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# L'apparition de maladies cardiovasculaires et le dépistage cardiaque par électrocardiogramme chez les sportifs de haut niveau

Lingxia Li

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COLLEGE EDUCATION, LANGAGES

DOCTORAL INTERACTIONS, COGNITION

BRETAGNE CLINIQUE, EXPERTISE



# THESE DE DOCTORAT DE

L'UNIVERSITE RENNES 2

ECOLE DOCTORALE N° 646

*Education, Langages, Interactions, Cognition, Clinique, Expertise*

Spécialité : *Sciences techniques des activités physiques et sportives*

Par **Lingxia LI**

## **The Occurrence of Cardiovascular Disease and Electrocardiogram -based Cardiac Screening in Competitive Athletes**

Thèse présentée et soutenue à Rennes, le 24 Septembre 2024

Unité de recherche : Laboratoire Mouvement Sport Santé (M2S)

### **Composition du Jury :**

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Maitresse de conférences-HDR / Université Côte d'Azur

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# ABSTRACT

Prolonged intensive endurance exercise may increase the risk of cardiovascular disease (CVD) in athletes. Sudden cardiac death (SCD) in athletes is a tragic event with far-reaching implications that has attracted widespread attention. However, the incidence and specific causes of CVD in athletes remain unclear. In this thesis, to better understand this phenomenon and prevent the occurrence of cardiac events in active individuals four studies were conducted.

To explore the role of sex in CVD risk, study 1 evaluated the sex differences in the incidence and causes of sudden cardiac arrest (SCA)/SCD in competitive athletes through a systematic review and meta-analysis. Of the sixteen eligible studies, 219 events occurred in female athletes (12.19%), and 1,578 in male athletes (87.81%); the incidence of SCA/D in females was approximately six times lower than in males. The most common cause in females was a congenital coronary anomaly (33.04%), and in males was hypertrophic cardiomyopathy (45.12%). Identifying the reasons for these differences may have implications for the prevention of SCD.

To determine the prevalence of cardiac events in elite triathletes, study 2 was conducted based on an Internet-based survey of athletes participating in triathlon championships. Of 1329 athletes (male 639, 48.08%), 12 cardiac events were identified (0.90%), and the mean onset age was  $29 \pm 7$  years. The prevalence of severe CVD was higher in males than females ( $p=0.03$ ). The prevalence of CVD in short/medium distance triathlons was higher than in long- and ultra-long distances ( $p=0.04$ ). This suggests that triathletes should be closely monitored, especially those in short-distance triathlons and with potential CVD.

Cardiovascular pre-participation screening, particularly electrocardiogram (ECG)-based cardiac assessment, is a powerful tool for detecting or raising suspicion of CVD that may cause sudden death in athletes. However, the sex-specific electrical characteristics in triathletes remain unclear. Therefore, study 3 was conducted to investigate the ECG-based cardiac changes in triathletes. Eighty-six triathletes (male 50, 58%) with a mean age of  $19.9 \pm 4.8$  years were included. Compared to females, the P wave was larger ( $p=0.02$ ), and the QRS complex was longer ( $p=0.006$ ) in males, suggesting that male triathletes were more susceptible to physiological changes than females. Although early repolarization (46.5%) and incomplete right bundle branch block (39.5%) were found to be the most common electrical manifestations in triathletes, these changes were physiological adaptations. Large samples are needed to better understand the ECG-based sex-specificities in elite triathletes.

In study 4, an ECG-based cardiac screening was performed on triathletes and cyclists to investigate the effects of sports disciplines on cardiac remodeling. One hundred and five male athletes were included; 42 were short-distance triathletes (40%), and 63 were cyclists (60%); the mean age was  $22.1 \pm 4.2$  years. Although the P wave amplitude was lower in triathletes than cyclists ( $p=0.005$ ), all the parameters were normal. The most common electrical patterns in athletes were early repolarization (60.95%) and incomplete right bundle branch block (43.81%), independent of the type of sport. This suggests that the cardiac changes in both populations are physiological adaptations to prolonged endurance exercise.

**Keywords:** Cardiovascular disease; Sudden cardiac death; Triathlon; Cycling; Electrocardiogram

# RÉSUMÉ

Un exercice d'endurance intensif et prolongé peut augmenter le risque de maladie cardiovasculaire (CVD) chez les athlètes. La mort subite d'origine cardiaque (SCD) chez les athlètes est un événement tragique dont les implications sont considérables et qui a attiré l'attention du plus grand nombre. Cependant, l'incidence et les causes spécifiques des maladies cardiovasculaires chez les athlètes restent floues. Dans cette thèse, quatre études ont été menées afin de mieux comprendre ce phénomène et de prévenir l'apparition d'événements cardiaques chez les personnes actives.

Afin d'explorer le rôle du sexe dans le risque de CVD, l'étude 1 a évalué les différences entre les sexes dans l'incidence et les causes des arrêts cardiaques soudains (SCA)/SCD et les étiologies chez les athlètes de compétition par le biais d'une revue systématique et d'une méta-analyse. Sur les seize études éligibles, 219 événements sont survenus chez des athlètes féminines (12.19%) et 1,578 chez des athlètes masculins (87.81%); l'incidence des SCA/D chez les femmes était environ six fois plus faible que chez les hommes. La cause la plus fréquente chez les femmes était une anomalie coronarienne congénitale (33.04%) et chez les hommes une cardiomyopathie hypertrophique (45.12%). L'identification des raisons de ces différences peut avoir des implications pour la prévention de la mort subite du nourrisson.

Ensuite, l'étude 2 a été réalisée à partir d'une enquête sur Internet auprès d'athlètes participant à des championnats de triathlon afin de déterminer la prévalence des événements cardiaques chez les triathlètes d'élite. Sur 1329 athlètes (639 hommes, 48.08%), 12 événements cardiaques ont été identifiés (0.90%), et l'âge moyen de survenue était de  $29 \pm 7$  ans. La prévalence des CVD graves était plus élevée chez les hommes que chez les femmes ( $p=0.03$ ). La prévalence des CVD dans les triathlons de

courte/moyenne distance était plus élevée que dans les triathlons de longue et d'ultra-longue distance ( $p=0.04$ ). Cela suggère que les triathlètes, en particulier ceux qui participent à des courses de courte distance, devraient être surveillés de près.

Le dépistage cardiovasculaire avant la participation, en particulier l'évaluation cardiaque basée sur l'électrocardiogramme (ECG), est un outil puissant pour détecter ou faire suspecter de nombreuses maladies cardiovasculaires à l'origine de la mort subite chez les athlètes. Cependant, les caractéristiques électriques spécifiques au sexe chez les triathlètes ne sont pas encore claires. C'est pourquoi l'étude 3 a été menée pour étudier les changements cardiaques basés sur l'ECG chez les triathlètes. Quarante-six triathlètes (hommes 50, 58%) avec un âge moyen de  $19.9\pm 4.8$  ans ont été inclus. Par rapport aux femmes, l'onde P était plus large ( $p=0,02$ ), et le complexe QRS plus long ( $p=0.006$ ) chez les hommes, ce qui suggère que les triathlètes masculins sont plus sensibles aux changements physiologiques que les femmes. Bien que la repolarisation précoce (46.5%) et le bloc de branche droit incomplet (39.5%) soient les manifestations électriques les plus courantes chez les triathlètes, ces changements sont des adaptations physiologiques à l'entraînement de longue durée. De grands échantillons sont nécessaires pour confirmer ces résultats et comprendre les spécificités de l'ECG en fonction du sexe chez les triathlètes d'élite.

Dans l'étude 4, un dépistage cardiaque basé sur l'ECG a été réalisé chez des triathlètes et des cyclistes afin d'étudier les effets des disciplines sportives sur le remodelage cardiaque. Cent cinq athlètes masculins ont été inclus; 42 étaient des triathlètes de courte distance (40%), et 63 étaient des cyclistes (60%) avec un âge moyen de  $22.1\pm 4.2$  ans. Bien que l'amplitude de l'onde P soit plus faible chez les triathlètes que chez les cyclistes ( $p=0.005$ ), tous les paramètres étaient normaux. Les schémas électriques les plus fréquents chez les athlètes étaient la repolarisation précoce (60.95%) et le bloc de branche droit incomplet (43.81%), indépendamment du type de



sport. Cela suggère que les changements cardiaques dans les deux populations sont des adaptations physiologiques à un exercice d'endurance prolongé.

**Mots-clés:** Maladie cardiovasculaire; Mort subite cardiaque; Triathlon; Cyclisme; Électrocardiogramme



# 摘要

长期从事高强度耐力运动可能会增加运动员罹患心血管疾病 (CVD) 的风险。运动员心源性猝死 (SCD) 是一个具有深远影响的悲剧事件，已引起社会各界的广泛关注。然而，运动员 CVD 的发生和具体诱导因素仍不清楚。为了更好地了解这一现象并预防运动相关的心血管疾病的发生，我们进行了四项研究。

为了探究性别在 CVD 风险中的作用，研究 1 通过系统回顾和荟萃分析评估了不同性别竞技运动员心脏骤停 (SCA) /SCD 的发病率和诱因。在 16 项符合条件的研究中，219 例发生在女性运动员中 (12.19%)，1578 例发生在男性运动员中 (87.81%)；女性运动员 SCA/D 的发生率比男性低约 6 倍。女性最常见的 SCA/D 的诱因是先天性冠状动脉异常 (33.04%)，男性最常见的是肥厚型心肌病 (45.12%)。揭示这些差异产生的原因对预防运动员 SCD 有重要意义。

为了明确 CVD 在铁人三项运动员中的发生率，研究 2 基于互联网对参加铁人三项锦标赛的精英运动员进行了调查。在 1329 名运动员中 (男性 639 人，48.08%)，发现了 12 例 CVD (0.90%)，平均发病年龄为  $29 \pm 7$  岁。严重的 CVD 的发病率具有显著的性别差异，男性运动员的发病率高于女性 ( $p=0.03$ )。短/中距离铁人三项运动员 CVD 的发病率高于长距离和超长距离铁人三项运动员 ( $p=0.04$ )。这表明，铁人三项运动员，尤其是男性、短距离的铁人三项运动员或者有潜在 CVD 的运动员应该接受密切的医学监督。

赛前心血管筛查，特别是基于心电图 (ECG) 的心脏评估，是发现或怀疑导致运动员猝死的 CVD 的有力工具。然而，铁人三项运动员 ECG 的性别特征尚不清楚。因此，我们开展了第 3 项研究，即基于 ECG 变化描述不同性别的铁人三项运动员的心电特征。研究共纳入 86 名铁人三项运动员 (男性 50 人，58%)，平均年龄为  $19.9 \pm 4.8$  岁。与女性运动员相比，男性运动员的 P 波更宽

( $p=0.02$ ), QRS 波群更长 ( $p=0.006$ ), 这表明男性铁人三项运动员比女性运动员对运动引起的生理变化更敏感。虽然早期复极化 (46.5%) 和不完全右束支传导阻滞 (39.5%) 是铁人三项运动员最常见的 ECG 表现, 但这些变化是对长期训练的生理适应。为了使这一结果更具有说服力, 并进一步明确铁人三项精英运动员 ECG 的性别差异, 需要进行大样本的研究。

在研究 4 中, 为了探究运动项目对运动员心脏重塑的影响, 我们基于 ECG 对铁人三项精英运动员和骑自行车运动员进行了心脏筛查。研究对象包括 105 名男性运动员, 其中 42 人为短距离铁人三项运动员 (40%), 63 人为骑自行车运动员 (60%), 平均年龄为  $22.1\pm 4.2$  岁。虽然铁人三项运动员的 P 波振幅低于骑自行车运动员 ( $p=0.005$ ), 但所有参数均正常。运动员最常见的心电模式是早期复极化 (60.95%) 和不完全右束支传导阻滞 (43.81%), 与运动类型无关。这表明, 这两种人群的心脏重塑都是对长时间耐力运动的生理适应。

