

Figure 40: Challenges in establishing a diagnosis of myocarditis in athletes following COVID-19 infection. CMR, cardiovascular magnetic resonance; LV, left ventricular; RV, right ventricular; TTE, transthoracic echocardiogram.

Reports from large cohorts of collegiate and professional athletes in the United States, indicate that the prevalence of myocarditis following mild to moderate COVID-19 infection is 0.6-3%.[196,197] These figures are a justified incentive for identifying affected athletes as evidenced by several consensus-based evaluation protocols for infected athletes in North America and Europe.[170,173,180,200–203] Given its widespread availability, the inclusion of a 12-lead electrocardiogram (ECG) is common to all protocols,[170,173,180,200–202] however, a single cross-sectional ECG is problematic because several physiological repolarisation changes affecting the J-point, ST-segment and T wave are also common manifestations in individuals with myopericarditis (figure 40).[46] Most elite sporting organisations, however, recommend annual assessments in athletes which provides an opportunity to investigate the significance of de-novo electrical changes, during or shortly after viral infection.

10.2 **Aim**

Further to our initial consensus-based recommendations, the aim of our study was to report on the prevalence and diagnostic significance of de-novo ECG patterns following COVID-19 infection in a well-defined cohort of elite soccer players in the English, Dutch and Brazilian league. We hypothesised that a cardiac screening programme in elite athletes, based on a clinical evaluation and 12-lead ECG with availability of serial ECGs for comparison is able to detect athletes at risk of inflammatory cardiac sequelae due to SARS-CoV-2 infection.

10.3 **Personal contribution**

I formulated the study hypothesis, obtained, reviewed and analysed a large dataset, performed quality control, statistical analysis, manuscript preparation and subsequent manuscript revisions. RTB presented the findings at national and international meetings.

10.4 **Methods**

10.4.1 Screening procedures and protocols during the pandemic: an overview of logistical considerations.

During the COVID-19 pandemic, our team devised meticulous screening procedures and protocols in collaboration with the charitable organisation Cardiac Risk in the Young (CRY). These protocols were formulated to adapt to the dynamic nature of disease epidemiology and evolving public health directives. Our approach was fully aligned with the guidance provided by Public Health England, available at www.gov.uk, which encompassed primary care, ambulatory care, and non-emergency outpatient clinical settings (table 33)

Table 33: Screening procedures and protocols during the pandemic: an overview of logistical considerations.

General concepts:

- Staff followed NHS guidelines, self-isolating if symptomatic or exposed to COVID-19.
- Equipment setup adhered to social distancing guidelines.
- Rigorous cleaning of screening station equipment was performed.
- A welcome station ensured hand sanitization, temperature checks, and mask distribution.
- Consent forms were signed, and staggered appointments maintained social distancing.
- Single-use PPE was disposed of properly.
- One-way systems and distancing measures were implemented.

Specific guidelines for different roles:

ECG Physiologists & Echocardiographers:

- Equipment was cleaned before and after each screening.
- Essential screening items were prepared.
- PPE included gloves, apron, mask, and face shield.
- Hand sanitization and glove change occurred before tests.
- Equipment and hands were cleaned thoroughly.
- Masks were worn until leaving.

Cardiologists:

- Regular surface cleaning and hand sanitization.

• Masks and face shields used when necessary. • Gown and gloves for physical examinations. • Result files handed to the screening manager.
Drivers: • Mask-wearing enforced. • Equipment setup managed with hand sanitization. • Efficient van loading with proper cleaning.
Screening Managers: • Ensured staff compliance with safety measures. • Coordinated equipment and oversaw cleanliness. • Managed reception areas and enforced distancing. • Guided individuals and managed result collection.
Administrators: • Wore masks. • Maintained clean reception areas. • Assisted with distancing measures. • Guided individuals and handled result collection.

In essence, our screening procedures and protocols were meticulously designed and implemented to prioritize the safety of both staff and individuals undergoing screenings during the pandemic. Each role within the screening process had specific guidelines to ensure compliance with hygiene and distancing measures, with a strong emphasis on the use of PPE and rigorous sanitization practices.

10.4.2 Setting

The English, Dutch and Brazilian Football Associations mandate at least an annual cardiac assessment in soccer players aged 16 years old and above. Our sports cardiology units, led by senior authors AK, AM, AV, DR, HJ, MP, RC, RS and SS serve several clubs and maintain records of serial assessments for all athletes. During the on-going COVID-19 pandemic, several clubs requested a minimum of a 12-lead ECG in athletes with confirmed COVID-19 infection. We compared ECGs performed during the last assessment, prior to testing positive for COVID-19 infection with ECGs performed following COVID-19 infection. The study was given ethical approval by the St. George's Research Ethics Committee (SGREC) 2021.0139. Written informed consent was obtained from each athlete, in accordance with the Football Association (FA) governance department, respective sporting bodies and team management in the Netherlands and Brazil, which acknowledge that anonymised clinical information may be used for medical research purposes. Pooled data was provided to authors RB and SS in a completely anonymised format as part of routine cardiological assessments performed during the pandemic which was guided by the respective sports cardiologists, clubs and team doctors. No athlete was identified or directly contacted outside of the study and routine cardiological assessments. Data will be made available upon reasonable request to the corresponding author.

10.4.3 Subjects

Fully anonymised data from 511 athletes was collected from 9 sports cardiologists serving 36 elite soccer clubs between 1st March 2020 and 15th May 2022 (figure 41). All athletes who were referred to a sports cardiologist following testing positive for

COVID-19 infection on polymerase chain reaction (PCR) and/or antibody test and in whom a previous ECG was available were included. All previous ECGs were reported in accordance with the International recommendations for ECG interpretation in athletes.[46] Athletes with a previously abnormal baseline ECG were excluded (n=6). These included athletes who were under regular surveillance due to marked repolarisation changes indicative of an overt cardiomyopathic phenotype. All pre-COVID-19 ECGs were performed during the routine cardiac evaluation at the onset of the soccer season.

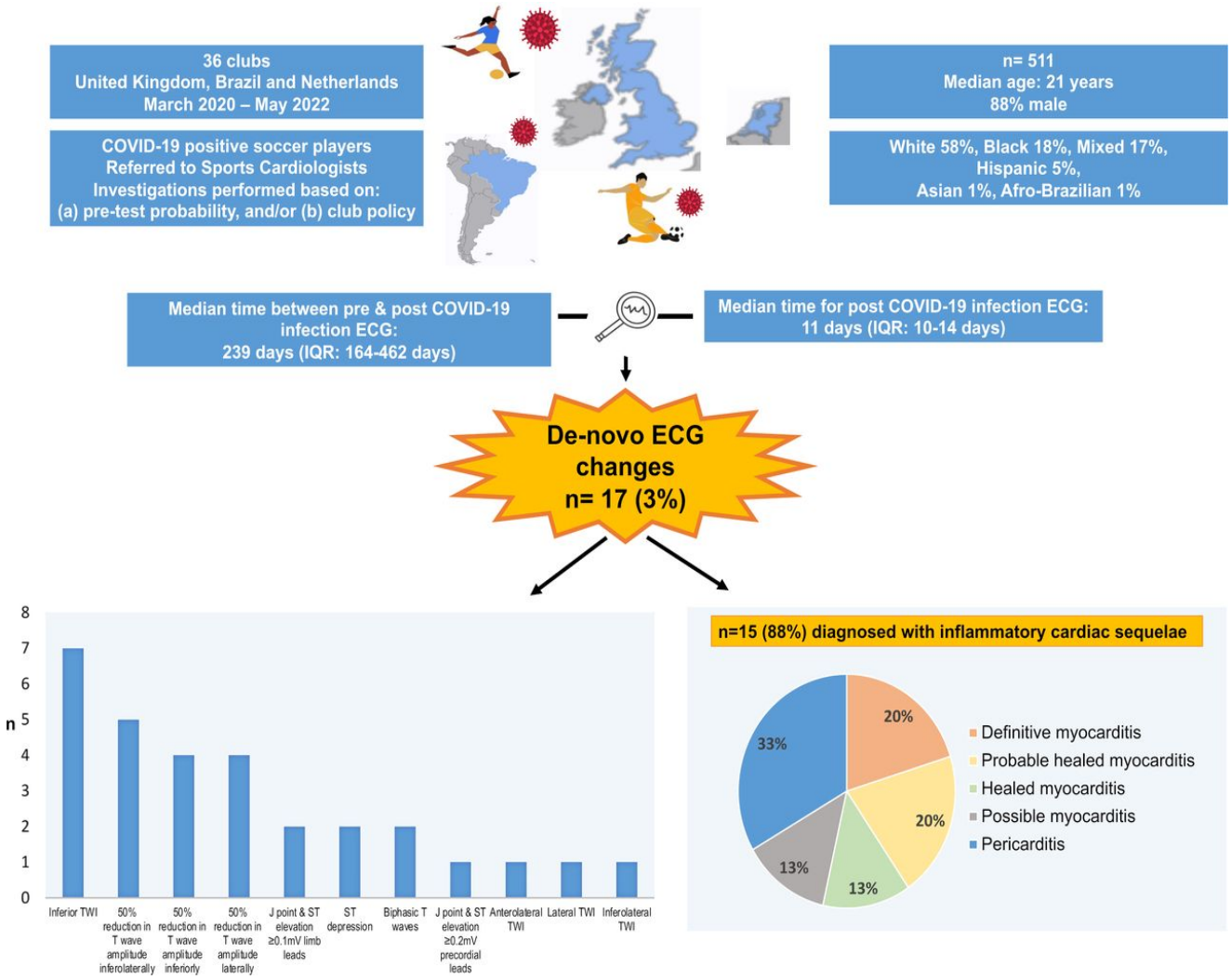

Figure 41: Central illustration. Prevalence and diagnostic significance of de-novo 12-lead ECG changes after COVID-19 infection: study overview. TWI, T-wave inversion.

All athletes underwent an initial clinical evaluation including a clinical history and 12-lead ECG. The clinical history pertained to the presence and duration of cardiovascular symptoms, as well as a comprehensive systems review. A standard 12-lead ECG was conducted in a supine position at a paper speed of 25 mm/s and voltage of 10mm/mV.[204]

10.4.4 De-novo ECG patterns: criteria for an abnormal post COVID-19 ECG

The International recommendations for ECG interpretation recommend further investigations in athletes with several anomalies that may reflect myopericarditis such as atrioventricular (AV) block, left bundle branch block, ST-segment depression, T-wave inversion (TWI) and ventricular extrasystoles.[46] Given that some repolarisation changes overlap between myopericarditis and athlete's heart, we also considered the following ECG patterns as abnormal (figure 42) if they were not detected on the pre-COVID-19 infection ECG: PR-segment depression, new J-point and ST segment elevation (≥0.2mV in the precordial leads and ≥0.1mV in the limb leads), low QRS voltages, complete right bundle branch block, QRS fragmentation, new ST-segment depression, new T-wave inversion, biphasic T-waves and a reduction in the T-wave amplitude by 50% or T-wave flattening.

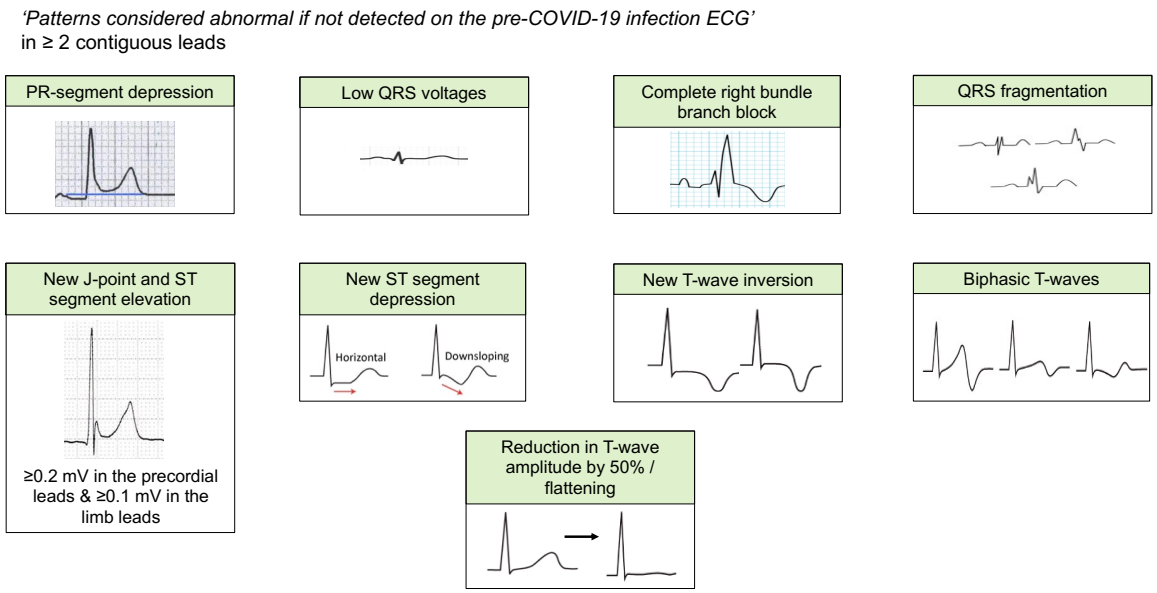

Figure 42: De-novo ECG changes following COVID-19 infection

10.4.5 Further investigation

Athletes with de-novo ECG changes, underwent transthoracic echocardiography (TTE) and cardiovascular magnetic resonance (CMR) imaging. One institution included CMR imaging in all athletes, with COVID-19 infection, irrespective of non-cardiac symptoms, mild disease severity or the absence of de-novo ECG changes.