**关键词:** 心血管疾病; 心脏猝死; 铁人三项运动; 骑自行车运动; 心电图

# PUBLICATIONS AND CONFERENCES

## Publications

- **Lingxia Li**, Frédéric Schnell, Vincent Menard, Shuzhe Ding, François Carré, Solène Le Douairon Lahaye. The prevalence of cardiovascular disease in world-class triathletes: an Internet-based retrospective study. (Accepted by the journal *Science & Sports*, 06 Feb 2024)
- **Lingxia Li**, Solène Le Douairon Lahaye, Shuzhe Ding, Frédéric Schnell. Sex differences in the incidence of sudden cardiac arrest/death in competitive athletes: a systematic review and meta-analysis. (Submitted to the journal *Sports Medicine*, 31 Mar 2024)
- Vincent Menard, Anna Barrero, Thibault Lachard, Lucien Robinault, **Lingxia Li**, Frédéric Schnell, François Carré, Solène Le Douairon Lahaye. Cardiac function and autonomic cardiac function during a multistage cycling event: a brief report. (Submitted to the journal *Frontiers in Sports and Active Living*, 15 Dec 2023)
- **Lingxia Li**, Jie Xia, Zhuochun Huang, Wenbin Liu, Zhiming Cui, Ye Zhang, Sen Zhang, Yong Zou, Weina Liu, Zhengtang Qi. Sugar-sweetened beverage consumption retarded weight gain but not induced depression and anxiety-like behaviors in mice. (Published in the journal *Life Science*, 15 Mar 2023, DOI: 10.1016/j.lfs.2023.121469)

## Conferences

- **Lingxia Li**, Frédéric Shnell, Shuzhe Ding, Solène Le Douairon Lahaye. Sex differences of the incidence of sudden cardiac arrest/death in athletes: a systematic review and meta-analysis. (Oral presentation, *International Conference of Sport Medicine and Sport First Aid (ICSMSFA)*, 25-26 Dec 2023, Vienna)

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- **Lingxia Li**, Frédéric Shnell, Shuzhe Ding, Solène Le Douairon Lahaye. The prevalence of cardiovascular diseases in world-class triathletes: an Internet-based study from 2006 to 2019. (Oral presentation, *International Conference of Sport Science (ICSS)*, 08-09 Sep 2022, Prague)
- **Lingxia Li**, Frédéric Shnell, Shuzhe Ding, Solène Le Douairon Lahaye. Cardiac risk in triathletes: prevalence and underlying mechanisms. (Oral presentation, *Conference of the 7th Nutrition-Food-Metabolism-Sports-Health*, 7 Dec 2021, Rennes)

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# LIST OF ABBREVIATIONS

AED, Automated external defibrillators  
AF, Atrial fibrillation  
ARVC, Arrhythmogenic right ventricular cardiomyopathy  
AY, Athlete-years  
BAV, Bicuspid aortic valve  
CAC, Coronary artery calcification  
CAD, Coronary artery disease  
CVD, Cardiovascular disease  
DCM, Dilated cardiomyopathy  
ECG, Electrocardiogram  
EF, Ejection fraction  
EICR, Exercise-induced cardiac remodeling  
HR, Heart rate  
HRV, Heart rate variability  
Incomplete RBBB, Incomplete right bundle branch block  
IRR, Incidence rate ratio  
ITU, International Triathlon Union  
LV, Left ventricular  
LVH, Left ventricular hypertrophy  
LVNC, LV non-compaction  
MET, Metabolic equivalent  
MF, Myocardial fibrosis  
RV, Right ventricular  
SCA, Sudden cardiac arrest  
SCD, Sudden cardiac death

SV, Stroke volume

TWI, T-wave inversion

$\dot{V}O_{2\max}$ , Maximal oxygen consumption

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# GENERAL INTRODUCTION

Regular physical activity benefits human health in various ways, and thus, being physically active is considered part of a healthy lifestyle. It is endorsed that “some activity is better than none, and more is better than some” [1]. Athletes are individuals who participate regularly in organized and systematic training. They are usually considered as models of healthy living [2]. Indeed, athletes typically have a longer life expectancy than the general population [3]. Prolonged intensive endurance exercise contributes to a sequence of electrical, morphological, and functional adaptive changes in the cardiovascular system of the athletes, referred to as the “athlete’s heart” [4]. The athlete’s heart represents a positive and benign physiological cardiovascular adaptation to prolonged intensive endurance exercise.

Recently, however, some researchers have questioned the cardiovascular health benefits of extremely high levels of exercise. Some studies have reported adverse clinical outcomes when endurance athletes are at their extreme upper exercise limits, raising the possibility that repeated high doses of exercise may harm the heart [5]. Substantial evidence has shown that long-term intensive physical activity may not only trigger cardiac events in susceptible individuals but also promote the development of cardiovascular disease (CVD) in asymptomatic athletes [6]. The adverse effects of repeated prolonged intensive endurance exercise on CVD, such as accelerated coronary artery calcification (CAC), myocardial fibrosis (MF), atrial fibrillation (AF), and even an increased risk of sudden cardiac death (SCD), have been reported in athletes [7].

Prolonged and repeated intensive endurance exercise can increase the risk of CVD, causing some of these athletes to stop their exercise exertion training and competition abruptly; moreover, in some severe cases, athletes might be at risk of losing their lives.

Although many studies have attempted to unravel the mysteries of the occurrence of CVD in athletes, there remains much to be determined. Therefore, to reduce the risk of cardiac death in athletes, this thesis aims to investigate the occurrence and potential mechanisms of CVD in athletes:

Firstly, SCD is the most tragic event in athletes. Despite the methodological challenges, previous studies have consistently reported a lower risk of SCD in female athletes than in males [8]. However, the sex differences of the potential causes and circumstances in athletes remain unknown. Unraveling the role of the sex effects in the incidence of SCD may reveal the underlying mechanisms and, consequently, allow the prevention of SCD in athletes of both sexes. Existing knowledge on the incidence of SCD has been determined mainly based on studies conducted under specific circumstances using specific methodologies (such as the data were collected based on the national registry records or the assurance claims), and often ignoring sex differences or considering only one sex (predominantly males) [9-12]. Moreover, the estimated incidence, potential causes, and pathogenic mechanisms of SCD in athletes have yet to be effectively addressed and thoroughly and systematically evaluated. Therefore, the first study of the thesis aims to assess the sex differences in the incidence of sudden cardiac arrest/death and etiologies in competitive athletes using systematic review and meta-analysis methodologies.

Secondly, in addition to the sex profile of athletes, which is essential in the context of exploring the potential mechanisms of SCD, the sports discipline practiced also plays a unique role in the occurrence of SCD during exercise. A retrospective study of 30 Olympic sports found a relatively unexpectedly high prevalence of cardiac events in endurance athletes, particularly in short-distance triathletes [13]. This study attracted our attention because, in the last decades, triathlon sports disciplines have become increasingly popular around the world [14]. Throughout the years, the number of sports-

related fatalities has generated concern about the safety of triathletes [15]. However, the risk of cardiac events in high-level triathletes remains unclear. Therefore, the second study aims to determine the prevalence of CVD in elite triathletes according to sex, practiced triathlon disciplines, and formats.

Intensive endurance exercise training and participation in competitive sports can trigger the onset of cardiac abnormalities in predisposed individuals [16]. However, over 80% of cases lack antecedent symptoms and family history [17]. There is, therefore, considerable interest in the early identification of at-risk populations [18]. According to the long-term experience in Italy and the recommendations from the European Society of Cardiology and the International Olympic Committee, electrocardiogram (ECG) assessment is a powerful tool for detecting or raising suspicion of many CVDs that causes sudden death in young athletes [19, 20]. Therefore, we believe cardiac pre-participation screening, especially ECG-based cardiac assessment, could prevent sudden death in these elite triathletes. The fact that ECG patterns vary considerably between sexes [21] and the sex-specific properties of ECG-based cardiac screening in triathletes remain unclear. Thus, the third study aims to investigate the cardiac status of elite triathletes in both sexes by ECG assessment.

Triathlon is an endurance-competitive multisport race consisting of swimming, cycling, and running, covering various distances [22]. The specific characteristics of triathlon determine that its effects on cardiovascular health may differ from other single sports. However, it remains to be seen whether the cardiac remodeling in triathletes is due to the high cardiovascular demands or the “triple effort” of the three sports. Therefore, the fourth study compares the ECG-based cardiac changes between triathletes and cyclists.









# PART 1. THE ATHLETE'S HEART

## 1 The health benefits of physical activity

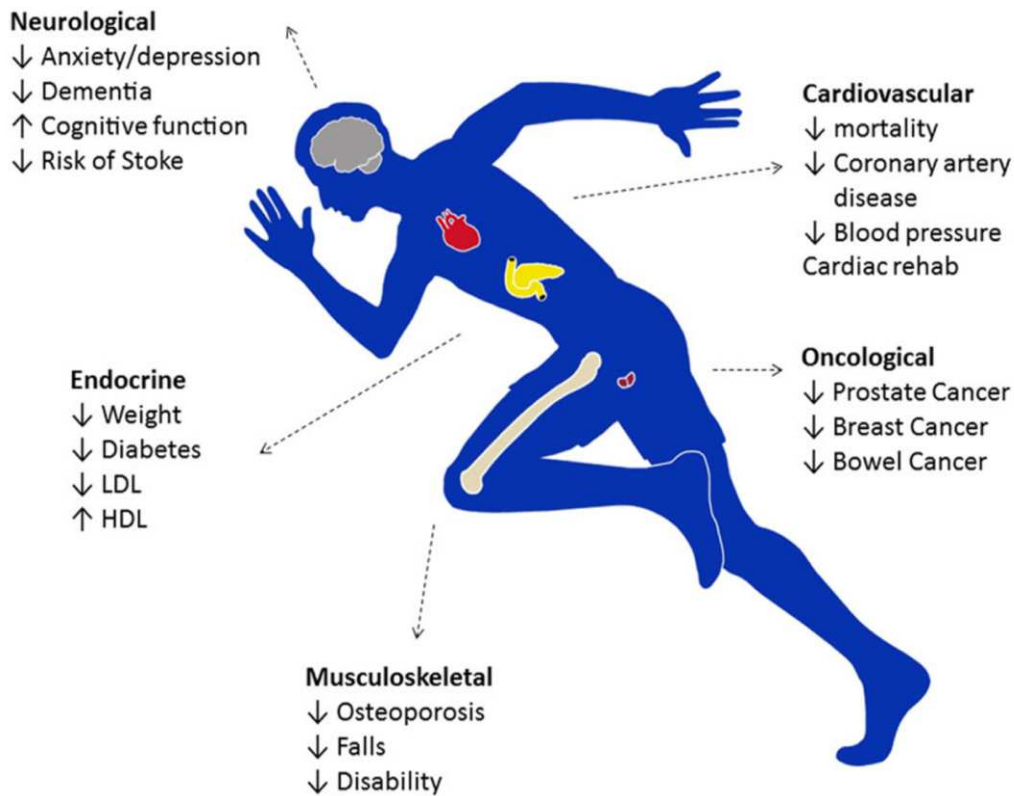
### 1.1 The health benefits of physical activity in the general population

Physical activity is a series of bodily movements produced by skeletal muscles that result in energy expenditure above the resting metabolic rate [23] and is broadly defined to encompass exercise, sports, and physical activities that are part of daily living, occupation, leisure, and active transportation [24]. Being physically active can benefit health and fitness in various ways. Regular physical activity improves weight management [25], strengthens bones and muscles [26], reduces the risk of developing and progressing of chronic diseases [27], promotes healthy aging [28] and increases life expectancy [29]. Additional benefits of regular exercise include improved mental health, such as enhanced cognitive function and reduced depression [30] (Figure 1).

For all these health benefits, the World Health Organization guidelines recommend that adults engage in 150 to 300 minutes of moderate-intensity or 75 to 150 minutes of vigorous-intensity physical activity each week or an equivalent combination of moderate and vigorous-intensity physical activity [23]. The Guidelines encourage people to engage in regular muscle-strengthening activities and reinforce that some physical activity is better than none. More physical activity is better for optimal health outcomes [23]. Meeting and maintaining at least the minimum public health recommendations would potentially prevent 46% of deaths associated with physical inactivity [31]. Every 15 minutes of physical activity above the minimum recommended daily amount, there is a 4% reduction in all causes of mortality and a 1% reduction in cancer mortality [29].

The cardiovascular system is one of the biggest beneficiaries of physical activity [32]. Cardiovascular benefits include lower blood pressure and triglyceride levels and improved inflammatory markers and insulin resistance [32]. Compared to sedentary individuals, physically active people have better body composition [33], well-controlled blood pressure, improved lipid profiles, increased metabolic fitness, lower risk of CVD, and better overall health [34].

Thus, physical activity is considered an effective strategy for both the primary and secondary prevention of CVD [35]. Individuals who engage in moderate physical activity have an approximately 20% to 25% reduction in the risk of developing coronary heart disease, and those who engage in vigorous physical activity have a further 30% to 35% reduction in risk compared to those who engage in low intensity of physical activity [36]. A 10-year follow-up of adults in the United States suggests that individuals can achieve substantial health benefits by walking a few days per week. Walking 8,000 or more steps per week is curvilinearly associated with a lower risk of all-cause and cardiovascular mortality [37]. Middle-aged and older adults, including those with CVD and cancer, can achieve substantial longevity advantages by becoming more physically active, regardless of their previous physical activity levels and established risk factors [31]. Exercise-related cardiac rehabilitation reduces cardiovascular mortality (7.6% to 10.4%) compared to inactive individuals [38]. The benefits are more significant in the secondary prevention group than the primary prevention group [39]. Every 500 metabolic equivalent (MET)/minute/week increase in physical activity is associated with a 14% reduction in the risk of death in the secondary prevention group and a 7% reduction in the primary prevention group [39]. Although the maximum amount of physical activity necessary to promote cardiac function and reduce cardiac risk remain unknown [40], most studies show a graded decline with increasing levels of activity [29].



**Figure 1. The health benefits of physical activity [41]**

## 1.2 The health benefits of physical activity in athletes

Athletes have always been a source of great interest to the public and the media and are often seen as models of optimal health. Nevertheless, who is an athlete?

Typically, an athlete is defined as a person who participates in an organized sport that requires systematic training and regular competition and places a high premium on athletic excellence and performance [2]. Although the definition of an athlete varies between studies [42], it is suggested that the minimum criteria to be defined as an athlete (all of which should be fulfilled): (1) training in sport to improve performances/results, (2) actively participating in sports competitions, (3) being formally registered with a local, regional or national sports association, and (4) having sports training and competition as the main activity or focus of personal interest, devoting several hours on

all or most days to these activities, exceeding the time spend on other professional or leisure activities [42]. Athletes participate in a planned, organized, and repeated physical activity designed to improve physical fitness, often viewed as physical exercise, a subcategory of physical activity [43].

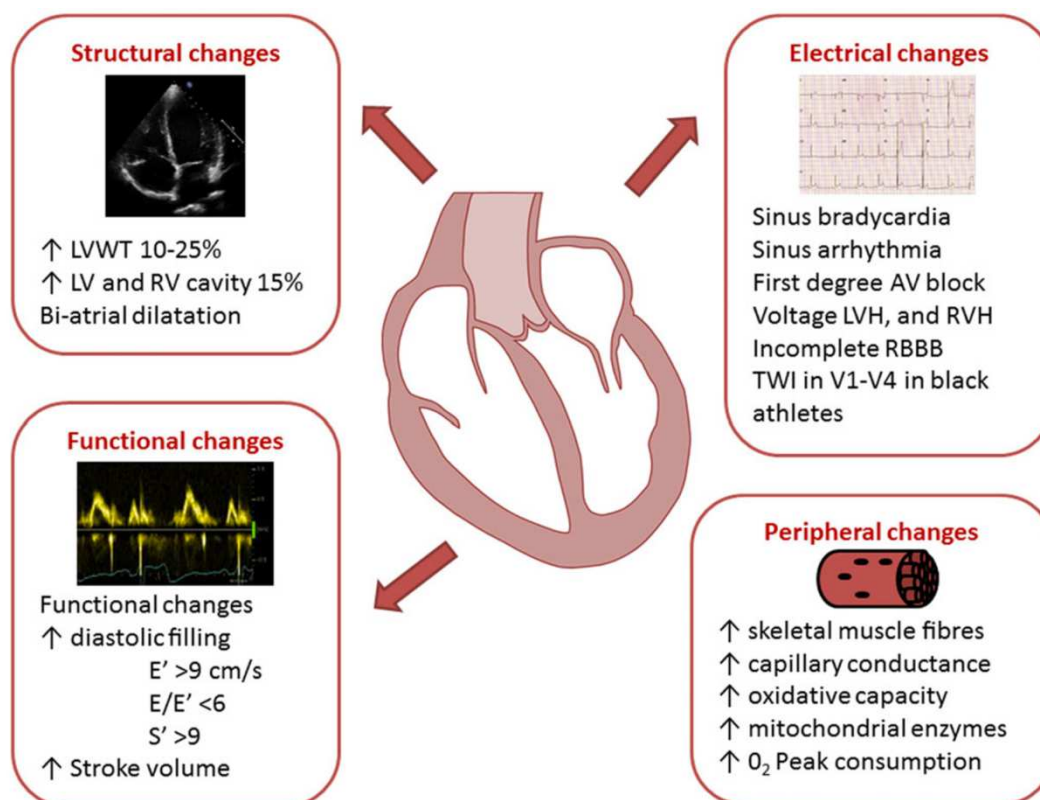
The beneficial effects of physical exercise in athletes are well described. Regular exercise has been shown to promote healthy aging by significantly improving cardiovascular function [44]. Well-trained athletes have better functional capacity than their sedentary counterparts and are often comparable to young non-athletes [44]. Studies showed that former athletes live longer and have a lower incidence of both CVD and cancer mortality than the general population [3]. Studies of medalist athletes in the Olympic Games revealed that Olympic medalists lived an average of 2.8 years longer than the general population, irrespective of the country, medal, or sport [45]. These longevity advantages are primarily attributable to a lower risk of cancer, which can reduce average life expectancy by 2.3 years [46]. After 53 weeks of exercise, the cardiovascular risk profile is reduced, insulin resistance is decreased, and the risk of overweight in athletes is lowered [47]. For every 1 MET increase in exercise capacity, the cardiovascular risk in athletes is reduced by 13%. Compared with those who achieved less than 5 METs, the death risk is about 50% lower for those with an exercise capacity of 7.1 to 10 METs and 70% lower for those who achieved over 10 METs [48].

Current European and US guidelines recommend at least 150 minutes of moderate-intensity exercise per week for adults. Competitive (and some recreational) athletes typically exceed these recommendations with more than 20 hours of vigorous exercise (15 METs) per week. This high-intensity exercise requires a sustained increase in cardiac output over a long period, achieved through various unique electrical, structural, and functional changes in the heart [41], grouped as “athlete’s heart.”

## 2 The athlete's heart

### 2.1 Definition of an athlete's heart

Prolonged repeated bouts of exercise exposure contribute to a sequence of changes in the cardiovascular system, named the “athlete's heart” [4], also known as exercise-induced cardiac remodeling (EICR) [49]. Characteristics of the athlete's heart include structural, functional, and electrical changes such as ventricular enlargement, cardiac function and compliance improvement, and electrical remodeling [4] (Figure 2). An enlarged heart in athletes previously appeared to be a pathology of overtraining, and prolonged intensive endurance exercise would lead to premature cardiovascular failure [50]. However, as it is better understood, the athlete's heart is now considered a benign phenomenon, representing a physiological adaptation to regular exercise [51].



**Figure 2. Exercise-induced cardiac remodeling in athletes.** AV, atrioventricular; LV, left ventricular; LVH, left ventricular hypertrophy; LVWT, left ventricular wall thickness; RV, right ventricular; RVH, right ventricular hypertrophy; TWI, T-wave inversion [41]

## 2.2 Physiological basis of an athlete's heart

EICR is stimulated by the hemodynamic and neurohumoral conditions present during exercise and is a fundamental component of applied sports physiology [52]. Physiological adaptation is evidenced by the athlete's high maximum oxygen consumption ( $\dot{V}O_{2\max}$ ).  $\dot{V}O_{2\max}$  is defined as the oxygen uptake that occurs at an individual's maximum volitional intensity or effort of exercise [52]. The best long-distance runners have a  $\dot{V}O_{2\max}$  of 85 ml/kg/min, and some exceptional athletes exceed 90 ml/kg/min. The highest value ever recorded is that of Norwegian cross-country skiing champion Bjørn Dæhlie, holder of eight Olympic gold medals: 96 ml/kg/min.

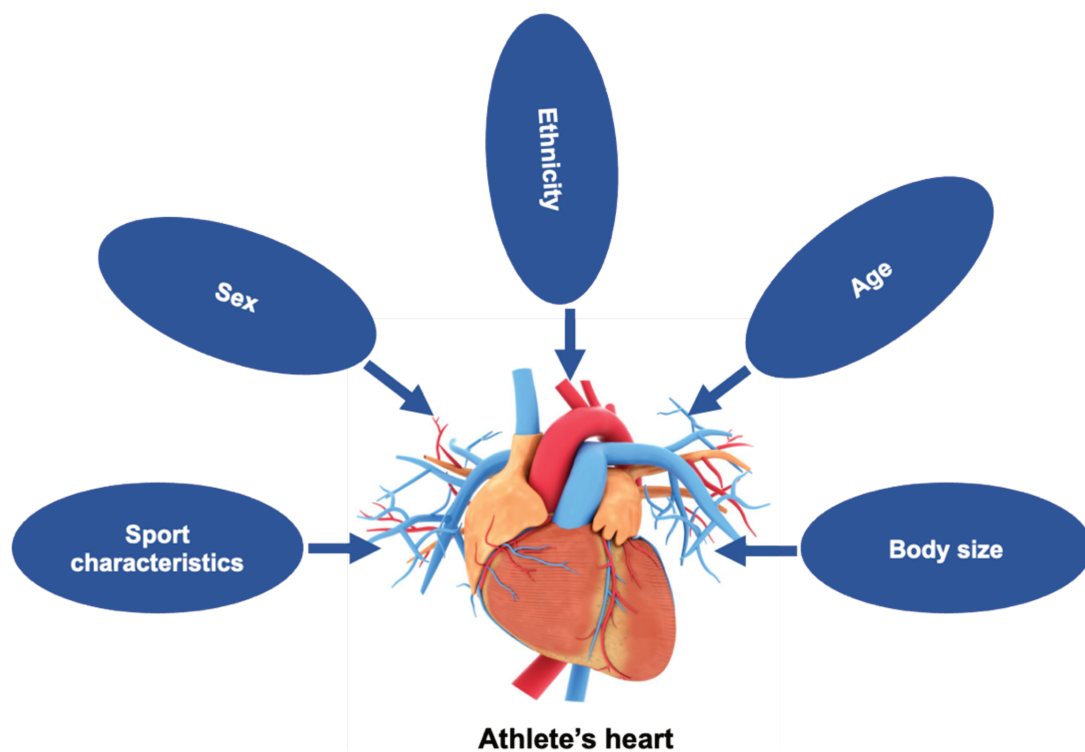
In exercising humans,  $\dot{V}O_{2\max}$  is limited by the ability of the cardiorespiratory system to deliver oxygen to the exercising muscles. This is demonstrated by three primary evidence: (1) when oxygen delivery is altered (by blood doping, hypoxia, or beta-blockade),  $\dot{V}O_{2\max}$  changes, accordingly; (2) the increase in  $\dot{V}O_{2\max}$  with training results primarily from an increase in maximal cardiac output; and (3) when a small muscle mass is over-perfused during exercise, it has an extremely high capacity for oxygen consumption. Therefore, oxygen delivery, rather than skeletal muscle oxygen extraction, is the primary limiting factor for  $\dot{V}O_{2\max}$  in exercising humans [53].