10.4.5.1 Transthoracic echocardiography (TTE)

TTE was performed by sonographers accredited by the British Society of Echocardiography (BSE) and/or the European Association of Cardiovascular Imaging (EACVI). Cardiac measurements and interpretation were conducted in accordance with a standardised minimum dataset and a joint policy statement of the BSE and Cardiac Risk in the Young (CRY), which accounts for physiological cardiac adaptations to vigorous exercise.[205]

10.4.5.2 Cardiovascular magnetic resonance (CMR) imaging

CMR imaging was considered as the gold-standard non-invasive modality to assess for myocarditis. Scans were performed either using a 1.5-tesla or 3-tesla scanner with ECG-synchronised cine acquisitions. Sequences included: multiple white blood steady-state free precession (SSFP) images and cines, multiple turbo spin echo (TSE) black blood images, T2 short tau inversion recovery (STIR) images, tissue characterisation and delayed enhancement images following gadolinium. In athletes with suspected acute or active myocardial inflammation, we applied the Updated

Lake Louise Imaging criteria.[135] All scans were performed in large volume tertiary centres and reported by experts formally accredited in CMR with particular expertise in inherited cardiac conditions and sports cardiology. Furthermore, most scans were dual reported by at least two experts in the field.

10.4.5.3 Inflammatory cardiac sequelae

To facilitate onward management and risk stratification, in a cohort of ostensibly healthy athletes, the authors considered the following clinical definitions to indicate inflammatory cardiac sequelae:

Acute pericarditis: the presence of at least two of the following criteria: (i) chest pain – typically sharp and pleuritic, alleviated by sitting up and leaning forward; (ii) ECG changes – with new PR depression or ST elevation; and (iii) the presence of a pericardial effusion, either using TTE or CMR imaging.

Definitive myocarditis: the presence of at least three of the following criteria (i) cardiac symptoms; (ii) where performed, an elevated serum cardiac troponin; (iii) the presence of de-novo ECG changes (iv) regional wall motion abnormalities or impaired left ventricular function (LVEF <50%) on TTE; and (v) CMR findings consistent with an episode of active inflammation.

Possible myocarditis**:** the presence of at least three of the following criteria (i) cardiac symptoms; (ii) where performed, an elevated serum cardiac troponin; (iii) the presence of de-novo ECG changes (iv) regional wall motion abnormalities or impaired left ventricular function (LVEF <50%) on TTE but where an athlete did not undergo CMR, or in absence of acute inflammation on CMR.

Probable myocarditis: the presence of at least three of the following criteria (i) cardiac symptoms; (ii) where performed, an elevated serum cardiac troponin; (iii) the presence of de-novo ECG changes (iv) regional wall motion abnormalities or impaired left ventricular function (LVEF <50%) on TTE; and (v) CMR findings consistent with subepicardial or mid-wall scar.

10.4.6 Statistical analysis

Data are expressed as medians (IQRs) or percentages as appropriate and analysed with Microsoft Excel version 16.61.1 and Statistica 13.1. Comparison between groups was performed using the Student t-test or U-Mann Whitney test for continuous variables, the decision on the test used was based on the outcome of the Shapiro-Wilk test for data distribution. The chi-square test was used for categorical variables, with the Fisher exact test considered in the cases with more than 20% of cells having expected frequencies <5. Statistical significance was defined as $p<0.05$.

10.5 **Results**

The median age of athletes was 21 years; interquartile range [IQR]: 18 to 26 years, of which 88% were male. The cohort was ethnically diverse consisting of 58% white athletes, 18% black athletes and 17% athletes of mixed ethnicity. In accordance with public health guidance at the time of the study, following a mandatory 7 to 10-day period of isolation, the median time for a sports cardiology specialist review following a positive COVID-19 PCR/antibody test was of 11 days (IQR: 10-14 days). From February 2022, the legal requirements around self-isolation for individuals who tested positive for coronavirus was abolished in the United Kingdom, which shortened the gap between an athlete testing positive for COVID-19 infection and

being reviewed by a sports cardiologist was a median of 7 days (IQR: 6-9 days). The median duration of illness was 2 days (IQR: 1-3 days). The median time interval between the pre and post COVID-19 ECG was 239 days (IQR: 164-462 days).

494 (97%) athletes had a normal post COVID-19 ECG. Of these, 4 (0.8%) reported persistent cardiac symptoms, with a median duration of illness of 12 days (IQR: 9-17 days) and downstream investigations, including CMR imaging resulted in a diagnosis of pericarditis in all 4 athletes. None of the athletes in this group revealed overt features of definite, probable, or possible myocarditis.

17 (3%) athletes demonstrated de-novo ECG changes, which included, a reduction in T-wave amplitude by 50% in ≥ 2 contiguous leads with the preceding R-wave taller than 0.3 mV in the inferior and lateral leads (n=5), isolated inferior leads (n=4) and isolated lateral leads (n=4); new T-wave inversion in the inferior leads (n=7), inferior and lateral leads (n=1), anterior and lateral leads (n=1) and isolated lateral leads (n=1); ST-segment depression (n=2); biphasic T-waves (n=2); new J-point and ST-segment elevation ≥ 0.2mV in the precordial leads (n=1) and new J-point and ST-segment elevation ≥ 0.1mV in the limb leads (n=2) (table 34). The median time from a positive PCR to a 12-lead ECG in individuals who revealed de-novo ECG changes was 13 days (IQR: 10-15 days).

10.5.1 Clinical characteristics of COVID-19 positive (PCR) athletes with de-novo ECG patterns diagnosed with inflammatory cardiac sequelae

Table 34: Clinical characteristics of COVID-19 positive (PCR) athletes with de-novo ECG patterns diagnosed with inflammatory cardiac sequelae

Case	Sex	Ethnicity	Symptoms and duration (days)	+ve PCR to ECG (days)	De-novo ECG changes	Cardiac MRI	Diagnosis
1	M	White	Myalgia, coryzal symptoms, dyspnoea, chest pain, palpitations; 21-days	26	Reduction in T-wave amplitude II & aVF; inverted T-wave III; >0.1mV J-point and ST elevation II, III, aVF, I, aVL. Resolved 209 days post +ve PCR	Symmetrical biventricular dilatation. RVEF: 50%; LVEF: 53%. T1: Basal lateral ↑ T1 times and ECV↑. Subepicardial LGE uptake (9%) basal to mid lateral & inferolateral wall	Definitive myocarditis
2	M	White	Chest pain, palpitations, malaise, night sweats, sore	35	TWI II, III, aVF, V3-V6	Normal biventricular size and systolic function. Normal	Definitive myocarditis

			throat; 20-days		Resolved 93 days post +ve PCR	myocardial STIR-T2 images & tissue characterisation. Mid-wall LGE basal inferior & inferolateral wall, subepicardial LGE mid lateral, apical lateral & inferior wall	
3	M	White	Fatigue, myalgia, chest pain, dyspnoea; 28-days	30	Reduction in T-wave amplitude II, aVF; biphasic T III Resolved 170 days post +ve PCR	Normal biventricular size and systolic function. Pericardial effusion basal inferior wall with ↑signal on T2-STIR images. Normal myocardial T2-STIR images. Abnormal T1 signal mid inferolateral wall.	Definitive myocarditis with localised pericardial inflammation

						Subepicardial LGE basal and mid inferolateral wall	
4	M	White	Mild coryzal symptoms, headache, anosmia, ageusia; 10-days	9	Reduction in T-wave amplitude II, III, aVF; down-sloping ST-depression III, aVF. Resolved 30 days post +ve PCR	Normal biventricular size and systolic function. Normal myocardial T2-STIR images. Normal tissue characterisation. LGE mid inferolateral wall	Probable healed myocarditis
5	M	Black	Asymptomatic	15	J-point elevation inferiorly and precordial leads with; ascending convex ST segments & deep asymmetric TWI (V2-V3); concave ST	Normal biventricular size and systolic function. Normal myocardial T2-STIR images & tissue characterisation. Trivial pericardial effusion. Subepicardial and	Probable healed myocarditis

					segment & deep TWI (V4); TWI III, aVF; reduction in T-wave amplitude V6, I, aVL Resolved 42 days post +ve PCR	mid-wall LGE basal lateral wall	
6	M	Black	Fever, fatigue, dyspnoea; 7-days	7	TWI III & aVF with down-slopping ST segments and reduction in T-wave amplitude II & V5-V6 Resolved 44 days post +ve PCR	Normal biventricular size and systolic function. T2-STIR images & tissue characterisation not performed. Subepicardial LGE mid lateral wall	Probable healed myocarditis
7	M	White	Fever, malaise, myalgia, cough,	10	Reduction in T-wave amplitude II, III, aVF	Normal biventricular size and systolic function. Normal	Healed myocarditis

			anosmia, ageusia; 7-days		Persistent ECG changes – 205 days post +ve PCR	myocardial T2-STIR images & tissue characterisation. Focal mid-wall fibrosis basal and mid inferior wall	
8	M	White	Rigors, fever, palpitations, dyspnoea; 4-days	10	Reduction in T-wave amplitude V5-V6 Resolved 24 days post +ve PCR	Upper limits of normal LV with normal LVEF (58%). Normal T1 and T2 mapping. Mid wall LGE basal inferior and inferolateral LV with ↑ myocardial ECV.	Healed myocarditis
9	M	Mixed	Dyspnoea, fever and fatigue; 7-days	13	TWI III, aVF, V4-V6; reduction in T-wave amplitude lead II. Resolved 47	Mild increase in LV cavity volume, no RWMA and preserved LVSF (57%). T2-STIR images & tissue characterisation	Possible myocarditis

					days post +ve PCR	not performed. No LGE	
10	M	White	Fever, lightheaded, fatigue, chest pain; 21-days	14	Reduction in T-wave amplitude II, III, aVF, V5 & V6 Resolved 48 days post +ve PCR	Biventricular enlargement. LVEF:49%; RVEF: 47%. Normal myocardial T2-STIR images & tissue characterisation. No LGE	Possible myocarditis
11	F	White	Fatigue, chest pain, dyspnoea; 4-days	11	TWI III, aVF; reduction in T-wave amplitude V4-V6 Resolved 146 days post +ve PCR	Normal biventricular size and systolic function. Pericardial effusion basal inferior wall. Tissue characterisation not performed. No LGE	Pericarditis
12	M	White	Mild coryzal symptoms,	14	Biphasic T-wave V3; TWI	Normal biventricular size and systolic	Pericarditis

			chest pain; 3-days		V4-V5, I, aVL, flat TWI V6 Resolved 196 days post +ve PCR	function. Trivial pericardial effusion. No LGE	
13	M	Black	Myalgia, fatigue and fever, chest pain; 3-days	12	Reduction in T-wave amplitude II, III, aVF, V5 & V6 Follow up ECG n/a (player has moved club)	Normal biventricular size and systolic function. Pericardial effusion basal inferior wall. No LGE	Pericarditis
14	M	Black	Fever, malaise, chest pain, dyspnoea, palpitations; 5-days	11	Reduction in T-wave amplitude II, V5 &V6; TWI III, aVF Follow up ECG n/a (player has moved club)	High normal LVEDV, mildly reduced LVEF (51%), normal RVEDV, normal RVEF (53%). Pericardial effusion basal inferior wall. No LGE	Pericarditis

15	M	Mixed	Chest pain, dyspnoea, fever, cough, fatigue, headache, myalgia; 4-days	13	Reduction in T-wave amplitude with bifid appearance II, V5 & V6; TWI III & aVF Resolved 41 days post +ve PCR	Mild biventricular dilatation and normal systolic function. Pericardial effusion basal and mid inferior LV and anterior RV wall. No LGE	Pericarditis

15 (88%) athletes with de-novo ECG changes were diagnosed with inflammatory cardiac sequelae including pericarditis (n=5), probable healed myocarditis (n=3), definitive myocarditis (n=3), possible myocarditis (n=2) and healed myocarditis (n=2) (table 34, figures 43 and figure 44). These changes occurred in individuals who had a median illness duration of 7 days (IQR: 4-14 days) and 12 (80%) of the athletes reported cardiac symptoms. 2 (0.4%) athletes demonstrated new inferior TWI (n=1), and inferolateral T wave flattening (n=1) showed no evidence of inflammatory cardiac changes on downstream testing. The overall prevalence of inflammatory cardiac sequelae in the cohort based on de-novo ECG changes was 3%. Among athletes without cardiac symptoms, the additional yield of de-novo ECG changes to detect cardiac inflammation was 20% (n=3; table 34: athlete number 4, 5, and 7 demonstrated the presence of late gadolinium enhancement, LGE).

12 athletes identified with inflammatory cardiac sequelae, demonstrated resolution of de-novo ECG changes (table 34, Figure 3 and 4); the ECG changes persisted in 1 athlete with healed myocarditis; and follow up ECG were not available in 2 players who moved clubs.

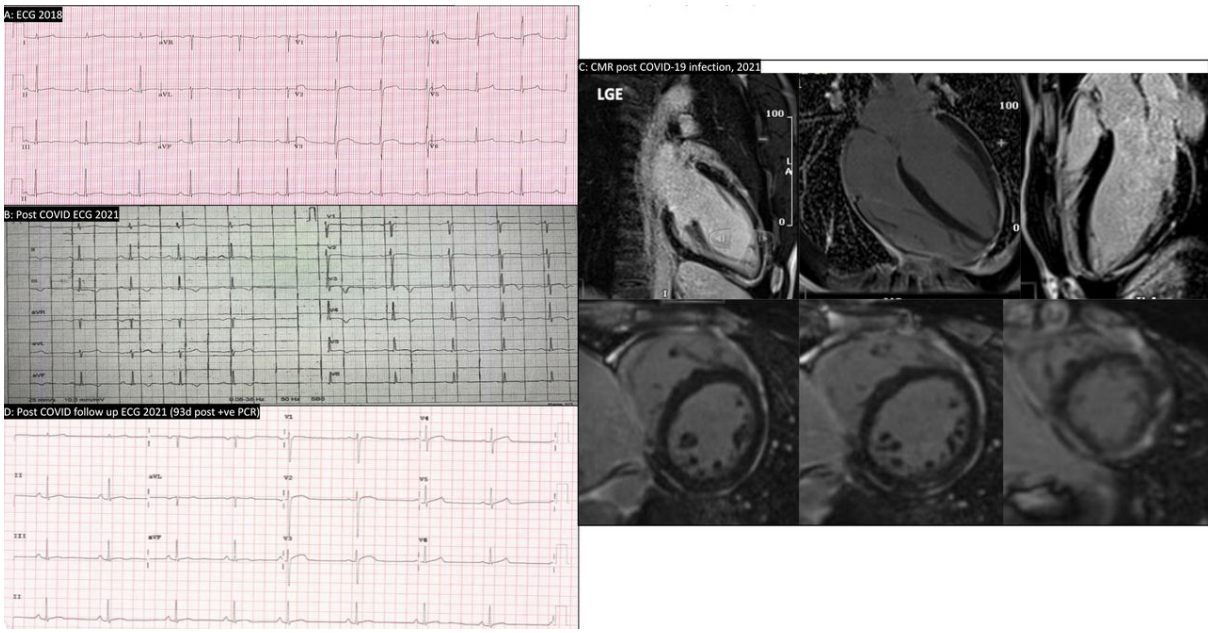

Figure 43: Athlete case 2. Twenty-day history of cardiovascular symptoms post COVID-19 infection. In comparison to his pre-COVID-19 ECG (A), new T-wave inversion was observed in leads II, III, aVF and V3–V6 (B); a cardiac MRI (C) demonstrated mid-wall LGE in the basal inferior and inferolateral wall; subepicardial LGE in the mid-lateral, apical lateral and inferior walls; with resolution of ECG changes 93 days post positive PCR (D). LGE, late gadolinium enhancement.

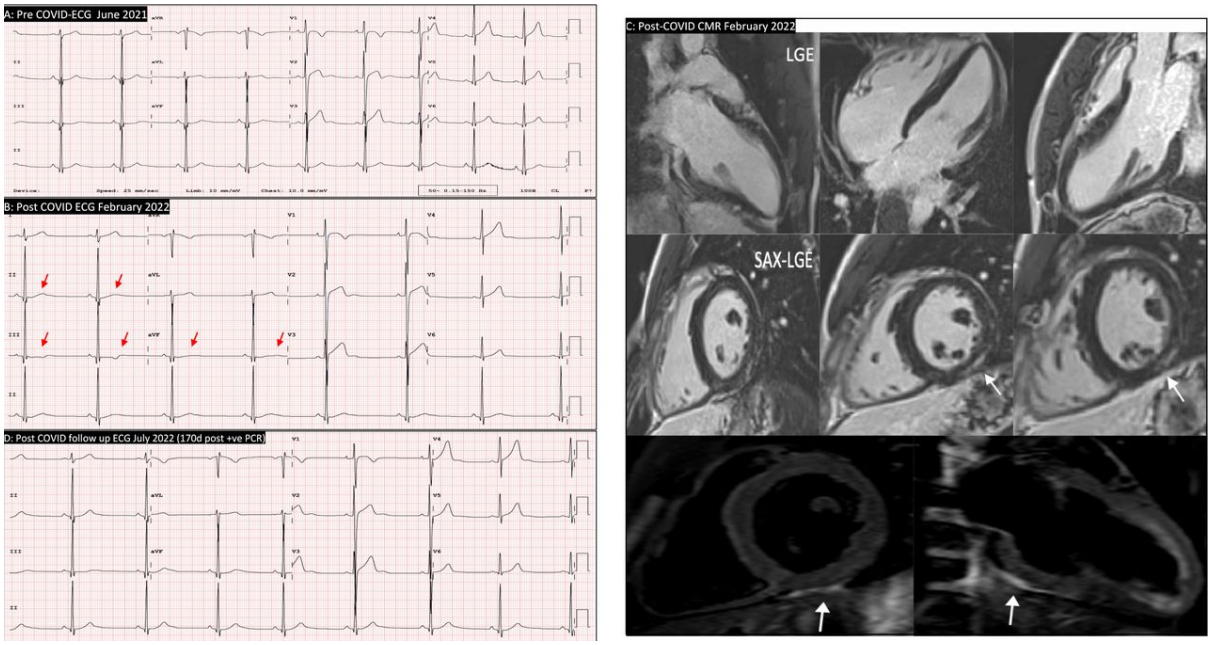

Figure 44: Athlete case 3. Twenty-eight-day history of symptoms post COVID-19 infection. In comparison to his pre-COVID-19 ECG (A), a reduction in T-wave amplitude II, aVF, biphasic T III was observed post COVID-19 infection (B). A cardiac MRI (C), a pericardial effusion around the basal inferior wall with ↑ signal on T2-STIR images, an abnormal T1 signal in the mid-inferolateral wall and subepicardial LGE in the basal and mid-inferolateral wall. Resolution of ECG changes was observed 170 days post positive PCR (D). LGE, late gadolinium enhancement; STIR, short-tau inversion recovery.

None of the 30 asymptomatic or paucisymptomatic athletes who were investigated with a CMR despite a normal ECG, revealed cardiac inflammation compared with

88% of the athletes with de-novo ECG changes (Table 35 and Table 36). Athletes revealing de-novo ECG changes had a longer symptom duration (median 5 days [IQR 3-10 days]) compared to athletes undergoing mandatory CMR assessment (median 0 days (asymptomatic) [IQR 0-3 days]; p<0.0001. There were no significant differences in quantitative CMR parameters between athletes with de-novo ECG changes and athletes who underwent mandatory CMR despite the absence of cardiac symptoms or abnormal ECG (Table 35).

Table 35: Comparison of CMR data between athletes demonstrating de-novo ECG changes and athletes undergoing a mandatory CMR.

	Athletes undergoing mandatory CMR assessment (n=30)	**Athletes demonstrating de-novo ECG changes undergoing CMR assessment (n=17)**	**P value**
Age	26 (19 - 30)	22 (19 - 25)	0.094
BSA (m2)	2 (1.9 - 2.1)	2 (1.9 - 2.1)	0.861
Symptom duration (days; 0=asymptomatic)	0 (0 - 3)	5 (3 - 10)	0.0001*
Positive PCR to ECG	11 (11 - 11)	12 (10 - 14)	0.298
Positive PCR to CMR	11 (11 - 11)	15 (11.5 - 19.5)	0.005*
LV MWT (mm)	10 (9 - 10)	9 (9 - 11)	0.770
LV EF (%)	59 (57 - 62)	60 (57 - 64.3)	0.415

LV mass indexed (g/m2)	72 (54 - 83)	82 (65 - 93)	0.094
RV EF (%)	53 (51 - 60)	58 (51 - 62.5)	0.179
Presence of inflammatory cardiac sequalae	0	15	

Values are expressed as median (IQR); *P value <0.05 deemed statistically significant. BSA: body surface area; CMR: cardiac magnetic resonance; ECG: electrocardiogram; LVEF: left ventricular ejection fraction; LVMWT: left ventricle maximal wall thickness; PCR: polymerase chain reaction; RVEF: right ventricular ejection fraction.

Table 36: Summary of cardiovascular symptom burden, de-novo ECG changes and MRI findings in overall cohort.			
	CV symptoms*	**De-novo ECG changes**	**Cardiac MRI**
Total cohort, n=511			
1) No de-novo ECG changes, n=494 (97%)	Persistent symptoms: n=4 (0.8%) None: n=490 (99%)	None: n=494 (97%)	4 athletes with persistent CV symptoms (median duration 12 days [IQR: 9-17 days]) had abnormal CMRs and were diagnosed with pericarditis.
(a) Includes, mandatory CMR group n=30 (6%)	None	None	All 30 athletes underwent a mandatory CMR: normal findings.
2) De-novo ECG changes group, n=17 (3%)	Yes: n=12 (71%) No: n=5 (29%)	Yes: n=17 (3%)	All underwent CMR ○ Normal: n=2 (12%) ○ Abnormal: n=15 (88%); all diagnosed with inflammatory cardiac sequelae (12 reported

			CV symptoms; 3 reported no CV symptoms)

CMRI: cardiovascular magnetic resonance imaging; CV: cardiovascular; ECG: electrocardiogram; IQR: interquartile range. *The clinical assessment as a minimum included a comprehensive history, systems review, examination, and electrocardiogram. Further onward investigations were performed based on the respective sports cardiologists, club or team doctor policy.

10.5.2 Follow-up

All athletes with confirmed cardiac inflammation were appraised by experts in the field. Conventional risk-stratification included a maximal exercise stress test, ambulatory Holter monitor, prolonged arrhythmia monitoring for up to 2-weeks in certain cases, and close surveillance by the club doctors and respective sports cardiologist. None of the athletes revealed significant impairment in functional and haemodynamic status on exercise testing and arrhythmia monitoring did not reveal any evidence of complex ventricular arrhythmia or myocardial ischaemia.

During a median follow up 270 days (IQR: 133-487 days), there were no adverse cardiac events among infected athletes in the entire cohort. All athletes identified with cardiac inflammation returned to play following conventional risk stratification tests and tailored exercise prescriptions without adverse events over a median follow up period of 479 days (IQR: 268-520 days).

10.6 Discussion

The resting 12-lead ECG has a low sensitivity for identifying individuals with myocarditis which is estimated at <50%.[175,206] Amongst athletes, the overlap between physiological repolarization changes and myocarditis indicates that the specificity of the ECG may be even lower than the sensitivity. However, the precise significance of de-novo ECG patterns following COVID-19 infection in athletes, has not been investigated. Our study revealed that 3% of professional soccer players revealed de-novo ECG changes, of which, 88% demonstrated features compatible with inflammatory cardiac sequelae.

ECG changes have been reported with other viral infections and may have prognostic relevance. Almost 30% of hospitalized patients with H1N1 influenza virus revealed anomalous patterns including T-wave inversion and ST-segment depression.[207] Specific ECG changes such as diminished QRS amplitude in COVID-19 infection or influenza infected hospitalized patients with pre-existing comorbidities was independently observed to precede clinical decompensation and were associated with an increased mortality.[208,209] As far as we are aware, this is the first study reporting the prevalence and significance of de-novo ECG changes in ostensibly healthy young athletes with COVID-19 infection of mild to moderate severity.

The most common ECG alterations following infection affected the inferior and lateral leads and are consistent with the typical cardiac MRI findings in individuals with myocarditis, who demonstrate a predilection for myocardial scar localised to the basal inferolateral wall.[210]

Only 3 of our athletes fulfilled the Updated Lake Louise criteria for acute myocardial inflammation, however it is noteworthy that these criteria were derived from a cohort of acutely unwell patients, where the CMR scan was performed in a timely fashion to detect myocardial oedema. In contrast, our athletes had mild or subclinical inflammation where the temporal relationship between confirmation of infection and CMR findings was probably too long to reveal acute inflammation but identified residual scar in most cases.

In the absence of a baseline CMR, it may be argued that the scar tissue may have been a compensatory response to decades of vigorous exercise.[104,211] However, we did not find any evidence of inflammation or scar in 30 asymptomatic or paucisymptomatic athletes who underwent a mandatory CMR despite an unchanged ECG.

Despite a different approach to the triad testing in North American studies in athletes[197], which included troponin measurements, our prevalence (2.9%) of inflammatory cardiac sequelae following COVID-19 infection, based on similar disease definitions[196,197,212] is similar to the upper limit of the prevalence reported by from American studies (3%).

Most athletes (80%) exhibiting de-novo ECG changes revealed symptoms compatible with myopericarditis and were symptomatic for a median of 7 days (IQR: 4-14 days). Our observations are in keeping with North American and European recommendations which indicate that cardiac symptoms should be the main driver

for selecting athletes for cardiac investigations post infection.[173,212] Although based on a small number of athletes, we noted that a minority of athletes who did not report cardiac symptoms but revealed de-novo ECG changes showed evidence of myocardial inflammation. It is well recognised from autopsy series that coryzal symptoms have predominated in a large proportion of decedents with viral myocarditis.[133,213]

The uncertainty surrounding the current pandemic dictates that some sporting organisations may continue to investigate asymptomatic athletes with COVID-19 infection. Our study shows that comparison of pre-and post-COVID-19 ECGs is a cheap and effective method for detecting asymptomatic athletes with cardiac inflammation and may importantly also be applicable to athletes playing at the grass-roots level.

Our approach raises concern about the possibility of false positive ECG results, however, our observations revealed that only 2 athletes (12%) with de-novo ECG changes failed to demonstrate any evidence of cardiac inflammation during subsequent investigation. A recent study which applied the International criteria for ECG interpretation in athletes[46], reported that as many as 4% of 378 collegiate athletes in whom pre and post COVID-19 ECGs were available revealed abnormalities following COVID-19 despite normal cardiac imaging[214]. The precise significance of the ECG abnormalities in this cohort is still unclear since only 22% of athletes with new ECG changes underwent CMR as opposed to all our athletes.

In our study, during a median follow up period of 270 days (IQR: 133-487 days) there were no adverse outcomes which is reassuring, though long-term studies are required to ascertain the outcomes in athletes with myocardial inflammation post-COVID-19 infection.