The cardiovascular system is responsible for transporting oxygen-rich blood from the lungs to the skeletal muscles, known as cardiac output. Cardiac output, the product of stroke volume (SV) and heart rate (HR) can increase 5 to 6 times during maximal exercise. Cardiopulmonary exercise testing showed that athletes demonstrate greater cardiac output, faster HR recovery, and higher oxygen consumption when compared to non-athletes [54]. SV increases significantly at rest and during exercise with prolonged intensive endurance training. Ventricular enlargement and the associated ability to generate large SV are the main adaptations conferred by EICR and are the cardiac hallmark of endurance-trained athletes. The HR increases proportionally with exercise

intensity and is responsible for most cardiac output increases during exercise. An athlete's HR can range from less than 40 beats per minute at rest to more than 200 beats per minute at peak exercise intensity. The increase in HR during exercise requires a coordinated autonomic nervous system response characterized by rapid and sustained parasympathetic withdrawal followed by sympathetic activation [49].

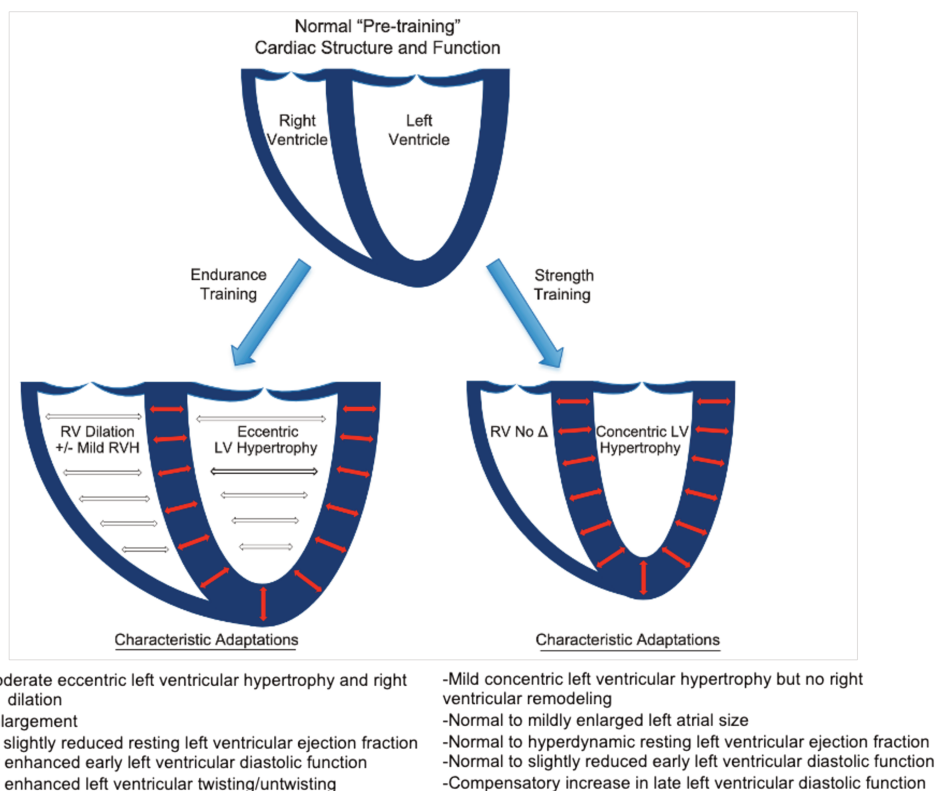
### 2.3 Determinants of an athlete's heart

EICR results from numerous determinants, including characteristics of sports practice, training volume and intensity, age, sex, ethnicity, and body size [55] (Figure 3).



**Figure 3. Determinants of the athlete's heart [55]**

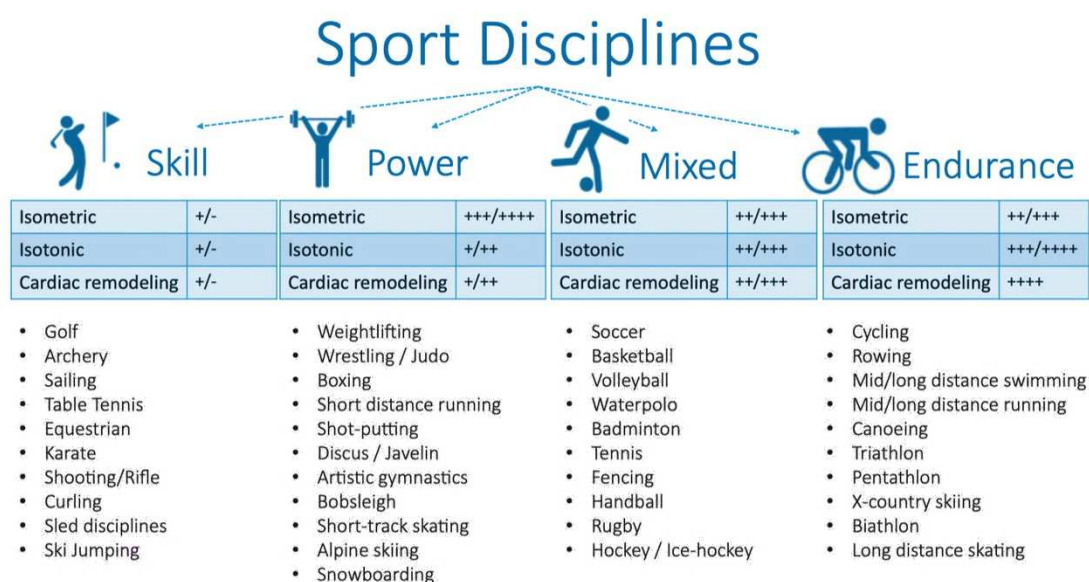
Sports can be classified according to their strength components, expressed as the relative intensity of static muscle contractions, and their endurance components, reflected by the relative intensity of dynamic exercise or the percentage of maximal aerobic power [51]. Isotonic exercise, commonly called endurance exercise, involves a sustained increase in cardiac output with normal or reduced peripheral vascular resistance. These activities result in a primary “volume” challenge to the heart, manifesting with time as an eccentric harmonious hypertrophy with increased wall thickness and all chambers dilation. Meanwhile, isometric exercise, commonly referred to as strength exercise, is characterized by short but intense bouts of increased peripheral vascular resistance and normal or only slight increase in cardiac output. This increase in peripheral vascular resistance causes transient but potentially marked systolic hypertension and left ventricular (LV) “pressure overload”, manifested with the time as LV wall thickening with mild LV dilation, resulting in concentric hypertrophy [49] (Figure 4).



**Figure 4. Exercise-induced cardiovascular remodeling [40]**



Although athletes present different characteristics of cardiac adaptation during dynamic and static exercise, the classification as an endurance-trained or a strength-trained heart is not an absolute and dichotomous concept but rather a relative concept [56]. Typically, sports with mixed physiological characteristics involving both static and dynamic components, such as rowing and triathlon, result in four-chamber dilatation with balanced increases in LV size and LV wall thickness or eccentric LVH [57]. Details can be illustrated by the model of a simple sports classification based on the main physiologic characteristics of exercise training [55] (Figure 5).



**Figure 5. The simplified classification of common Olympic sport disciplines, according to the relative isometric and isotonic components of exercise and cardiovascular adaptation [55]**

In addition to disciplines, the characteristics of the athlete's heart are also affected by the duration and intensity of exercise training [58]. It is even assumed that cardiac remodeling is more influenced by the total exercise load (intensity  $\times$  time) than the sports discipline [59]. EICR requires repeated and sustained exercise exposure stimulus, but the minimum intensity and duration of exercise needed to stimulate this process remains largely unexplored [60]. Evidence showed that a minimum of 3

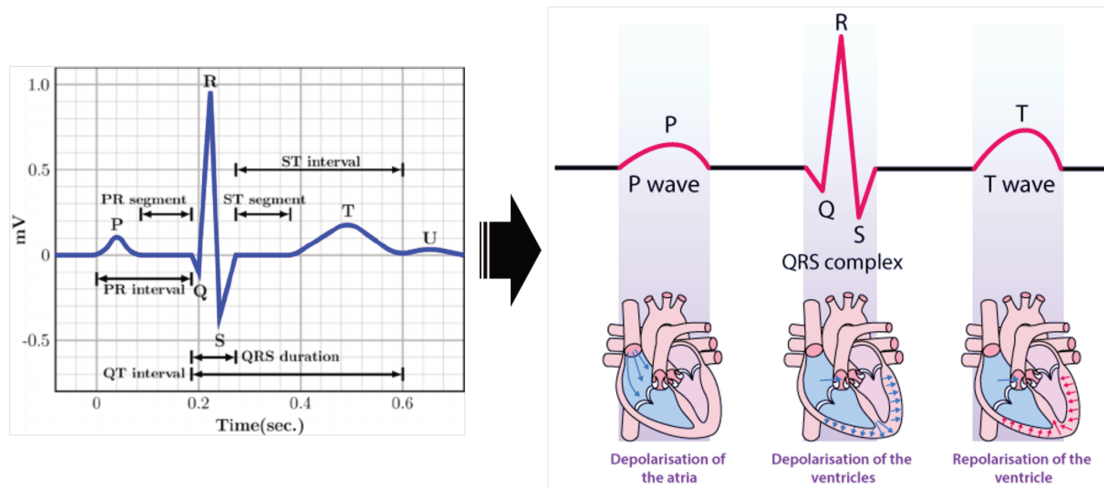
hours/week of current exposure and a lifetime exposure of at least 3000 hours seem needed to lead to athlete's heart [60]. Longitudinal studies in trained athletes showed that 90 days of intense training ( $13.1 \pm 0.9$  hours/week) induced cardiac remodeling in athletes, as evidenced by a disproportionate increase in ventricular wall thickening [61]. Prolonged intensive endurance training of previously sedentary young subjects over a year found that these subjects exhibited adaptive cardiac morphological changes comparable to those observed in elite athletes [62]. In endurance athletes, EICR follows a diphasic response with increased LV chamber size, early diastolic function, and systolic twist during an acute augmentation phase of exercise training. This is followed by a chronic adaptation phase characterized by increasing wall thickness and regression of LV twist. This suggests that training duration is a critical determinant of EICR and has implications for assessing myocardial structure and function [63].

Overall, the development of the athlete's heart is the result of various factors. The combined effects of these factors on myocardial electrical, structural, and functional aspects of the athlete's heart can be determined by the results of ECGs and echocardiograms.

## 2.4 Specificities of athlete's heart

### 2.4.1 Electrocardiography specificity

ECG is a method used to record the electrical activity of cardiomyocytes [41] (Figure 6).