We appreciate that the current ESC 2020 sports cardiology guidelines recommend a minimum of 3 months of rest prior to considering intensive exercise or competitive sport provided (i) ventricular function is preserved, (ii) there is no evidence of on-going inflammation on the CMR and (iii) no evidence of complex ventricular arrhythmias during exercise. However, given that our athletes were professionals, treated in the community i.e., not hospitalised with a severe illness and with limited myocardial inflammation, we often made the decision to reduce the rest period to 6 weeks. The exact timeframe that an athlete took to return to train was largely dependent on a shared decision-making (SDM) approach between the athlete and sports cardiologist, after appropriate risk-stratification as discussed above. Often cases were discussed with a panel of experts taking into account comprehensive evaluations and regular surveillance. This approach, considering the novelty of the pandemic and an athlete's occupation as well as mental health may be regarded as liberal but emphasises the importance of a tailored approach to exercise prescription.

10.7 **Limitations**

Our study has several limitations which warrant mention. The cohort of interest, notably, athletes with de-novo ECG changes was relatively small and reflects the low

prevalence of myocarditis in athletes infected with COVID-19. It is possible that some of the de-novo ECG changes reflected change in variation in training intensity. However, most of our pre COVID-19 ECGs were performed as part of routine cardiac evaluations just prior to the onset of the season when players are extremely conditioned. The absence of cardiac inflammation in equal numbers of athletes with normal ECGs who underwent CMR suggests that the de-novo ECG changes we observed were a genuine representation of cardiac pathology. Importantly, we did not rely on inflammatory markers and/or biomarkers of cardiac damage and systemic inflammation. In view of public health measures to curtail viral spread, which largely included a mandatory period of self-isolation for athletes, by which time we were mindful that measures of inflammation might have normalised. Furthermore, many of our asymptomatic athletes continued to partake in regular physical activity whilst isolating which is a recognised cause of transient elevation in their serum cardiac troponin. We did not consider vaccination status as a variable, as this information was not available or volunteered by the majority of athletes.

10.8 Conclusions

3% of athletes developed de-novo ECG changes following COVID-19 infection, of which 88% revealed inflammatory cardiac sequelae. Whereas most athletes in question reported cardiac symptoms and would have been assessed as standard of care, a small minority were asymptomatic. In the absence of cardiac symptoms de-novo ECG changes post COVID infection contributed to 20% of all cases of cardiac inflammation.

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10.9 Clinical implications

Our study demonstrates that comparison of pre and post COVID-19 ECGs is a pragmatic way of identifying athletes with inflammatory cardiac sequalae. This is particularly relevant in the cardiac screening environment, where otherwise ostensibly healthy athletes usually undergo some form of cardiac evaluation, which usually includes a 12-lead ECG where abnormalities may be identified.[46]

The benefit of sequential ECGs in elite athletes who have frequent cardiac screening is an emerging concept. Data from Italy suggests that diseases at risk of sudden death were more often identified on repeated evaluations.[215] However, our study has solely focussed on the identification of inflammatory cardiac sequalae based on serial ECGs, in the context of a novel viral pandemic, which has never been done.

Sports cardiology and the cardiac screening arena are rapidly expanding. Our findings highlight the significant benefit of open multi-centre collaborations and enhanced governance procedures to store high quality data, particularly electronic versions of ECGs. Working with experts from different centres and countries, truly broadens the relevance of research findings and this is reflected in the broad range of ethnicities included in our study.

Whilst the International Recommendations for ECG interpretation in athletes[46] have markedly reduced false positives[47,48] and provided a robust framework for ECG interpretation in elite athletes, there is growing interest into the significance of novel ECG indices which do not feature in the recommendations as things stand. This includes the relevance of isolated low QRS voltages in young athletes, which has been demonstrated to be the hallmark of underlying left ventricular scar with a propensity for ventricular arrythmias.[216] As such, our findings in the context of pandemic offers novel insights into how an athlete's ECG may change following viral infection and may of course be of relevance to future guidelines as well as pandemics (Figure 45). Certainly, our findings whereby ECG changes were largely transient and reverted to baseline, demonstrate the importance of contextualising ECG findings with the clinical presentation.

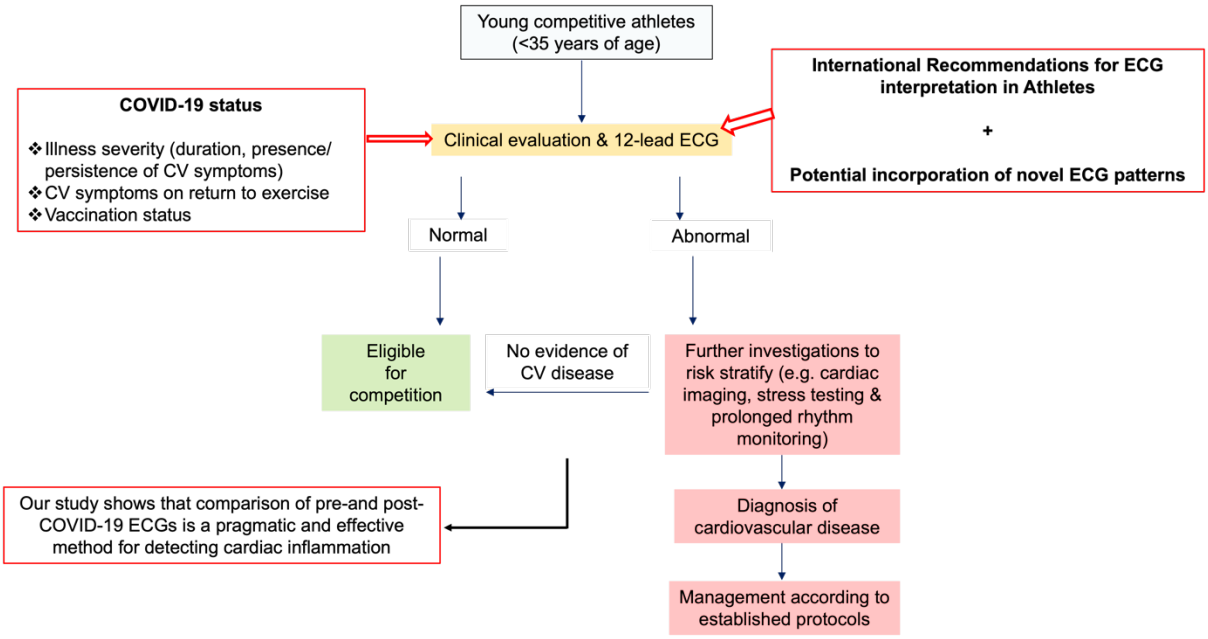

Figure 45: Cardiovascular screening in the COVID-19 era.

Our study underscores that elite athletes predominantly experience a mild and self-limiting illness after contracting COVID-19 infection. It is imperative to acknowledge that not all athletes underwent comprehensive cardiac MRI scans, thus, the possibility of undetected cases of subclinical myocarditis remains. Nevertheless, during a substantial follow-up period approaching 12 months, our analysis did not uncover any detrimental cardiovascular consequences within the cohort. This includes athletes who returned to active participation after a diagnosis of inflammatory cardiac sequelae. Such findings provide a reassuring outlook for the well-being of young individuals reliant on athletic pursuits for their livelihood, as well as the multitude of sport enthusiasts who derive enjoyment from their performances and achievements.

Finally, it is also worth acknowledging that as a result of the current pandemic, certain factors will need to be considered by sporting organisations and public health

authorities for the future planning of competitions and pandemic preparedness, which is an important and topical initiative globally.

Prior to hosting any sporting competition, relevant health authorities and sporting governing bodies in respective countries will need to conduct a detailed analysis on the impact of COVID-19 and potentially emerging variants or other infections in their own countries whilst simultaneously learning from the global experiences. This will include details of disease incidence, prevalence and natural history. Several factors should be considered, including meticulous medical assessments of the athletes, their environment, travel, accommodation and local health care infrastructure (Figure X). The safety of spectators should also be considered given the highly contagious nature of the viruses and close proximity of stadium and arena seating. Rapid point of care testing for COVID-19 and/or other viruses might be possible at sporting venues if required. Similar testing for influenza viruses during the 2018 Winter Olympic Games in PyeongChang, South Korea allowed timely identification of the aetiology of respiratory infections and in certain cases facilitated treatment.[217]

Our group postulated certain factors in the assessment of the safety of future sporting assessments in the first wave of the pandemic (figure 46), all of which remain relevant going forwards.

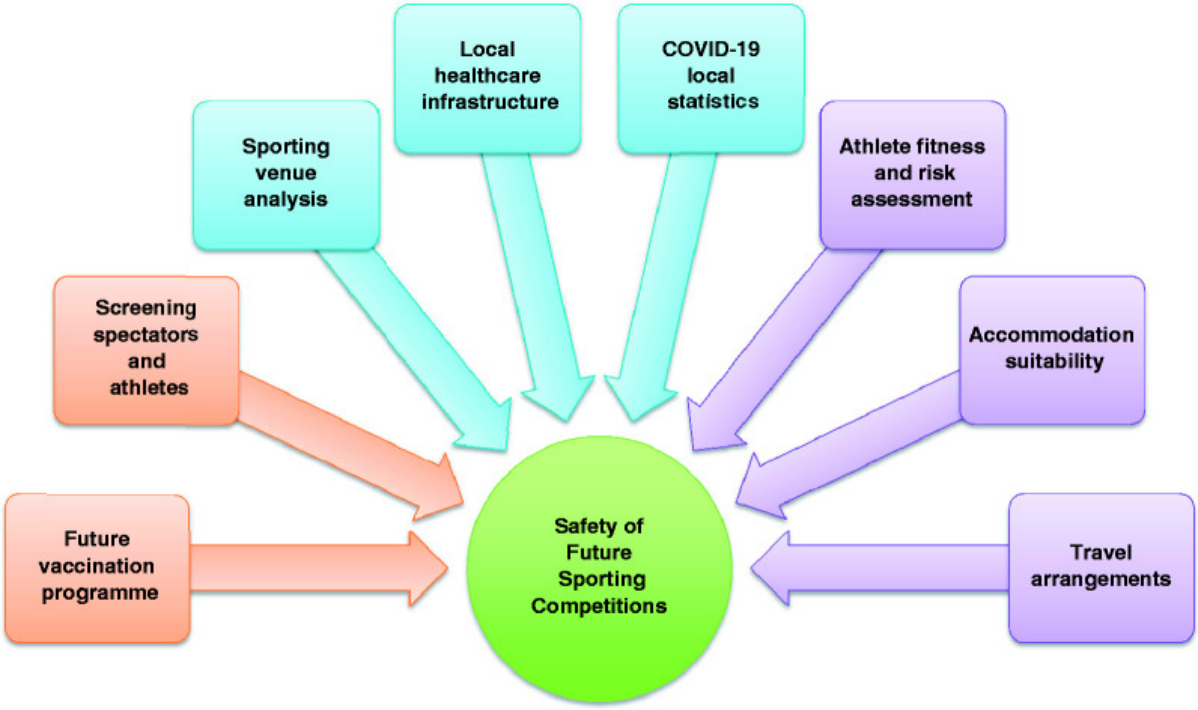

Figure 46: Factors to be considered in the assessment of the safety of future sporting competitions. Bhatia RT, Marwaha S, Malhotra A, et al. Exercise in the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) era: A Question and Answer session with the experts Endorsed by the section of Sports Cardiology & Exercise of the European Association of Preventive Cardiology (EAPC). *Eur J Prev Cardiol*. 2020;27(12):1242-1251.

10.9.1 Myocardial scar and the risk of adverse cardiac events in athletes

In our experience, whilst the exact figure is unknown, a proportion of athletes are identified with myocardial scar due to healed myocarditis either on an (a) an incidental research CMR imaging scan, (b) after investigation of CV symptoms, (c) the presence of abnormal resting ECG, (d) exercise induced arrhythmias or (e) the presence of reduced left ventricular contraction on transthoracic echocardiography.

In this context, there is a paucity of data for predicting the risk of recurrent fatal arrhythmias in young fit athletic individuals with myocardial scar due to probable or

possible healed myocarditis. Most data as discussed below, however, is derived from the general population.

A large Italian registry 670 individuals who were followed up for 5 years after a clinical diagnosis of myocarditis suggests that the risk of death in doubled from 0.9% to 1.7% per annum in individuals with scar complicating myocarditis compared with individuals without scar. This risk is also dependent on the left ventricular function and is lower in individuals who with myocardial scar who have good cardiac function (1.2%) per annum.[218]

Colleagues from Italy have reported clinical characteristics, in-hospital management, and long-term outcome of patients with acute myocarditis based on a retrospective multicenter registry from 19 Italian hospitals.[219] This included 684 non-athletic individuals with suspected acute myocarditis during a 6-year period. The mean age in the study was 34 years. 118 patients (27%) had a left ventricular ejection fraction (LVEF) <50% or evidence of sustained ventricular arrhythmias. In comparison, 325 (73%) of individuals had no such complications. After a follow-up period of 5-years, the major cardiac events following the acute phase, occurred in 2.8% of the cohort, with a higher incidence in individuals with a LVEF < 50% or in those demonstrating the presence of ventricular arrhythmias.

The prognostic significance of myocardial scar in individuals with normal left ventricular systolic function, in the absence of established coronary artery disease was recently reported as part of large single centre study in the United Kingdom.[220] The primary outcome was actual or aborted sudden cardiac death. Amongst 748 individuals enrolled in the study (401, with myocardial scar; 347 with no evidence of

myocardial scar – utilised as a control group) the median age was 50 years and LVEF was 66%. No patient experienced SCD and only 1 with evidence of myocardial scar (0.13%) had an aborted SCD in the eleventh follow-up year.