**Figure 6. The electrocardiogram** (<https://byjus.com/neet/electrocardiogram/>)

ECG changes in athletes are common and usually reflect structural and electrical remodeling of the heart in adaptation to regular exercise. It represents the properties of the athlete's heart [64]. Trained athletes often (up to 80%) show ECG changes such as sinus bradycardia, first-degree atrioventricular block, incomplete right bundle branch block (incomplete RBBB), early repolarization, and isolated increase of QRS voltages for LV hypertrophy (LVH), which are due to physiological adaptation of the cardiac autonomic nervous system to exercise conditioning by increasing vagal tone and attenuating sympathetic activity [65] (Table 1). The development of the athlete's heart in terms of ECG changes is a gradual process; sinus bradycardia appears to be an early sign of the development of an athlete's heart, while first-degree atrioventricular block seems to occur as a late sign, possibly reflecting structural remodeling rather than functional adaptation [66].

**Table 1. Normal ECG findings in athletes [65]**

Normal ECG findings in athletes	Definition
Increased QRS voltage	Isolated QRS voltage criteria for left (SV1 + RV5 or RV6 >3.5 mV) or RVH (RV1 + SV5 or SV6 >1.1 mV)
Incomplete right bundle branch block	rSR' pattern in lead V1 and a qRS pattern in lead V6 with QRS duration <120 ms
Early repolarization	J-point elevation, ST-segment elevation, J waves, or terminal QRS slurring in the inferior and/or lateral leads
Black athlete repolarization variant	J-point elevation and convex ('domed') ST-segment elevation followed by T-wave inversion in leads V1-V4 in black athletes
Juvenile T-wave pattern	T-wave inversion V1-V3 in athletes age <16 years of age
Sinus bradycardia	≥30 beats/minutes
Sinus arrhythmia	HR variation with respiration: rate increases during inspiration and decreases during expiration
Ectopic atrial rhythm	P waves are a different morphology compared with the sinus P-wave, such as negative P waves in the inferior leads ('low atrial rhythm')
Junctional escape rhythm	QRS rate is faster than the resting P-wave or sinus rate and typically <100 beats/minutes with narrow QRS complex unless the baseline QRS is conducted with aberrancy PQ interval 200-400 ms
First-degree atrioventricular block	PR interval 200-400 ms
Mobitz type I second-degree atrioventricular block	PR interval progressively lengthens until there is a non-conducted P-wave with no QRS complex; the first PQ interval after the dropped beat is shorter than the last conducted PQ interval

The typical spectrum of cardiac electrical changes in trained athletes varies with different factors, such as sex, age, ethnicity, fitness level, and type of sport [64]. For example, sports-related ECG changes are more common in endurance athletes than in non-endurance populations [67]. Endurance athletes exhibit the most profound modifications of electrical patterns, such as bradyarrhythmia and repolarization [68].

Concerning sex, recent literature found a clear difference in the type and extent of EICR between sexes [68]. For example, female athletes are more likely to have anterior T-wave inversion (TWI), whereas males are more likely to have elevated QRS voltage and early repolarization [57]. The higher prevalence of standard ECG patterns in females is expected to be due to several factors, including the milder morphological LV changes induced by training in females and the lower participation rates in specific disciplines (such as rowing), which have a significant impact on ECG patterns [64].

### *2.4.2 Echocardiography specificity*

An echocardiogram is a non-invasive and sensitive means of assessing cardiac dimensions and function, providing an in-depth understanding of cardiovascular physiology at rest and during exercise [69]. EICR is associated with ventricular enlargement, increased LV mass, and modest aortic root enlargement to accommodate increased physiological demands [70]. When compared to sedentary healthy controls, athletes generally show a 10% to 20% greater LV wall thickness, a 10% to 15% greater LV and right ventricular (RV) cavity size [55], and increased end-diastolic and systolic volume in both LV and RV [71].

Adaptations to exercise are dependent on the specific type of training performed. Endurance and strength training lead to distinctly different changes in cardiac function. Although linear regression models show an independent positive association of RV peak velocity  $E$  (m) with LV SV and maximal exercise on a bicycle ergometer in both endurance- and strength-trained athletes [72], studies found that strength-trained athletes have increased wall thickness and relative wall thickness. In contrast, LV SV and LV and RV end-diastolic diameters are greater in endurance-trained athletes [72]. Similarly, in professional athletes, strength training decreases LV end-systolic diameter, whereas endurance exercise increases LV end-diastolic diameter and left atrial volume index [73].

EICR occurs in both male and female athletes but is usually less pronounced in females than in males [69]. Typically, female athletes have approximately 10% smaller absolute LV chamber size, 10% to 20% smaller LV wall thickness, and 20% to 55% smaller absolute LV mass compared to males [57]. Studies in British athletes revealed that the upper normal limits of LV wall thickness and diastole LV internal diameter are 14 mm and 65 mm for male athletes and 11 mm and 60 mm for females [74]. LV end-diastolic cavity dimensions typically range from 43 to 79 mm in males, whereas in

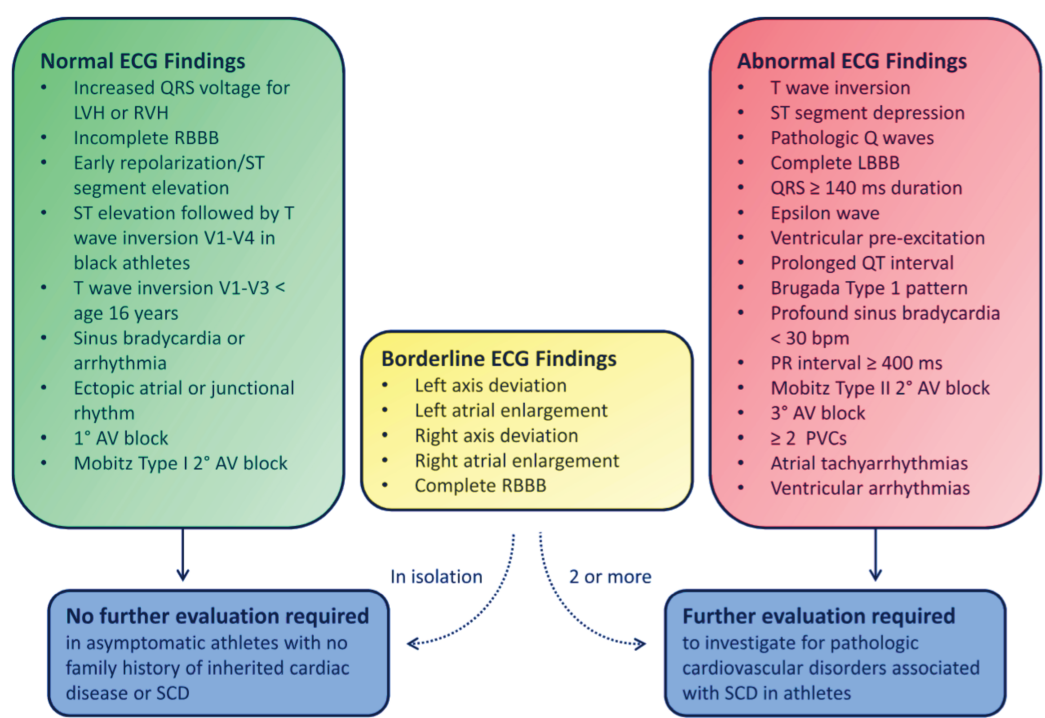
females, the ranges are generally 38 to 66 mm [75]. Although the geometry is generally within the normal ranges in athletes, females tend to develop eccentric hypertrophy, whereas males often exhibit concentric remodeling; only 4% of females had concentric hypertrophic hypertrophy compared to 15% of males [76]. This indicated the need for a sex-specific approach to interpreting the unique features of the athlete's heart [77].

All these suggest that regular and sustained participation in intensive endurance exercise training is typically associated with electrical and structural changes in the heart. All these changes are benign physiological adaptations. Nevertheless, in a minority of athletes, their cardiac phenotype may resemble that of specific cardiac diseases, reflecting diagnostic uncertainty (a diagnostic dilemma known as the “grey zone”) [78]. As the consequences of a misdiagnosis can be catastrophic, it is essential to identify and differentiate those athletes who fall into the grey zone [79].

### 3 The grey zone in athletes

#### 3.1 The grey zone of electrocardiographic findings in athletes

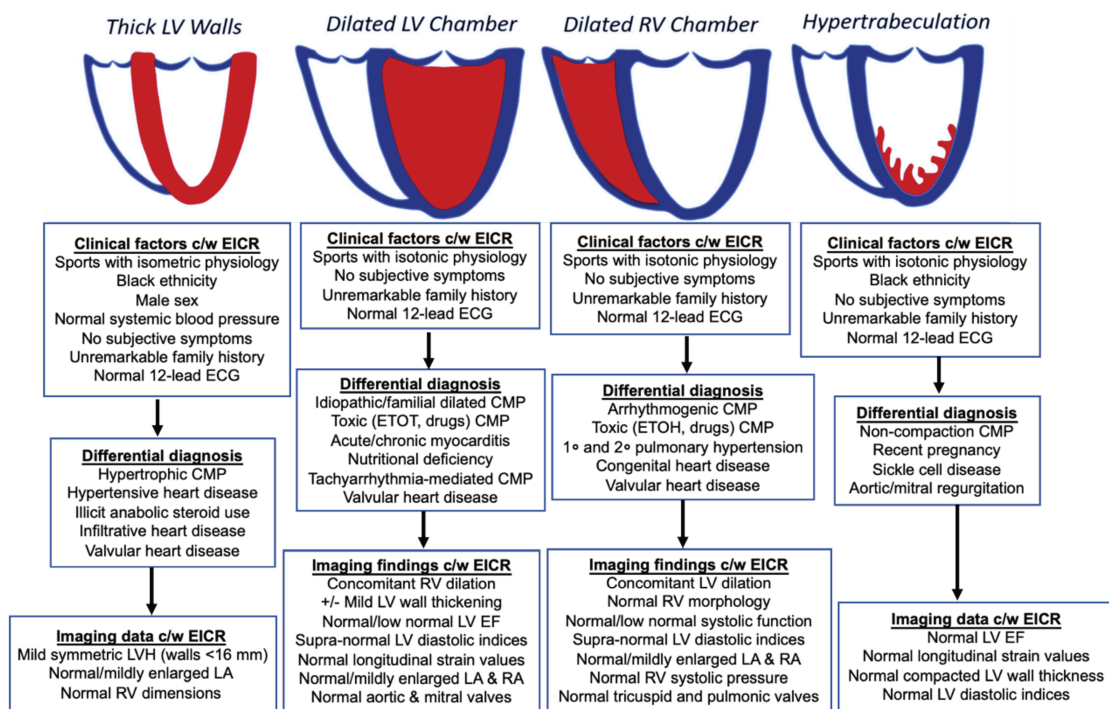
ECG changes in athletes are commonly used to reflect the remodeling of the heart as an adaptation to regular exercise. However, the abnormalities in athlete's ECG results may be a sign of underlying CVD that puts them at risk of death during exercise. Thus, it is essential to distinguish the ECG abnormalities caused by intense exercise from those potentially related to increased cardiac risk [64]. The international consensus for ECG interpretation in athletes suggests that when findings in athletes are considered physiological adaptations to repetitive exercise, this does not require further evaluation. However, for borderline findings, when these findings are present individually, they do not need additional examination, whereas when two or more findings are present simultaneously, further examination is required [80] (Figure 7).



**Figure 7. Borderline ECG findings in athletes.** AV, atrioventricular block; LBBB, left bundle branch block; RBBB, right bundle branch block; RVH, right ventricular hypertrophy; PVC, premature ventricular contraction; SCD, sudden cardiac death [80]

### 3.2 The grey zone of echocardiogram findings in athletes

Functional echocardiography, including tissue Doppler and speckle tracking imaging [49], is another essential tool in diagnosing grey zone athletes. EICR frequently results in echocardiogram findings that overlap with the common forms of myocardial disease associated with adverse events in CVD. Therefore, differentiating EICR from myocardial pathology is one of the most critical tasks for clinicians. The term “grey zone” has been used to describe the clinical overlap between EICR and pathology. According to the research and clinical framework, combined with the findings of echocardiograms, there are four basic variants of the “grey zone”: (1) LV wall thickening, (2) LV chamber dilatation, (3) RV dilatation, and (4) LV hypertrabeculation. Each leads to different differential diagnoses [52] (Figure 8).



**Figure 8. The echocardiogram findings of “grey zone”.** CMP, cardiomyopathy; EICR, exercise-induced cardiac remodeling; ETOH, ethyl alcohol; LA, left atrium; RA, right atrium; LV, left ventricular; RV, right ventricular; EF, ejection fraction [52]



### **3.3 The overlap between cardiac remodeling and genetic cardiomyopathy**

Physiological electrical and structural changes in athletes are generally reversible after detraining; however, a small proportion may have more profound changes that overlap with those observed in individuals with morphologically mild expressions of genetic cardiomyopathies [41]. Genetic cardiomyopathies are a complex family of diseases that include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and isolated LV noncompaction cardiomyopathy (LVNC) [81]. The assessment should be conducted in such circumstances as a misdiagnosis of cardiomyopathy can lead to disqualification from sport. Conversely, a misdiagnosis of an athlete's heart in a person with cardiomyopathy may endanger a young life [41].

#### *3.3.1 Hypertrophic cardiomyopathy*

HCM is the most common genetic cardiac disorder and represents the most common cause of death in young athletes [82]. Early detection and correct diagnosis of HCM, especially in asymptomatic athletes, is paramount in cardiac pre-participation screening [83]. Hypertrophic adaptation in athletes is generally characterized by mild symmetric hypertrophy, rarely exceeding 13 mm and never 16 mm. In contrast, HCM is typically manifested by myocardial hypertrophy with maximal LV wall thickness of more than 15 mm in the end-diastolic phase, most often with asymmetric involvement [84]. Although distinguishing definitive pathology hypertrophy from a normal myocardium could be relatively easy, a certain number of athletes show intermediate features (e.g., in males, LV wall thickness between 13 and 15 mm; in females, it is between 12 and 15 mm) [84]. Almost 50% of healthy elite athletes who train intensively and regularly can reach the grey zone of hypertrophy [85]. Of the athletes with HCM

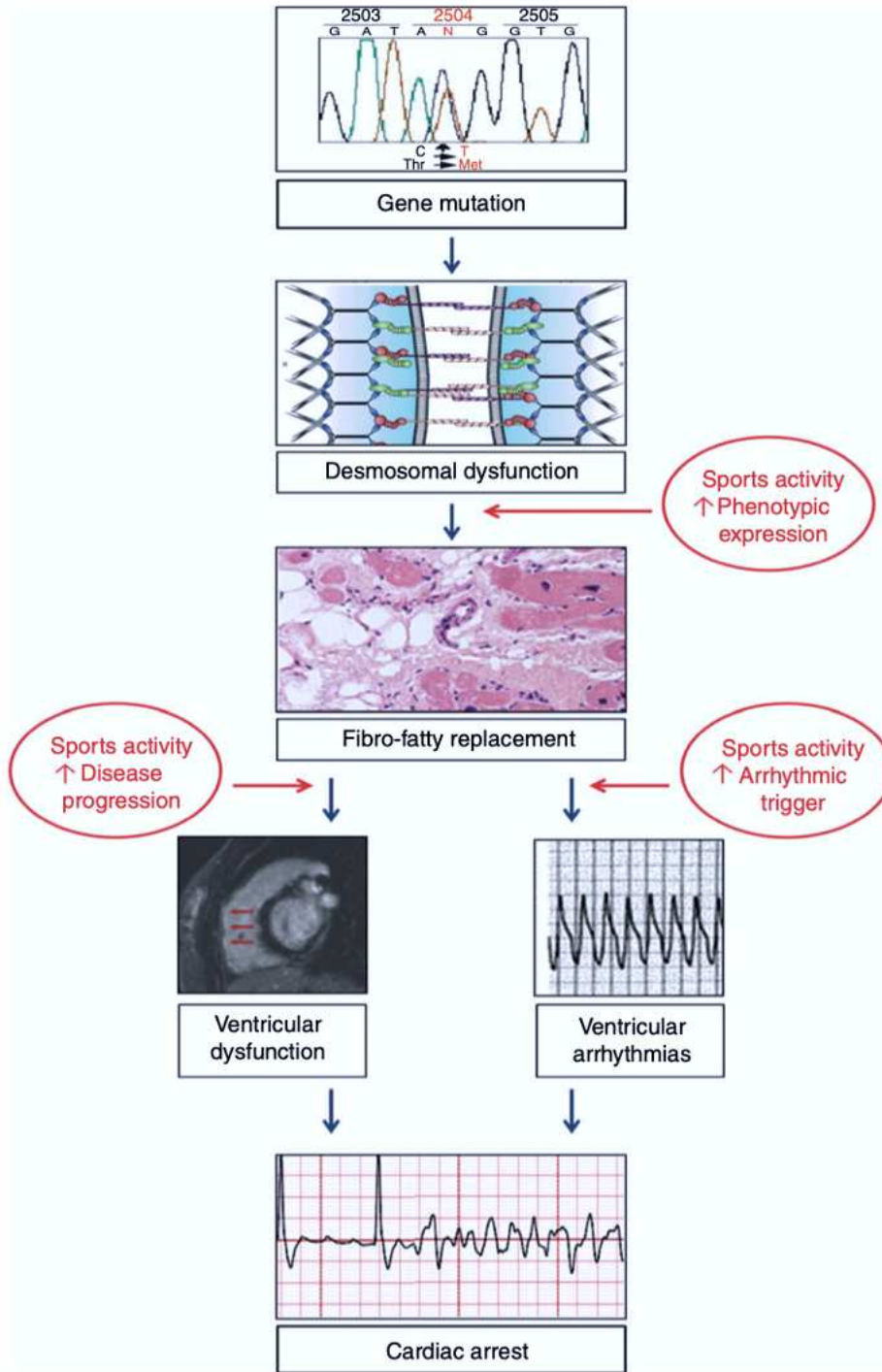
fall into the conventional grey zone of mild concentric LVH, echocardiographic parameters alone are insufficient to differentiate HCM from physiological LVH. Additional structural and functional assessments should complement them to minimize the risk of false reassurance [86]. Cardiopulmonary exercise testing revealed that athletes with LVH have a significantly greater  $\dot{V}O_{2max}$ , anaerobic threshold, and oxygen pulse than patients with HCM. A  $\dot{V}O_{2max}$  exceeding 50 ml/kg/min or 20% above predicted  $\dot{V}O_{2max}$  could differentiate the athlete's heart from HCM [87].

### *3.3.2 Dilated cardiomyopathy*

Endurance athletes with reduced ejection fraction (EF) represent a clinical overlap between the athlete's heart and DCM [88]. In these athletes, marked echocardiographic LV dilation is frequent and often associated with a low LVEF [89]. Studies showed that 1 in 6 elite endurance athletes had reduced EF, raising the suspicion of subclinical DCM [88]. In a study, LVCD varied widely (38 to 66 mm in females and 43 to 70 mm in males) and were within generally accepted normal limits in most participants (55% of athletes less than 54 mm). Nevertheless, nearly 15% of participants had strikingly cavity enlargement with the end-diastolic dimension of up to 66 mm in female athletes and 70 mm in males, markedly increased to a degree consistent with primary DCM [75]. However, distinguishing early DCM from physiological LV dilation with LVEF less than 55% in athletes (grey zone) is challenging [90]. Without systolic dysfunction, this cavity dilatation most likely represents an extreme physiological adaptation to intensive athletic training [75]. An RV/LV end-diastolic volume ratio of more than 1.2 and impaired RV function (RVEF less than 45%) are strong predictors of pathology [91]. A comprehensive evaluation showed that exercise echocardiography had the greatest discriminatory value in distinguishing grey zone athletes from asymptomatic patients with DCM [90].

### 3.3.3 Arrhythmogenic right ventricular cardiomyopathy

ARVC is caused by gene mutations encoding desmosomal proteins that predominantly affect the RV and can lead to ventricular tachyarrhythmias and cardiac death [92]. In athletic populations, ARVC accounts for approximately 4% of sudden death [93]. Prolonged endurance exercise can acutely increase RV volume, stressing these abnormal desmosomal junctions [94]. Intensive endurance training increases the risk of ventricular tachyarrhythmias and heart failure in ARVC desmosomal gene carriers [95]. Compared with inactive patients and those who participate in recreational sports, those who participate in competitive sports are associated with a twofold increased risk of ventricular tachyarrhythmias/death and earlier onset of symptoms [92] (Figure 9). Although the RV outflow tract is generally larger in endurance athletes than in the general population, the RV inflow appears to be more dilated. It is predominantly the RV outflow that is enlarged in ARVC. Therefore, a dilated RV inflow may more represent physiological conditioning in this setting [78]. As RV dilation is one of the most relevant phenotypic manifestations of ARVC, an increase in exercise-induced RV size may mimic pathological RV remodeling in ARVC. Therefore, differential diagnosis in athletes is sometimes challenging and may lead to misdiagnosis of a rare and life-threatening disease in healthy individuals; it may also lead to underdiagnosis in athletes, putting them at risk of sudden death, especially during competition [96]. Despite the lack of absolute evidence from randomized controlled clinical trials, the detrimental effects of exercise training on ARVC are now well accepted, and recent guidelines recommend avoiding intensive exercise in patients with ARVC [4].

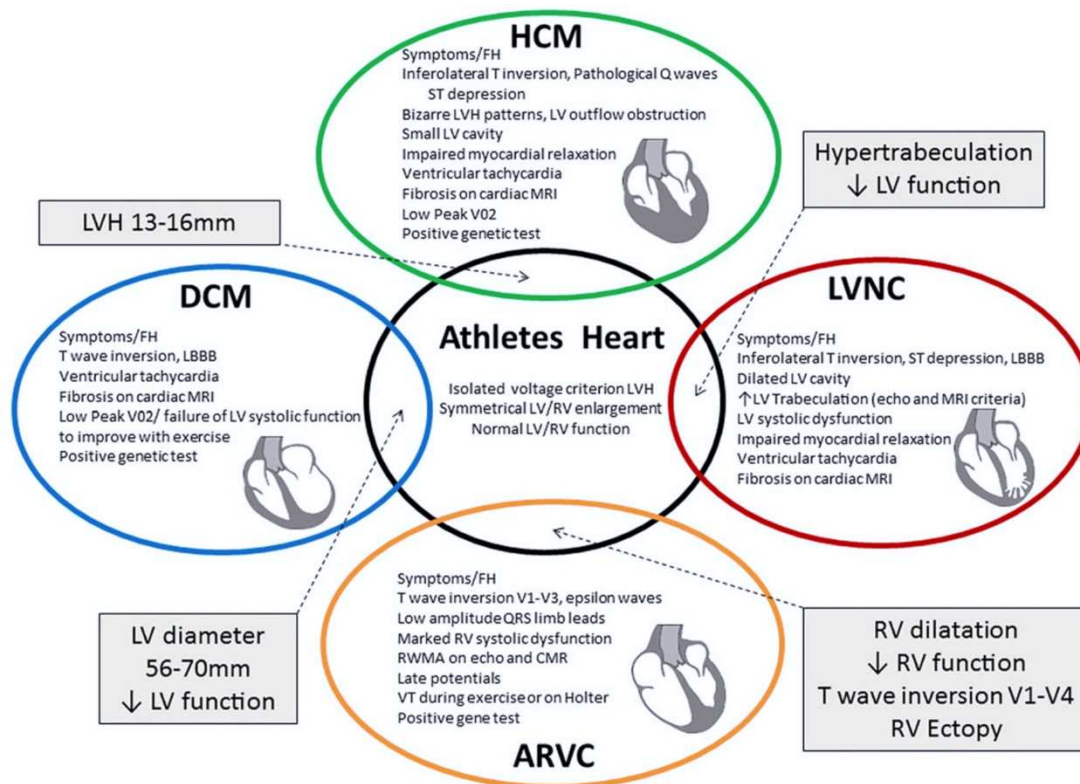


**Figure 9. Schematic representation of the progression of ARVC from desmosomal gene mutation to phenotypic expression and cardiac arrest due to ventricular fibrillation [18]**

### *3.3.4 Isolated left ventricular non-compaction*

LVNC has traditionally been considered a rare cardiomyopathy that can present with a broad spectrum of symptoms at initial presentation, ranging from asymptomatic to ventricular arrhythmias, systematic embolism, and even sudden death in athletes [97]. With advances in diagnostic imaging and the increased use of pre-participation ECG screening, apparent LVNC is recognized in an increasing proportion of athletes [98]. Clinical diagnosis is based on imaging studies showing a bi-layered myocardial structure consisting of an outer (compacted) and an inner (trabeculated or non-compacted) layer, with a ratio of the thickness of non-compacted to compacted layers of over two [79]. However, current diagnostic criteria are non-specific in elite athletes, as a large proportion of young athletes meet the usual criteria for LVNC [99]. Studies revealed that 18.3% of young athletes exhibited a higher prevalence of increased LV trabeculation, and 8.1% of athletes fulfilled conventional criteria for LVNC compared to healthy controls [99]. Therefore, high-risk athletes should have a complete medical history focusing on cardiac symptoms, family history of premature CVD, physical examination, ECG, echocardiogram, and possibly cardiac magnetic resonance imaging with gadolinium contrast. In addition, stress echocardiography, or 24 to 48-hour Holter monitoring, may be required to assess risks in athletes fully [98] (Figure 10).