Whilst the data from the aforementioned studies signal a low SCD risk during long term follow up in individuals with myocardial scar, normal LVEF and low ventricular arrhythmia burden, these cohorts are exclusively non-athletic individuals. As emphasised earlier, caution must be advised in extrapolating this data to the athletic population, whereby, the propensity for vigorous exercise to increase the risk of SCD in vulnerable individuals with myocardial scar must remain at the forefront of a share-decision making approach, which respects athlete autonomy. In this respect our COVID-19 study on elite soccer players identified with inflammatory cardiac sequalae offers unique insights in this field.

Conclusions to the thesis

My thesis adopts an integrated approach in the field of young sudden cardiac death, combining clinical and histopathological findings. Utilising inspiration from a seminal study by Papadakis et al.,[13] for the first time, we demonstrate a downward trend in overall cardiac mortality over a two-decade period in young individuals aged under the age of 34-years. Simultaneously, my work has provided an up-to-date estimate on incidence of sudden and cardiac death in young individuals in England and Wales, offering valuable insights for healthcare policy makers, charitable organisations and families dedicated to prevention young SCD.

My work underscores that among individuals under the age of 34, ischaemic heart disease remains the primary cause of cardiac mortality, followed closely by deaths attributed to cardiomyopathies and deaths which encompass the entity SADS. Notably, SADS continues to contribute towards a significant number of deaths in young individuals and is likely underrepresented in official mortality statistics due to coding errors and a degree of ambiguity. Detailed analysis of age and gender trends in mortality identifies at-risk groups, particularly within the age ranges of 10 to 19 and 20 to 29, where mortality from cardiomyopathies and SADS peak. These observations overall complement data from SCD registries such as the CRY-CCP, which may be receiving a select number and type of referrals.

Throughout my thesis, a core theme has been an emphasis on the vital role of expert cardiac histopathologists performing the autopsy, particularly in the setting of sudden

unexpected death. This focus led to four specific areas of research. Firstly, our work has facilitated the distinguishment of two entities that have often caused significant confusion not only in the literature, but also clinically, namely hypertrophic cardiomyopathy and idiopathic left ventricular hypertrophy. In addition, to ascertaining the presence of pathognomonic findings of myocardial disarray in individuals with hypertrophic cardiomyopathy, we have demonstrated that mitral valve abnormalities are over four fold more common in individuals with hypertrophic cardiomyopathy and may be regarded as additional macroscopic markers to distinguish between these two pathologies and may of course be of relevance in terms of antemortem cardiac imaging, particularly in young individuals where incomplete penetrance of cardiomyopathies occurs. Secondly, SCD occurs less frequently in female athletes than male counterparts, with SADS being more common in females. Mortality from myocardial disease and ischaemic heart disease predominated in males. Linking in with trends from aforementioned analysis from the ONS, data from the CRY-CCP, suggests that SADS is more common in young individuals, particularly adolescents. Thirdly, by investigating circumstances of death in young individuals with hypertrophic cardiomyopathy, our findings suggest that individuals aged 10 to 15 are the most vulnerable in terms of exercise related sudden cardiac death, which again, exemplifies the importance of preventative cardiac screening in young individuals who might be harbouring quiescent cardiac conditions associated with young sudden cardiac death.

My research tenure has been closely intertwined with the COVID-19 pandemic, which raised concerns from inflammatory cardiac sequalae in young athletes. To glean insights into this entity from our histopathological registry, we demonstrated

that over a 29-year period, which intersected with the pandemic, myocarditis is a relatively rare cause of sudden cardiac death in non-hospitalized individuals and the majority of individuals die at rest. 20% of individuals reported prodromal cardiac symptoms prior to death which continues to highlight challenges in case identification antemortem and appropriate early management. Although limitations exist as discussed in our analysis, based on data from the CRY-CCP, there was no temporal rise in deaths attributed to myocarditis during the COVID-19 pandemic.

From a cardiac screening perspective in elite soccer players, our research revealed that following COVID-19 infection, the 12-lead ECG changes in 3% of athletes of which 88% of athletes were diagnosed with cardiac inflammation. Most athletes exhibited cardiac symptoms; however de-novo ECG changes contributed to a diagnosis of cardiac inflammation in 20% of athletes without cardiac symptoms. our findings supported athletes to returning back to play following comprehensive cardiac evaluation by experts in the field, with no adverse cardiac sequalae on subsequent follow up.

Future work generated by thesis

This thesis has generated several aspects for future research. Based on findings from ONS, my findings demonstrate the importance of accurate mortality coding. Now, with the advent of ICD-11 codes, which specifically have a designated code for inherited conditions such as SADS, long QT syndrome, Brugada syndrome and arrhythmogenic cardiomyopathy, future work can revisit the epidemiological analysis performed in this thesis. This is specifically important in terms of understanding the true burden of SADS, which as we have demonstrated remains an important cause of mortality with likely continued errors in mortality coding into entities such as those encompassed in class B.

I anticipate, however, that the implementation of the new codes into clinical practice nationally, will take considerable time, perhaps years. This emphasises the importance and relevance of our work at this stage, which has spanned over two decades to provide the best possible estimates of epidemiological data. Our findings also provide impetus for research upon differences in mortality based on ethnic, geographical, and physical activity levels including athletes, on a population level in the United Kingdom. Apart from geographical data, presently, this data is not systemically gathered by ONS but lends itself into data linkage-based studies using primary care records, which is next on my pursuits.

Mortality datasets such as from ONS, do not include individuals who succumbed to SCA, and this has historically remained a weakness of several epidemiological

analyses. Future research may choose to integrate outcome data from primary care records which specifically may code survivors of SCA.

Data from the CRY-CCP continues to contribute to our understanding of the causes of SCD in young individuals. However, our findings are currently limited with the absence of systematic findings from the molecular autopsy, and provides impetus for future work, whilst continuing to expand upon the growing numbers of individuals systemically entered into the dataset on a population level in the UK. An example of such prospective work which is now underway, includes, a national pilot study of SCD across seven sites across the UK, undertaken by NHS England, Genomics England, British Heart Foundation (BHF) and Cardiac Risk in the Young (CRY), where all genetic testing will be systematically undertaken within the National Health Service (NHS). Furthermore, such work will undoubtedly continue to emphasise the requirement for specialist cardiac histopathology centres, and logistical considerations for all members of the multidisciplinary team involved in the investigations and prevention of SCD.

Limitations of non-indexed autopsy measurements such a heart weights (g) are evident in several aspects of autopsy-based studies. The lack of standardization based on body size poses a significant challenge. Although antemortem studies have established correlations between heart weight and factors like ethnicity, sex, age, and body weight, the absence of adjustments for body size variations at the post-mortem may be regarded as the next frontier which needs to be addressed in future work. Furthermore, where antemortem data exists, taking a hybrid approach

with post mortem findings may provide further longitudinal insights into anatomical measurements for accurate diagnostic assessments.

In the context of COVID-19 infection in elite sport, our findings are reassuring, in that most individuals have a mild and self-limiting illness duration. All athletes were ostensibly healthy prior to infection, and even in those athletes diagnosed with inflammatory cardiac sequalae, no adverse events were reported on subsequent follow up. However, there is growing concern, regarding the burden of long-COVID sequalae in young individuals of varying physical activity and demographics. Future work may include investigating the role of physical activity in viral illness duration and severity, particularly in young, non-hospitalized individuals.

Whilst significant attention in elite sport during the pandemic rightly focussed on the risk of myocarditis, from a cardiac screening perspective, knowledge gaps persist in terms of general cardiac screening strategies in female and male sports. This includes studies with robust outcome data and follow up in other disciples in the UK such as Rugby, which do not receive the same amount of financial endowment compared to other sports such as football. Linked to this, and similar to the utilisation of baseline screening tests as a comparison, future work should incorporate the additional value of repeat screening and also, integrate the utility of different screening tools such as the value of echocardiography, which again is not performed on an annual basis or at all in certain sports in the UK, unless clinically warranted.

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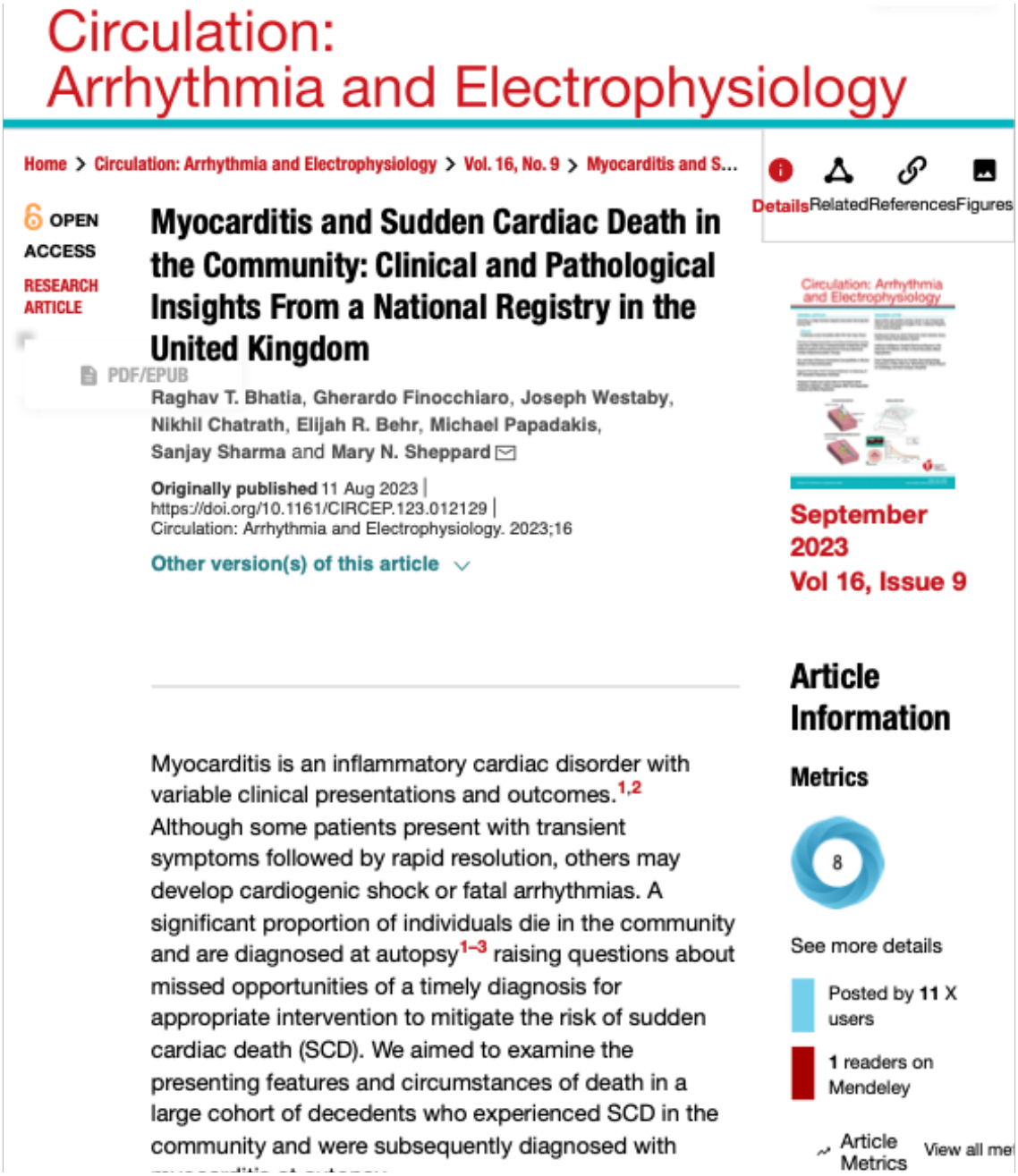
Appendix 1: Key publications



Circulation:
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OPEN ACCESS

RESEARCH ARTICLE

Myocarditis and Sudden Cardiac Death in the Community: Clinical and Pathological Insights From a National Registry in the United Kingdom

PDF/EPUB

Raghav T. Bhatia, Gherardo Finocchiaro, Joseph Westaby, Nikhil Chatrath, Elijah R. Behr, Michael Papadakis, Sanjay Sharma and Mary N. Sheppard

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Myocarditis is an inflammatory cardiac disorder with variable clinical presentations and outcomes.[1,2] Although some patients present with transient symptoms followed by rapid resolution, others may develop cardiogenic shock or fatal arrhythmias. A significant proportion of individuals die in the community and are diagnosed at autopsy[1–3] raising questions about missed opportunities of a timely diagnosis for appropriate intervention to mitigate the risk of sudden cardiac death (SCD). We aimed to examine the presenting features and circumstances of death in a large cohort of decedents who experienced SCD in the community and were subsequently diagnosed with

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Original research

Prevalence and diagnostic significance of de-novo 12-lead ECG changes after COVID-19 infection in elite soccer players

Raghav T Bhatia ,[1] Aneil Malhotra ,[1,2] Hamish MacLachlan,[1] Sabiha Gati ,[1,3] Sarandeep Marwaha,[1] Nikhil Chatrath ,[1] Saad Fyyaz ,[1] Haroldo Aleixo,[4] Samar Al-Turaihi,[1] Aswin Babu ,[1] Joyee Basu,[1] Paul Catterson,[5] Robert Cooper,[6] Joelle J N Daems ,[7] Harshil Dhutia,[1] Filipe Ferrari ,[8] Juliette C van Hattum ,[7] Zafar Iqbal,[9] Alexandros Kasiakogias,[1] Antoinette Kenny,[10] Tamim Khanbhai,[11] Shafik Khoury,[1] Chris Miles ,[1] David Oxborough ,[12] Kashif Quazi,[1] Dhrubo Rakhit,[13] Anushka Sharma,[1] Amanda Varnava,[14] Maria Teresa Tome Esteban ,[1] Gherardo Finocchiaro ,[1] Ricardo Stein,[8] Harald T Jorstad ,[7,15] Michael Papadakis ,[1] Sanjay Sharma [1]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/heartjnl-2022-322211).