In some cases, despite extensive investigation, the diagnostic dilemma remains unresolved, and a period of detraining for 6 to 8 weeks is recommended to monitor the regression of the electrical and structural abnormalities and minimize the cardiac risk. Although such an approach seems sensible and pragmatic, persuading competitive athletes to take a break is difficult, as it affects fitness and team selection [41].



**Figure 10. Distinguishing between physiological cardiac changes and cardiomyopathy in athletes.** CMR, cardiac magnetic resonance; FH, family history; LVH, left ventricular hypertrophy; RV, right ventricular; RWMA, regional wall motion abnormalities; VT, ventricular tachycardia [41]

In conclusion, we can say that, in most cases, the adaptations that occur in an athlete's heart are physiological and positive in improving cardiovascular performance. Nevertheless, the tragic events of cardiac death during competition have been reported in some apparent healthy elite athletes. For example, a Cameroonian international footballer, Marc-Vivien Foé, died after suffering a heart attack while playing for the national team against Colombia during the Confederation Cup in 2003; a Spanish footballer, Antonin Puerta, who died from cardiorespiratory arrest during a match in 2007; and a Belgian cyclist, Michael Goolaerts, who suffered cardiac death after SCA during Paris-Roubaix race in 2018. These cases suggest that some underlying CVD may have been subtly missed in the screening of these athletes, leading to tragic events [100]. Thus, athletes might remain at risk for CVD despite the well-documented benefits of regular physical activity on health and cardiac morbidity.





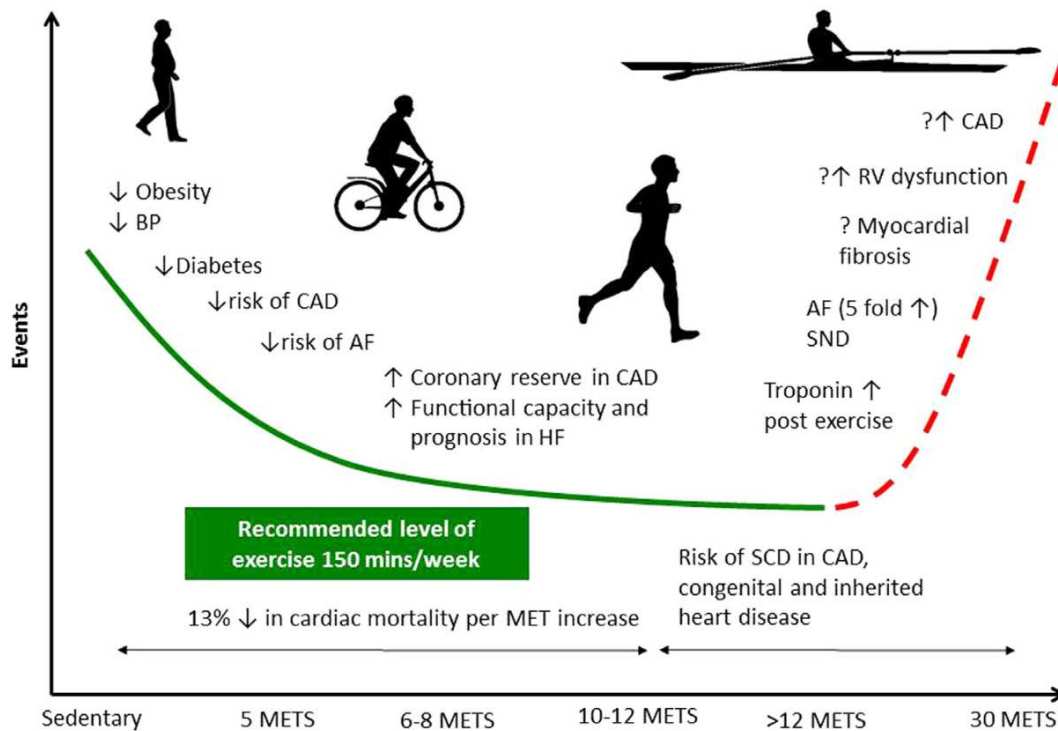


# PART 2. CARDIAC RISKS IN ATHLETES

## 1 The sport paradox

If the health benefits of exercise are undeniable [41], the cardiovascular health benefits of intensive endurance exercise have been questioned by some researchers [101]. Maintaining physical fitness through regular physical activity can help to reduce the frequency of events, as a disproportionate number of events occur in the least physically active individuals undertaking unaccustomed physical activity [102]. In contrast, participation in sports may temporarily increase the risk of adverse cardiac events, particularly in those with certain cardiac conditions. This phenomenon is known as the “sports paradox” [7, 103]. Studies have reported adverse clinical outcomes when endurance athletes are at their extreme upper exercise limits, raising the possibility that high exercise doses may harm the heart [5].

Emerging data revealed a U-shaped relationship between exercise intensity and cardiovascular health; moderate exercise is better than a sedentary lifestyle, but intensive endurance exercise may be deleterious to some individuals [79] (Figure 11). Prospective cohort studies of running participation have shown that increasing the dose of running is likely to achieve significant public health and longevity benefits. Any amount of running, even once a week, is better than none, but higher amounts of running are not necessarily associated with greater mortality benefits; this hypothesis is supported by the Copenhagen City Heart Study research conducted in healthy joggers [104, 105]. Indeed, findings have shown that people who reported being vigorously active every day had a higher CVD risk than those who reported being vigorously active 2 to 3 times a week [106], suggesting that the benefits of an active lifestyle may be at a plateau or even in decline in extreme athletes [107].

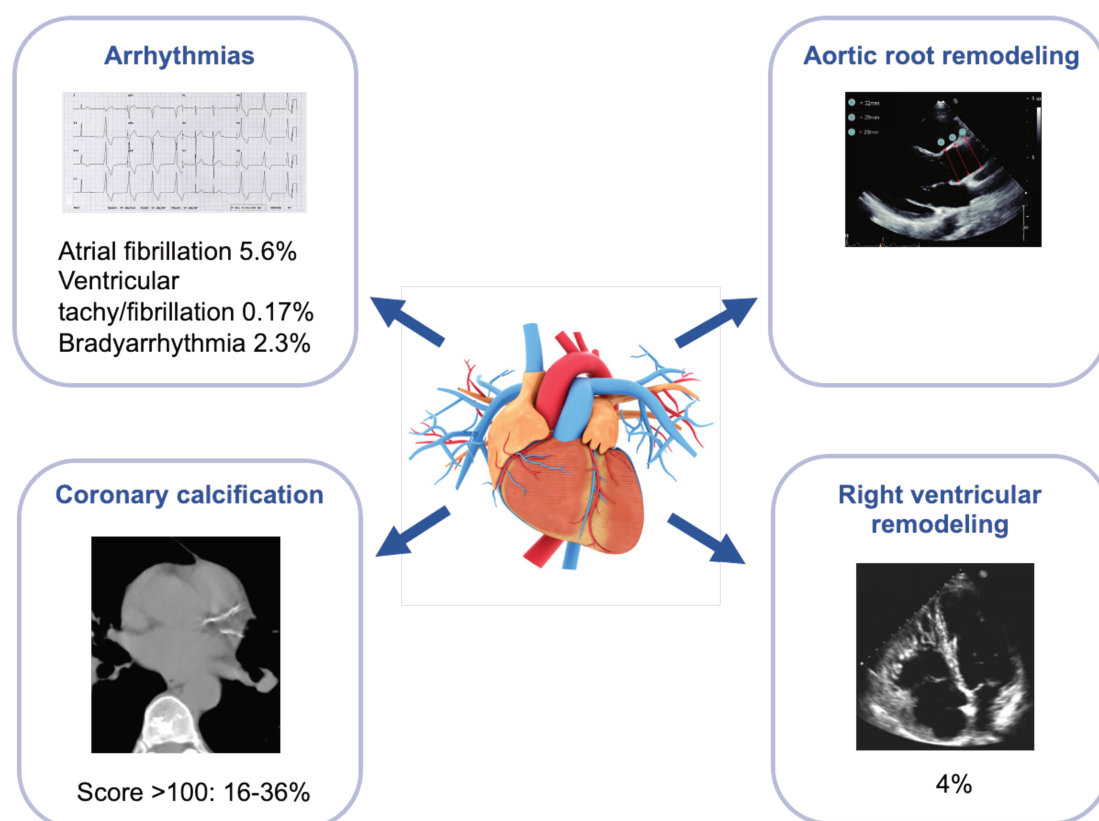


**Figure 11. The U-shaped curve relationship between exercise intensity and cardiovascular health.** CAD, coronary heart disease; BP, blood pressure; AF, atrial fibrillation; SND, sinus node disease; RV, right ventricular [79]

## 2 The cardiovascular risks of prolonged intensive endurance exercise training in athletes

Emerging findings from epidemiological investigations and observational cohort studies of endurance athletes suggest that long-term high-volume and high-intensity exercise training may result in potentially adverse cardiovascular manifestations that may attenuate the health benefits of a physically active lifestyle [108]. Substantial evidence has suggested that strenuous physical activity may not only trigger cardiac events in susceptible individuals but also promote the development of CVD in athletes with no previous cardiovascular abnormalities [6]. Indeed, in healthy, robust Olympic athletes, there is a relatively high prevalence of cardiac abnormalities, including a small

but not negligible proportion of pathological conditions at risk, suggesting that despite the absence of symptoms or astonishing performances, they are not immune to CVD and may be exposed to an unpredictable high risk of SCD during intensive endurance exercise [109]. Accelerated coronary artery calcification (CAC), MF, AF, and even an increased risk of SCD have been reported in those healthy athletes [7] (Figure 12).