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ABSTRACT

Background and aim The efficacy of pre-COVID-19 and post-COVID-19 infection 12-lead ECGs for identifying athletes with myopericarditis has never been reported. We aimed to assess the prevalence and significance of de-novo ECG changes following COVID-19 infection.

Methods In this multicentre observational study, between March 2020 and May 2022, we evaluated consecutive athletes with COVID-19 infection. Athletes exhibiting de-novo ECG changes underwent cardiovascular magnetic resonance (CMR) scans. One club mandated CMR scans for all players (n=30) following COVID-19 infection, despite the absence of cardiac symptoms or de-novo ECG changes.

Results 511 soccer players (median age 21 years, IQR 18–26 years) were included. 17 (3%) athletes demonstrated de-novo ECG changes, which included reduction in T-wave amplitude in the inferior and lateral leads (n=5), inferior leads (n=4) and lateral leads (n=4); inferior T-wave inversion (n=7); and ST-segment depression (n=2). 15 (88%) athletes with de-novo ECG changes revealed evidence of inflammatory cardiac sequelae. All 30 athletes who underwent a mandatory CMR scan had normal findings. Athletes revealing de-novo ECG changes had a higher prevalence of cardiac symptoms (71% vs 12%, p<0.0001) and longer median symptom duration (5 days, IQR 3–10) compared with athletes without de-novo ECG changes (2 days, IQR 1–3, p<0.001). Among athletes without cardiac symptoms, the additional yield of de-novo ECG changes to detect cardiac inflammation was 20%.

Conclusions 3% of athletes demonstrated de-novo ECG changes post COVID-19 infection, of which 88% were diagnosed with cardiac inflammation. Most affected athletes exhibited cardiac symptoms; however, de-novo ECG changes contributed to a diagnosis of cardiac inflammation in 20% of athletes without cardiac symptoms.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The efficacy of pre-COVID-19 and post-COVID-19 infection 12-lead ECGs for identifying athletes with myopericarditis has never been reported.

WHAT THIS STUDY ADDS

⇒ De-novo ECG patterns following COVID-19 infection (3%) characterised by anomalies in the inferior and lateral leads, including low-amplitude T waves, flat T waves or inverted T waves, identify athletes with cardiac inflammation (88%) on cardiovascular magnetic resonance (CMR) imaging.

⇒ Whereas most affected athletes express cardiac symptoms, such de-novo ECG changes identify an additional 20% athletes presenting with non-cardiac symptoms.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The presence of cardiac symptoms and/or de novo ECG changes offer a greater diagnostic yield to detect cardiac inflammation in comparison to offering a mandatory CMR, irrespective of symptomatology or ECG findings.

⇒ Despite a different approach, our data on the prevalence of inflammatory cardiac sequelae (2.9%) following COVID infection are similar to data reported in North American professional and collegiate athletes.

⇒ Our approach is a cheap and pragmatic method of identifying athletes with sub-clinical myocarditis in a setting where serial cardiac assessments including ECGs are conducted on an annual basis and may also be applicable to athletes playing at the grass-roots level.

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ESC European Society of Cardiology

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INVITED EDITORIAL

Female sex and persistent inequalities in the care of patients with hypertrophic obstructive cardiomyopathy: a call to action

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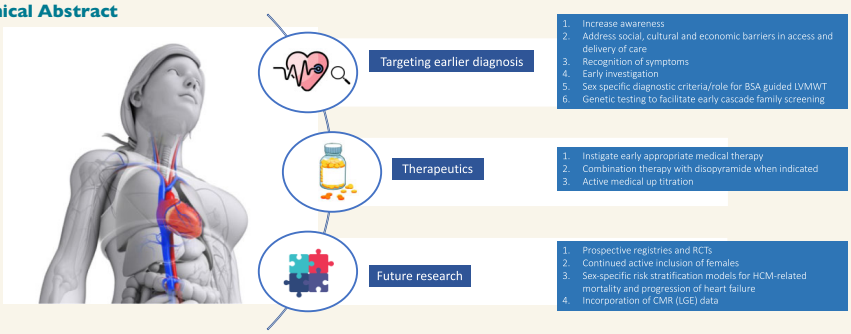
Graphical Abstract



BSA, body surface area; CMR, cardiac MRI; HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement; LVMWT, left ventricular maximal wall thickness; RCTs, randomized control trials.

This editorial refers to 'Factors Associated with Excess Female Mortality in Obstructive Hypertrophic Cardiomyopathy', by D. Javidgonbadi *et al.*, https://doi.org/10.1093/eurjpc/zwac078.

According to the ancient Indian scripture, the Bhagavad Gita

'Everyone is equal to the wise one'

Inequalities in healthcare have existed for decades and have been exemplified by the COVID-19 pandemic. Specific characteristics such as sex, ethnicity, age and disability, social, cultural and economic factors, and geography have all been implicated. Cardiovascular disease (CVD) has historically been viewed as a '*man's disease*'. Although campaigns have helped to increase awareness, CVD in females remains understudied, under-recognized, underdiagnosed, and undertreated.[1] While biological differences between females and males likely contribute to differences in outcomes, disparities in preventive strategies, diagnosis, and appropriate treatment also play a role. Scientific societies and the World Health Organization, recognize the complex interplay between sex and gender as important factors, in addition to the biological science, which when addressed holistically, may reduce the burden of CVD.[1–3]

Similar to other CVDs, sex related differences have been reported in hypertrophic cardiomyopathy (HCM). Olivotto *et al.*[4] studied 969 consecutive HCM patients in Italy and North America, with a follow-

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JACC JOURNALS

JACC: Clinical Electrophysiology

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ISSN 2405-500X/$36.00

Letters

RESEARCH LETTER

Sudden Cardiac Death During Exercise in Young Individuals With Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is an inherited cardiac condition that is defined by the presence of left ventricular hypertrophy in the absence of abnormal loading conditions and is characterized by myocyte disarray at histology.[1] Sudden cardiac death (SCD) is the most feared complication, particularly among young individuals and athletes. The aim of this study was to report on the circumstances of SCD in young individuals whose autopsy was consistent with HCM.

We reviewed a database of 6,860 consecutive cases of SCD referred to the Cardiac Risk in the Young (CRY) center for cardiac pathology which is based at St. George's University of London, between 1994 and 2020. SCD was defined as death from a cardiovascular cause within 12 hours of apparent well-being. Clinical information was obtained from referring coroners who were asked to complete a detailed health questionnaire that was filled at the time of the post-mortem examination. All cases underwent detailed autopsy evaluation of the heart, including histological analysis, by expert cardiac pathologists (M.N.S., J.W.). A minimum of 10 blocks of tissue were taken for histological analysis, and HCM was defined as reported previously.[2] The current study focused on young individuals (≥10 and ≤30 years of age). Death during exercise was defined as occurring while the individual was engaging in exercise, as opposed to death during daily activities or rest. Four age brackets were chosen a priori, with the scope to analyze differences in terms of circumstances of death. Ethical and research governance approval have been granted for this study (10/H0724/38). Results are expressed as mean ± SD for continuous variables or as number of cases and percentage for categorical variables. Comparison of groups was performed using Student's *t* test for continuous variables with correction for unequal variance when necessary and chi-square test for categorical variables.

Of the total cases of SCD, 264 (4%) were due to HCM; our cohort of young decedents comprised 66 individuals (average age 21 ± 5 years, 76% males, 91% white Caucasian). Bystander cardiopulmonary resuscitation was performed in 70% of cases, and 23% of cases received automatic external defibrillation. For the majority (n = 52 [79%]), the diagnosis was made only following the autopsy examination. The main features are described in **Figure 1A**. The bracket in which SCD was more common was between 16 and 20 years of age (n = 24) (**Figure 1B**). Death occurred during exercise in 26 (39%) individuals (most commonly during football and running activities) (**Figure 1C**) and at rest or during daily activities in the remaining 40 (62%), including 5 individuals who died during sleep. LV fibrosis was slightly more common in individuals who died during exercise. While younger (age bracket 10-15 years) died mostly during exercise (80%), in other age brackets death occurred mainly at rest (33% in the age bracket 16-20 years, 30% in the age bracket 21-25 years, 33% in the age bracket 26-30 years) (**Figure 1B**).

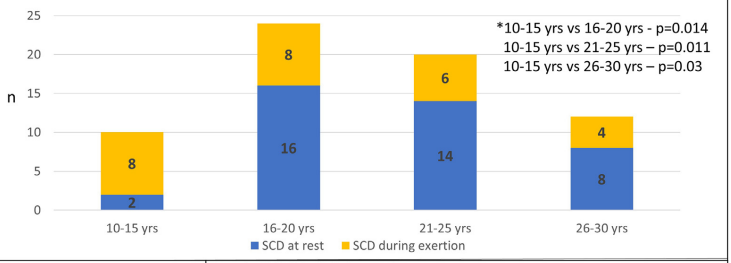
Although HCM is historically reported as the predominant cause of SCD in young athletes,[3] it is unclear to what degree exercise is a trigger for possible fatal arrhythmias in these patients. When a diagnosis of HCM is made, current international guidelines recommend against competitive sport in most cases.[4] In our cohort of SCD victims with HCM, death occurred during exercise in 39% of the cases. Interestingly, we observed that younger individuals (10-15 years of age) died suddenly mostly during exercise (in 80% of the cases), as opposite to slightly older (>16 years of age) individuals in whom death occurred more at rest (in 70% of the cases). Some may speculate that this difference is explained by younger kids being more physically active than their adult counterparts. However, a sedentary lifestyle appears increasingly common among adolescents.[5] The current study is not meant to assess causality, but we speculate that since phenotypic conversion often occurs during prepuberal and puberal age, myofibers may be particularly susceptible to exercise-induced arrhythmias at this very stage. The appropriate age

FIGURE 1 Circumstances of SCD in Young Individuals With HCM

A

	Total (n=66)	SCD at rest (n=40)	SCD during exercise (n=26)	p
Age (years)	21±5	21±5	21±5	0.913
Males n(%)	50 (76)	28 (70)	22 (85)	0.167
Heart weight (grams)	507±152	499±165	519±131	0.620
LV fibrosis n(%)	36 (54)	20 (50)	16 (61)	0.384
Maximal wall thickness (mm)	21±7	22±7	21±6	0.822

B



C

Age	Type of activity if death during exercise
10-15 (death during exercise n=8)	4 running, 3 football , 1 rugby
16-20 (death during exercise n=8)	3 football, 2 running , 1 sexual intercourse, 1 golf, 1 general exercise
21-25 (death during exercise n=6)	3 running, 1 football, 1 rugby, 1 general exercise
26-30 (death during exercise n=4)	1 football, 1 running, 2 general exercise

(A) Differences between individuals in whom SCD occurred at rest and during exercise. **(B)** Age brackets and circumstances of SCD. **(C)** Type of exercise activity that triggered SCD. *Differences in proportion of SCD during exercise among age bracket (specifically we compared the age bracket 10–15 years with the other age brackets). HCM = hypertrophic cardiomyopathy; LV = left ventricular; SCD = sudden cardiac death.

to start cardiac screening in various contexts (pre-participation screening in athletes, family screening) is not well defined. Our findings suggest that individuals 10 to 15 years of age are the most vulnerable in terms of exercise-related SCD, at least in the context of HCM.

Our study has some limitations, including the small sample size (especially in the younger group), the retrospective assessment of clinical data, and the absence of genetic testing (molecular autopsy).

In conclusion, SCD occurs during exercise in approximately 40% of young patients with HCM. While younger individuals (10 to 15 years of age) die mostly during exercise, death occurs more frequently at rest after 16 years of age. An early diagnosis of HCM even in asymptomatic patients appears relevant especially in individuals <15 years of age, as exercise prescription tailored to the individual condition and risk profile may have the potential to prevent exercise-induced SCD.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

REFERENCES

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HeartRhythm Heart Rhythm Society

RESEARCH LETTER

Mitral valve abnormalities in decedents of sudden cardiac death due to hypertrophic cardiomyopathy and idiopathic left ventricular hypertrophy

Check for updates

Raghav T. Bhatia, MBBS, MRCP,* Shafik Khoury, MD,* Joseph Westaby, MBBS,* Elijah R. Behr, MA, MBBS, MD, FRCP,* Michael Papadakis, MBBS, MRCP, MD,* Sanjay Sharma, BSc, MBChB, MD, FRCP,* Gherardo Finocchiaro, MD, PhD,*†‡§[1] Mary N. Sheppard, MBBCH, BAO, BSc, MD, FRCPath*‖[1]

*From the *Cardiovascular Clinical Academic Group, St. George's, University of London, St. George's University Hospitals NHS Foundation Trust, London, United Kingdom, †Cardiothoracic Centre, Guy's and St Thomas' Hospital, London, United Kingdom, ‡King's College London, London, United Kingdom, §Cardiovascular Research Centre, Royal Brompton and Harefield NHS Foundation Trust, London, United Kingdom, and ‖Cardiovascular Pathology Department, St George's, University of London, London, United Kingdom.*

Hypertrophic cardiomyopathy (HCM) is defined as left ventricular (LV) hypertrophy (LVH) in the absence of abnormal loading conditions and characterized by myocyte disarray at histology.[1] After sudden cardiac death (SCD), the sole identification of significant LVH at autopsy may lead to an erroneous diagnosis of HCM. Data suggest that idiopathic LVH (ILVH) and HCM may be separate entities.[2] We aimed to report the prevalence and nature of mitral valve (MV) abnormalities in SCD victims with postmortem findings consistent with HCM and ILVH. We hypothesized that MV abnormalities are more common in individuals with HCM and considered as additional macroscopic features to differentiate between these 2 entities.

We reviewed 6860 consecutive cases of SCD referred to our specialist cardiac pathology center between 1994 and 2020. *SCD* was defined as death due to a cardiovascular cause within 12 hours of apparent well-being. All cases underwent detailed autopsy, and a minimum of 10 tissue blocks underwent histological analysis.[3] *ILVH* was defined as unexplained LVH (heart weight >500 g in males and >400 g in females) and LV wall thickness > 15 mm in the absence of myocardial disarray or secondary causes of LVH.[2] The MV was examined for patency, circumference, thickening, nodularity, ballooning, bulging between cords, perforation, endocarditis, and the presence of impact lesions in the LV outflow tract and aortic outlet.

Ethical approval was granted for this study (10/H0724/38).

Of the total cases of SCD, 264 (4%) were due to HCM (mean age 41 ± 18 years; 78% males; LV maximal wall thickness 19 ± 6 mm) (Figure 1). Antemortem symptoms were reported in 44 cases (17%), and for the majority (n = 217 [82%]), the diagnosis of HCM was established at postmortem. Death was attributed to ILVH in 253 cases (3%; mean age 43 ± 16 years; 80% males; LV maximal wall thickness 18 ± 4 mm). MV abnormalities were found in 58 decedents with HCM (22%; mean age 38 ± 17 years; 72% males) and 13 decedents with ILVH (5%; mean age 55 ± 5 years; 77% males; $P < .001$). Myocardial fibrosis was observed in 162 cases of HCM (61%) and 99 cases of ILVH (39%) ($P < .001$).

Of the 58 cases with HCM and MV abnormalities (22%), 15 (6%) had multiple MV abnormalities. These included impact lesions associated with thickening of the anterior MV leaflet (n = 39) and degenerative changes (n = 34) such as bulging and ballooning as well as thickening and nodularity. Decedents with HCM exhibiting MV abnormalities were younger than decedents with a normal MV (38 ± 17 years vs 45 ± 19 years; $P = .08$).

Of the 253 decedents with ILVH, 13 (5%) exhibited MV abnormalities, which largely included degenerative changes (n = 12). Among decedents with HCM and ILVH exhibiting MV abnormalities, the former was significantly younger (38 ± 17 years vs 55 ± 15 years; $P = .001$).

MV abnormalities were identified in 22% and 5% of decedents of SCD attributed to HCM and ILVH, respectively. Imaging studies, predominantly on cohorts with dynamic LV outflow tract obstruction, have reported mitral MV malformations in up to 70% of patients with HCM.[4,5] The lower

KEYWORDS Hypertrophic cardiomyopathy; Idiopathic left ventricular hypertrophy; Left ventricular hypertrophy; Mitral valve; Sudden cardiac death

(Heart Rhythm 2022;19:1684–1685)

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ESC European Society of Cardiology
European Heart Journal (2021) **42**, 215–227
doi:10.1093/eurheartj/ehaa742
CARDIOPULSE

The Impact of COVID-19 on the Continuity of Cardiovascular Care

The authors discuss the challenges and offer potential solutions to facilitate safe and effective clinical care during and after this unique pandemic

Perspective

Healthcare services globally are combating the impact of SARS-CoV-2 and associated COVID-19 infection, which has caused significant morbidity and mortality across all affected countries.[1] Whilst the medical community and resources have focused on this pandemic, it is important to consider that cardiovascular disease remains the most common cause of death globally and accounts for in excess of 17.8 million deaths annually.[2] Of concern, there was an alarming reduction in healthcare seeking behaviours during the enforced lockdown period to contain viral spread.[3–5] Admissions to hospital with an acute coronary syndrome significantly dropped and individuals who eventually sought medical help experienced a higher fatality rate.[3–6] These observations are difficult to accept when prognostically important therapies such as primary percutaneous coronary intervention were widely used prior to the pandemic. Moreover, as lockdown measures are tentatively eased we enter a precarious period when delivery of cardiovascular care will face several challenges and will need to constantly adapt to the pandemic's evolution. In this article, we aim to provide an overview of these challenges and suggest potential solutions based on current models of care.

Healthcare service delivery

It has been well established that there is a higher incidence of COVID-19 related complications, including death, amongst individuals with cardiovascular disease.[7–9] Fear of this increased risk has resulted in a reluctance in patients seeking healthcare which has been associated with an increase in morbidity and mortality independent of COVID-19 status, therefore, strategies to engage with patients, which facilitate their trust in the medical infrastructure to serve them effectively and efficiently whilst minimizing the risk of developing COVID-19 infection are of paramount importance going forwards (*Figure 1*).

The pandemic compromised delivery of acute care across the breadth of cardiology and has resulted in a backlog of elective work,

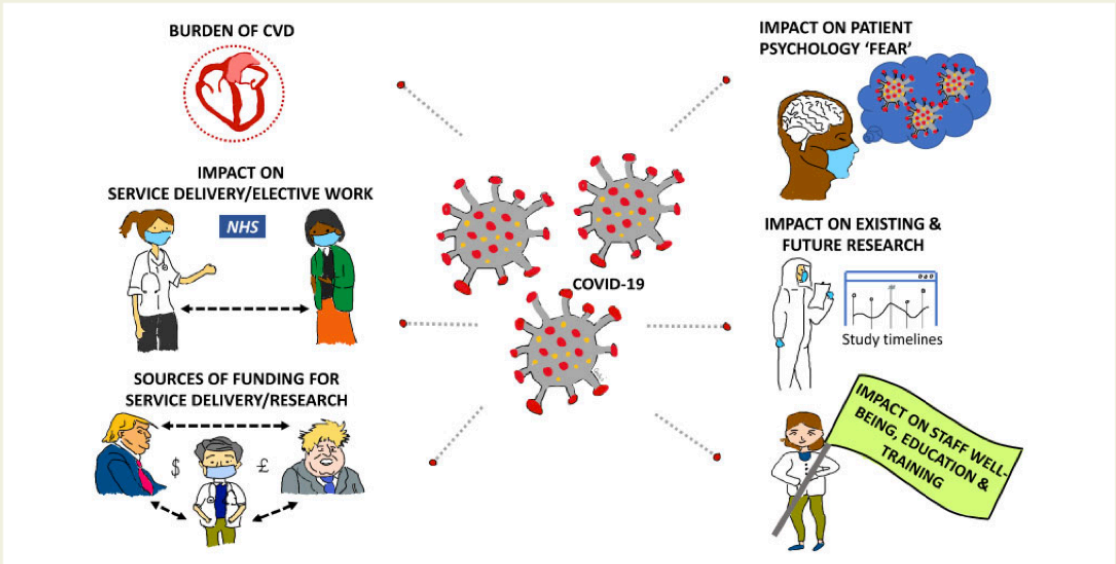

Figure 1 The challenges ahead in the COVID-19 era.

Circulation
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RESEARCH LETTER

Sudden Death in Female Athletes: Insights From a Large Regional Registry in the United Kingdom

Gherardo Finocchiaro, MD, PhD, Joe Westaby, MBBS, Raghav Bhatia, MBBS, Aneil Malhotra, MSc, MRCP, PhD, Elijah R. Behr, MA, MBBS, MD, Michael Papadakis, MBBS, MRCP, MD, Sanjay Sharma, BSc, MBChB, MD, and Mary N. Sheppard, MBBCH, BAO, BSc, MD

Nonstandard Abbreviations and Acronyms

SADS	sudden arrhythmic death syndrome
SCD	sudden cardiac death

Sudden cardiac death (SCD) in sport often affects apparently healthy individuals.[1] There is consistency among studies that women are less prone to exercise-related SCD than men,[2,3] but knowledge pertaining to the specific cause and precipitating circumstance is sparse. The increase in the number of women who participate in various sports, including disciplines historically dominated by men, calls for a more focused perspective surrounding exercise-related SCDs in female athletes. We investigated the causes and circumstances of SCD in a large cohort of female athletes in whom cardiac autopsy was conducted by an expert cardiac pathologist.

European Journal of
Preventive Cardiology

EAPC
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Clinical practice

European Journal of
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ESC
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Exercise in the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) era: A Question and Answer session with the experts Endorsed by the section of Sports Cardiology & Exercise of the European Association of Preventive Cardiology (EAPC)

Raghav T Bhatia[1], Sarandeep Marwaha[1], Aneil Malhotra[2], Zafar Iqbal[3], Christopher Hughes[4], Mats Börjesson[5], Josef Niebauer[6], Antonio Pelliccia[7], Christian Schmied[8], Luis Serratosa[9], Michael Papadakis[1]* and Sanjay Sharma[1]*

Abstract

Regular exercise has multiple benefits for physical and mental health, including the body's ability to combat infections. The current COVID-19 pandemic and the social distancing measures employed to curtail the impact of the infection are likely to reduce the amount of usual physical activity being performed by most individuals, including habitual exercisers. The uncertainties relating to the impact of the SARS-CoV-2 virus on the heart may cause increased anxiety, particularly in athletes who need to sustain a vigorous exercise regime in order to maintain their skills and fitness in preparation for return to competition after a short re-training period. The aim of this document is to provide practical answers to pertinent questions being posed by the sporting community, in an attempt to offer reassurance, promote safe participation in exercise during as well as after the COVID-19 pandemic and provide a framework of management for physicians caring for athletes.

Keywords

COVID-19, athlete, exercise, sports cardiology, screening

Received 24 April 2020; accepted 10 May 2020

The current SARS-CoV-2 virus is responsible for COVID-19 infection, which has resulted in a pandemic. Cardiac involvement is a recognised complication of the infection and has potential implications for athletes, who push their cardiovascular system to the limits on a regular basis to maintain skill and fitness for competition, but also for physicians and coaches worldwide involved in their care. This document aims to provide practical answers to pertinent questions being posed by the sporting community. The article is divided into three parts: Part 1 provides a brief overview of the COVID-19 infection; Part 2 is a 'question and answer' section aimed specifically at exercising

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[5]Department of Molecular and Clinical Medicine Institute of Medicine, Centre for Health and Performance, Gothenburg University and Sahlgrenska University Hospital/Ostra, Gothenburg, Sweden
[6]Institute of Sports Medicine, Prevention and Rehabilitation, Paracelsus Medical University Salzburg, Austria
[7]Institute of Sports Medicine and Science, Rome, Italy
[8]University Heart Centre, Zurich, Switzerland
[9]Hospital Universitario Quironsalud Madrid, Spain

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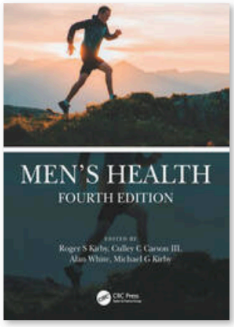

Chapter

Cardiovascular Screening For Athletes

By Raghav T. Bhatia, Sarandeep Marwaha, Sanjay Sharma

Book Men's Health 4e

Edition	1st Edition
First Published	2021
Imprint	CRC Press
Pages	8
eBook ISBN	9780429347238

ABSTRACT

The cardiovascular benefits of regular physical activity and systematic exercise are well-established. Exercise results in a favourable atherosclerotic risk profile and increased cardiorespiratory fitness; both factors are associated with a significantly lower prevalence of adverse cardiovascular events in middle and older age, and increased longevity of life. Genetic diseases include the primary cardiomyopathies such as hypertrophic cardiomyopathy (HCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC); channelopathies such as long-QT syndrome (LQTS), catecholamine polymorphic ventricular tachycardia (CPVT) and Brugada syndrome; aortopathies such as Marfan syndrome and premature atherosclerotic coronary artery disease (CAD) due to familial hypercholesterolaemia. The clinical history pertains to identifying cardiovascular symptoms such as exertional chest discomfort, dyspnoea, palpitations and syncope. The societal impact of a sudden death in an athlete may be considered as an important public health issue. Most deaths in exercising individuals affect middle aged and older athletes.

"Clinical Cardiovascular Genomic Medicine- Principles and Practice"

Edited by-

Professor Dhavendra Kumar, Professor Arthur AM Wilde and Professor Perry Elliott

Chapter: 28. Preventive cardiology

Diagnostic and preventive aspects of cardiovascular medicine with reference to risks associated with inherited cardiovascular conditions.

Raghav T. Bhatia and Michael Papadakis

Abstract

The inherited cardiac conditions (ICC's) represent a diverse spectrum of conditions affecting the heart, its conduction system, and vasculature. The varied clinical presentations include asymptomatic individuals identified with an abnormality at a routine medical check-up, during community or sports-related cardiac screening, evaluation following a relevant family history, evaluation of individuals presenting with cardiac symptoms and occasionally the first presentation is with a sudden cardiac arrest (SCA) or sudden cardiac death (SCD). In recent years, increased awareness, enhanced diagnostic tests, advancement of genetics and growing expertise in the field, have significantly improved our understanding of the epidemiology, aetiology and management of ICC's, including strategies to prevent SCD. This chapter will focus on addressing primary and secondary prevention strategies, focusing on SCD prevention in a variety of settings where ICC's might be identified.

BMJ Journals
Heart

Cardiology in focus

British Cardiovascular Society Young Investigator Award 2022

doi:10.1136/heartjnl-2023-322582

Chris Orsborne,[1] Raghav T Bhatia,[2] Ziwen C Li,[3] Hamish MacLachlan,[2] Marco Spartera,[4,5] Victoria M Stoll [6]

At the annual British Cardiovascular Society meeting marking the 100th centenary of the oldest Cardiac Society in the world five finalists were selected for the Young Investigator Award. The prize was established to 'recognise excellence among young researchers intending to pursue a career in cardiovascular clinical medicine or research'. Finalists were selected following submissions of brief communications of original research from a large number of competitive applicants. Each finalist gave a 10 min oral presentation, followed by 5 min of questioning by the judges.

WINNER: DR CHRIS ORSBORNE

Dr Chris Orsborne is a clinical research fellow at the British Heart Foundation Manchester Centre for Heart and Lung Magnetic Resonance Research and a PhD student at the University of Manchester. His multidisciplinary supervisory team is led by Professor Chris Miller.

Dr Orsborne's research focuses on inherited metabolic cardiomyopathy, specifically Fabry disease. Cardiac manifestations of Fabry disease are common and the leading cause of death, yet they are poorly understood and in the absence of robust prognostic models, it is difficult to identify and treat at-risk individuals. Dr Orsborne uses contemporary and novel imaging biomarkers to understand the pathophysiology, prognostication and treatments of Fabry disease. His primary goal is to develop a tool that identifies at-risk patients with Fabry disease, so that timely interventions can be made (figure 1).

Figure 1 Dr Chris Orsborne.

Dr Orsborne's research developed and internally validated a risk prediction model that accurately predicts the 5-year risk of adverse cardiac outcomes for individual patients, of either gender, with Fabry disease. The model performed excellently and could be easily integrated into clinical care. External validation in a large multinational cohort is warranted and is the subject of further collaborative work.

Figure 2 Dr Raghav Bhatia.

RUNNER UP: DR RAGHAV BHATIA

Dr Raghav Bhatia graduated from Norwich Medical School in 2011 and became a member of the Royal College of Physicians in 2014. As a Cardiology Registrar in North and East Yorkshire, he attained competencies in interventional cardiology, inherited cardiac conditions, cardiac imaging and sports cardiology. In 2020, he secured a competitive research grant with Cardiac Risk in the Young (CRY) to undertake his PhD at St. George's, University of London, under the guidance of Professor Michael Papadakis and Professor Sanjay Sharma. He was a runner-up in the ESC young investigator awards for his research into sudden cardiac death during exercise in young individuals with hypertrophic cardiomyopathy and also won other abstract prizes at the BCS 2022 conference. He is a lecturer and module lead on the MSc in Sports Cardiology, at St. George's (figure 2).

Dr Bhatia's research focuses on the prevention of young sudden cardiac death and includes insights from the office of national statistics, an extensive national cardiac pathology registry and outcomes from the CRY screening programme, as well as incorporating the challenges posed by the COVID-19 pandemic. His presented research was a multicentre study assessing the prevalence and diagnostic significance of de-novo ECG patterns following COVID-19 infection in elite soccer players.

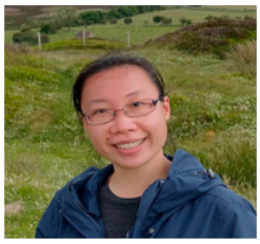

Figure 3 Dr Ziwen Cass Li.

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[5]Great Western Hospital NHS Foundation Trust, Swindon, UK
[6]Adult Congenital Heart Disease, Royal Papworth Hospital Foundation Trust, Cambridge, UK

Correspondence to Dr Victoria M Stoll, ACHD, Cardiology, Royal Papworth NHS Foundation Trust, Cambridge, UK; v.m.stoll@bham.ac.uk

Appendix 2: Short Curriculum Vitae

Dr Raghav T. Bhatia

[redacted]

EDUCATION

1990-1999	Early to mid-years	Vasant Valley School, New Delhi.
1999-2004	Secondary school	Hull Grammar School, Kingston-Upon-Hull
2011	MBBS(Hons)	Norwich Medical School; Open scholarship for duration of studies and attainment of distinction in basic science research.
2014	MRCP(UK)	Royal College of Physicians, London
2016	Cardiology NTN	National training number in Cardiology, Health Education England, North and East Yorkshire

2017	BSE	British society of echocardiography exam
2018	EEGC/ KBA	Completion of European Cardiology Accreditation
2020	PhD(c)	St. George's, University of London
2022	EACVI-ESC	Level 3 European CMR Accreditation - in progress
2023	Fellowship	Clinical and research 3½ year fellowship in ICC, Sports Cardiology and CMR at St. George's, University of London and Cardiac Risk in the Young (CRY)

PRESENT APPOINTMENT

May 2023 Final year, Cardiology registrar,
Hull University Teaching Hospitals NHS Trust
Inherited Cardiac Conditions, Cardiac MRI and Sports Cardiology

Feb 2020 Clinical lecturer
St. George's, University of London
Inherited Cardiac Conditions, Cardiac MRI and Sports Cardiology

PRIZES/ AWARDS

June 2023 Best of the Best Abstract British Cardiovascular Society

April 2023 Young Investigator Award Finalist- European Association of Preventative Cardiology

August 2022 Young Investigator Award Finalist- European Society of Cardiology

June 2022 Young Investigator Award Finalist- British Cardiovascular Society

June 2022 Best of the Best Abstract and Presentation Winner- British Cardiovascular Society

June 2022 Best of the Best Abstract and Presentation Runners up- British. Cardiovascular Society

July 2020 Voted Best United Kingdom British Junior Cardiology Association Representative- British Cardiovascular Society

July 2019 Voted Best United Kingdom British Junior Cardiology Association Representative- British Cardiovascular Society

August 2014 Teaching award for junior doctors- Norfolk and Norwich University Hospitals

June 2010 Awarded prestigious Internship- University of Michigan Hospitals, Ann Arbor, USA

POSITIONS OF LEADERSHIP AND RESPONSIBILITY

2023-to date Cardiologist to Cardiac Risk in the Young and leading myheart.org focus groups for patients and athletes with inherited cardiac conditions

2022- to date British Cardiovascular Intervention Society Training Culture Focus Group Member

2021- to date Football Association (FA) assisting in cardiac pre-participation assessments

2020-2022 Clinical rota manager for cardiac research fellows, St. George's University

2020-to date	Module lead/co-lead, MSc Sports Cardiology, St George's, University of London
2020-2022	Lead coordinator for cardiac research fellows, national screening programme, Cardiac Risk in the Young
2018- to date	British Junior Cardiology Association (BJCA) Council, North and East Yorkshire
2018- to date	Focused Echocardiography in Emergency Life Support (FEEL) course faculty
2014-2015	Core Medical Training North and East Yorkshire Deanery Representative
2005	Raleigh International: successful completion of youth expedition trip to Costa Rica and Nicaragua. Working in remote, rural areas to improve access to safe water and sanitation, build community resilience, sustainably manage natural resources, and to protect vulnerable environments.
2000-2004	Captain of Hull Grammar School Men's Cricket First Team IX
2003-2004	Prefect Hull Grammar School, Kingston upon Hull

TEACHING AND TALKS

2020-to date	Regular lectures delivered for St George's, University of London
2020-to date	Admissions Tutor and Module Lead for Sports Cardiology MSc, St. George's University.
2014-to date	Teacher for the Royal College of Physicians PACES examination
2014- to date	Undergraduate Teacher for MBBS at Hull York Medical School

2011-2013 Undergraduate Teacher for MBBS at Norwich Medical School, Norwich, East Anglia

In addition, ongoing mentorship for allied health professionals, supervising specialist nurses on prescriber course, teaching specialist nurses how to perform clinical examinations for postgraduate studies and facilitating/ teaching for academic visitors to the cardiovascular academic group at St. George's, University of London

Regular invited talks at annual BCS, ESC, EAPC, CRY conferences.

RESEARCH AND PUBLICATIONS

Growing international reputation in research relating to athlete's heart, cardiomyopathies, ion channel diseases and pre- participation screening in athlete's heart, with over 31 publications (including 16 PubMed indexed articles and 190 citations) and 2 book chapters. Invited speaker at national and international scientific meetings including British Cardiovascular Society, European Society of Cardiology, and European Society of Preventative Cardiology and the annual

RESEARCH CAREER

I am an outgoing CRY clinical and research fellow/lecturer in inherited cardiac conditions, cardiac MRI and sports cardiology. I enjoy the intellectual rigor of academic medicine and combining this with the practical challenges of cardiology provides the optimum environment in which I thrive. A lifelong career in academic cardiology with a robust clinical emphasis is my aspiration and I believe that through hard work and determination, I will achieve this.

INTERESTS AND ACTIVITIES

I enjoy a variety of sports including, tennis and cricket (all to University level) and in particular running. In 2022, I ran the Vitality London 10k as part of a group of likeminded colleagues and friends at St. George's, University of London. We raised in excess of £10,000 for the charity Cardiac Risk in the Young. I am multilingual and fluently speak Hindi, Punjabi and Urdu which have facilitated clinical and academic progression and forging links globally.

MEDIA WORK

The nature of my work in inherited cardiac conditions and sports cardiology attracts significant media attention. My clinical and academic work has regularly been featured on, local media outlets including newspapers and national/ international radio stations. In addition, I have given live interviews on Sunrise Radio for the charity Cardiac Risk in the Young. Audio and video files of my interviews are available online including social media outlets and YouTube. Recent media work that I have been part of has been featured in the UK Parliament Commons Chamber:

Sudden Cardiac Death: Young People Volume 727: debated on Wednesday 1 February 2023 and a live BBC interview televised on BBC Look North.

SELECTED LIST OF PEER-REVIEWED PUBLICATIONS

- **Bhatia RT,** Malhotra A, MacLachlan H, et al. Prevalence and Diagnostic Significance of De-novo 12-lead ECG Changes After COVID-19 Infection in Elite Soccer Players. March 2023 BMJ Heart. DOI: 10.1136/heartjnl-2022-322211

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- **Bhatia RT**, Gati S, Papadakis M, Sharma S. The Impact of COVID-19 on the Continuity of Cardiovascular Care. Eur Heart J. 2021;42(3):215-217.

- **Bhatia RT**, Papadakis M. Female Sex and Persistent Inequalities in the Care of Patients with Hypertrophic Obstructive Cardiomyopathy: A Call to Action [published online ahead of print, 2022 Jun 16]. Eur J Prev Cardiol. 2022;zwac120. doi:10.1093/eurjpc/zwac120.

- Marwaha S, **Bhatia R**, Papadakis M, Marciniak A. Mending the broken valentine heart: a case report. Eur Heart J Case Rep. 2022;6(8):ytac325. Published 2022 Aug 5. doi:10.1093/ehjcr/ytac325.

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- **Bhatia RT**, Khoury S, Westaby J, et al. Mitral valve abnormalities in decedents of sudden cardiac death due to hypertrophic cardiomyopathy and idiopathic left ventricular hypertrophy. Heart Rhythm. 2022;19(10):1684-1685. doi:10.1016/j.hrthm.2022.04.026.

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- Dhutia, H., Malhotra, A., Finocchiaro, G., Parpia, S., **Bhatia, R**., D'Silva, A., Gati, S., Mellor, G., Chandra, N., Narain, R., Behr, E., Tome, M., Papadakis, M., & Sharma, S. (2022). Electrocardiogram screening programme in detecting sudden cardiac disease in the young: cost efficiency and diagnostic yield-Authors' reply. Europace doi.org/10.1093/europace/euab235.

- **Bhatia RT**, Browne OT, Naudeer S, Allgar V, Bhandari S. Examining determinants of patient outcome in a low clearance clinic. Nephron. 2015;129(4):263-268. doi:10.1159/000381477.

- George A, **Bhatia RT**, Buchanan GL, et al. Impaired Glucose Tolerance or Newly Diagnosed Diabetes Mellitus Diagnosed during Admission Adversely Affects Prognosis after Myocardial Infarction: An Observational Study. doi:10.1371/journal.pone.0142045.

- MacLachlan H, Dhutia H, **Bhatia R**, et al. Results of a nationally implemented cardiac screening programme in elite cricket players in England and Wales. J Sci Med Sport. 2022;25(4):287-292. doi:10.1016/j.jsams.2021.12.00.

- Chatrath N, **Bhatia R**, Fyyaz S, et al. An Athlete With Bicuspid Aortic Valve Regurgitation and Left Ventricular Dilatation. J Am Coll Cardiol Case Rep. null2022, 0 (0) .doi.org/10.1016/j.jaccas.2022.05.021.

- Finocchiaro G**, **Bhatia R**,** Westaby J, et al. Sudden Cardiac Death During Exercise in Young Individuals With Hypertrophic Cardiomyopathy. J Am Coll Cardiol EP. null2023, 0 (0) doi.org/10.1016/j.jacep.2022.12.007 (**joint 1st authors).

- Finocchiaro G, Westaby J, **Bhatia R**, et al. Sudden Death in Female Athletes: Insights From a Large Regional Registry in the United Kingdom. Circulation. 2021;144(22):1827-1829. doi:10.1161/CIRCULATIONAHA.121.055535

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- **Bhatia RT et al**. "Coronary artery anomalies and the role of echocardiography in pre-participation screening of athletes: a practical guide." Echo research and practice vol. 11,1 5. 22 Feb. 2024.

- MacLachlan H, Antonakaki A, **Bhatia RT**, et al. Prevalence and Clinical Significance of Electrocardiographic Complete Right Bundle Branch Block in Young Individuals. Eur J Prev Cardiol. Published online February 27, 2024.

- Book chapter. **Bhatia RT**, Sharma S. Cardiovascular screening for Athletes. Men's Health 4th edition. Published 2021.

- Book chapter. **Bhatia RT**, Papadakis M. Preventative cardiovascular genomic medicine. Clinical Cardiovascular Genomic Medicine – Principles and Practice 3rd Edition. In Press.

- British association of sports and exercise medicine (BASEM)– Sports Cardiology Edition Handbook. **Bhatia RT**. 3 articles contributed. Published January 2021.

In addition, an array of conference papers and abstracts published in supplementary section of high-impact journals, including, European Heart Journal, European Journal of Preventive Cardiology. See ResearchGate profile for further details.

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