**Figure 12. Cardiovascular risk associated with intensive sports [7] (with modifications)**

## 2.1 Coronary artery calcification

CAC is a collection of calcium in the two main arteries of the heart [110]. Increased CAC and atherosclerotic plaques are associated with the amount and intensity of prolonged exercise [111]. Athletes have higher CAC and atherosclerotic plaque than sedentary controls, and the most active athletes have higher CAC and atherosclerotic plaque than less active athletes [112]. Intensive endurance exercise is associated with a

lesser CAC score, whereas very intensive endurance exercise is associated with a significant increase in CAC score [111]. CAC and atherosclerotic plaque are strong predictors of future cardiovascular morbidity and mortality. It is reported that CAC is present in 34% to 71% of athletic cohorts, and 11% to 36% have CAC scores exceeding 100, a value which is often used as a marker of increased risk [113]. The development of CAC is highly correlated with cardiovascular risk variables. For example, CAC is present in 71% of 108 marathon runners, 12% of whom had a history of hypertension and 57% of whom are current (4.6%) or former (52%) smokers [114], compared with 48% of 106 athletes without cardiovascular risk factors [115]. Exercise intensity and sports discipline may also affect the results. Cyclists appeared to have a lower risk of atherosclerotic plaque and CAC than runners and individuals who participated in other sports (e.g., soccer and hockey) [116]. In addition, female marathon runners have minimal CAC, a lower prevalence of coronary plaque, and a smaller calcified plaque size compared to sedentary female volunteers [117]. At the same time, male athletes are more likely to have a CAC score over 300 Agatston units or coronary plaque compared to sedentary male subjects with similar risk profiles [115].

Interestingly, studies showed that the most active population had a lower prevalence of mixed plaques and a higher prevalence of calcified plaques than the least active population. This observation has important clinical implications, as mixed plaques are associated with a higher likelihood of future cardiovascular events than calcified plaques [113]. This indicates that the pathophysiological mechanisms for plaque formation may differ in athletes than in sedentary people. However, advanced CAC appears to contribute to increased myocardial damage and appears to impair outcomes. This suggests that frequent intensive endurance exercise may not protect these athletes from the risk of coronary events [114]. Thus, developing management strategies for athletes with coronary atherosclerosis might be valuable in clinical decision-making and management of athletes with elevated CAC levels [112].

## 2.2 Atrial fibrillation

AF is a heart condition that causes an irregular and usually abnormally fast HR. AF is characterized by a loss of synchronous atrial electrical activity and contraction and is associated with an increased risk of thromboembolism and heart failure, reduced quality of life, and increased risk of mortality [6]. AF is the most prevalent arrhythmia in athletic populations [118]. Recent studies revealed that the risk of AF is higher in athletes than in non-athlete counterparts, with an odds ratio of 5.29 [119], athletes participating in mixed sports and younger athletes are at greater risk [120]. Nevertheless, there is evidence that endurance training produces a variety of cardiac adaptations, including changes in electrophysiological function, which may make endurance-trained athletes more susceptible to AF [121]. It is reported that after 30 years of age, lifelong exercise of more than 1,500 hours and 5 hours of intensive training per week increases the risk of AF [41]. A faster finishing time and a higher number of completed races are associated with a higher risk of AF and arrhythmia [122]. Considering the sex differences in the risk of AF, a 20-year study found that of the 20 athletes with AF, only one occurred in female athletes [123]. Risk factors for AF include all conditions that increase the size or pressure of the left atrium, such as hypertension, left systolic or diastolic heart failure, and stenosis or regurgitation of the mitral valve. Increased parasympathetic and sympathetic tone also increase the risk of AF [121]. The most devastating complication of AF is systemic thromboembolism. Blood clots are formed in the left atrium, particularly in the left atrial appendage, due to the blood stasis produced [124]. An international online survey provides evidence that veteran endurance athletes who develop AF may be at increased risk of developing stroke [125]. About 15% of strokes in the United States are associated with AF. These strokes tend to be large and devastating [124].

### **2.3 Aortic root dilation**

Aortic root dilatation is when the aortic root becomes abnormally dilated, which can lead to life-threatening consequences [126]. It is assumed that the hemodynamic stress of exercise, particularly the pressure overload of resistance training, may lead to aortic remodeling. A meta-analysis of the aortic root size in elite athletes found that the weighted aortic root diameter and size are greater in athletes than in controls [127]. Studies found that aortic root diameters in all segments of the aortic root are significantly greater in elite strength-trained athletes compared to age- and height-matched populations [128]. However, studies of young competitive athletes found that although a significant proportion of young athletes had aortic root dilatation, there is no correlation with arterial stiffness. This might suggest that the aortic root dilation in young athletes does not alter the pulse waveform and pulse reflection. Thus, there is no increased cardiovascular risk in these subjects [129].

Nevertheless, weightlifting-related acute aortic coarctation appears to be a reality, and there is growing evidence that intensive endurance exercise is associated with this catastrophic aortic event. Moderate aortic dilatation predisposes to exercise-induced aortic coarctation [130]. An aortic root dimension exceeding 40 mm in highly conditioned male athletes and exceeding 34 mm in female athletes is uncommon. It is most likely an expression of a pathological condition mandating close clinical surveillance [131]. Approximately 1% of males in apparently healthy athletes have aortic enlargement above the upper threshold. Athletes with aortic enlargement may experience a further dimensional increase in midlife, leading to clinically relevant aortic dilation. Occasionally, the dilatation may be severe enough to warrant consideration of surgical treatment. Therefore, serial clinical evaluation is recommended in athletes when the aortic root exceeds sex-specific upper limits [132].

## 2.4 Myocardial fibrosis

MF results from cardiac interstitial dilation due to the deposition of extracellular matrix proteins [133]. It is common in the late stages of several heart diseases and is a predictive factor of SCD [134]. MF reduces ventricular compliance, leading to heart failure with preserved EF, atrial enlargement, AF, and systolic heart failure [40]. Cardiac magnetic resonance combined with late gadolinium enhancement found a non-negligible increased risk of MF in athletes compared with healthy sedentary controls [135]. Studies of marathon runners who had completed at least five marathon races showed that intense marathon training led to an unexpectedly high rate of MF in these athletes [136]. Compared with zero cases in age-matched veteran controls and young athletes, an unexpectedly high prevalence (50%) of MF is observed in healthy, asymptomatic, lifelong veteran athletes [137]. Lifelong veteran endurance athletes with MF have larger cardiac dimensions and normal global cardiac function. Fibrotic areas may show co-localized regional cardiac dysfunction as evidenced by affected cardiac strain [138]. MF in athletes has been identified predominantly in the intraventricular septum and at the RV septal junction. Although the clinical consequences of MF in athletes are mainly unknown, evidence is mounting that genetic predisposition, silent myocarditis, pulmonary artery pressure overload, and prolonged exercise-induced repetitive micro-injury are contributors to the development of MF [134]. Researchers suggest that the presence of MF requires appropriate clinical follow-up to assess the possibility of future adverse cardiovascular outcomes [108]. This evidence indicates that prolonged intensive endurance exercise training can be detrimental to cardiovascular health [40]. Intensive endurance exercise places a great deal of hemodynamic stress on the human heart, sometimes resulting in profound cardiac remodeling. These changes may potentially become maladaptive and increase the risk of several CVDs, such as the increased risk of CAC, AF, and MF. All of the maladaptation are strongly associated with the risk of SCD [7].

### **3 The sudden cardiac death in athletes**

#### **3.1 Sports-related sudden cardiac death in athletes**

Sports-related sudden death is the most tragic event in athletes. The tragic episode usually receives significant media coverage and generates intense discussion in the lay and medical communities [139]. Sudden death from a cardiac cause known as SCD [140], which is the leading medical cause (accounting for more than 90%) of the death in athletes [2]. An unexpected collapse due to a cardiac cause in which cardiopulmonary resuscitation or an automated external defibrillator (AED) shock is administered to athletes who survived is defined as sudden cardiac arrest (SCA) [140]. In some studies, intensive endurance exercise has been described as a trigger for SCD in athletes. Consistently, habitual active individuals had a much lower risk of sudden death associated with an episode of intensive endurance exercise than those who exercised less than once a week; however, in all analyses, the risk remained significantly elevated during and after intensive endurance exercise in the most active people [141]. Although many studies have attempted to unravel the mysteries of SCD in athletes, much remains to be determined. Consequently, exploring the risk and etiology of SCD in athletes may lead to the development of monitoring strategies for the cardiac health of athletes and the prevention of tragic events on the sports field.

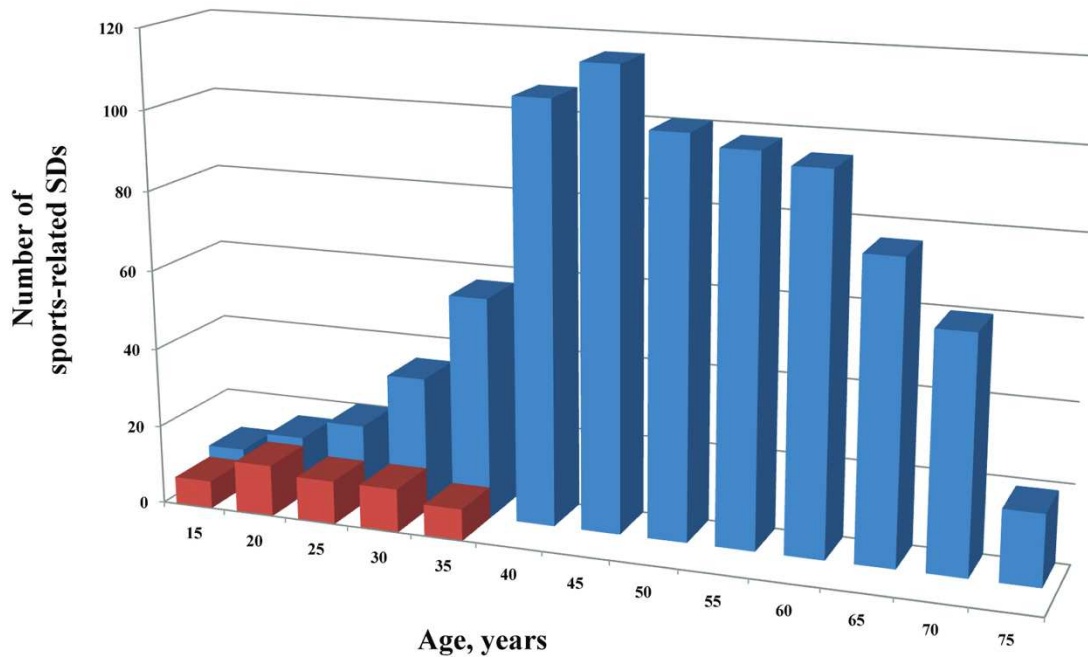
#### **3.2 Incidence of sudden cardiac death in athletes**

Despite the highly visible and considerable public and media attention of SCD in athletes, the exact incidence of SCD in those populations remains controversial. Estimates vary dramatically depending on the definition of an athlete, the methods of data collection, the lack of compulsory reporting in many countries, the inclusion or



exclusion of cases based on the time and place of the event, the inclusion of all cardiac events (including survivors) versus only those resulting in death, the population studied, and the calculation of the denominator [142].

In terms of the incidence of SCD in athletes, it is reported that competitive athletes have a higher risk of sports-related sudden death than noncompetitive sports participants [143] (Figure 13). Studies from a nationwide registry of sport-related SCD in Germany showed that the overall incidence in athletes ranges from 1.2/100,000 athlete-years (AY) to 1.5/100,000 AY [144]. Case series studies of adult participants in US triathlon races from 1985 to 2016 showed a relatively high incidence of death and cardiac arrest among triathletes at 1.74/100,000 AY. The risk increased substantially with age, much higher in those aged 60 and older, where the incidence peaked at 18.6/100,000 AY [14]. Young athletes are individuals 12 to 35 years of age who are engaged in regular exercise training and participating in official athletic competitions [145]. It is estimated that the overall incidence of SCD occurring among young athletes is approximately 1/50,000 AY [146]. Middle-aged and older athletes ( $\geq 35$  years of age) have a significantly higher risk of SCD than younger athletes [147]. A nationwide study in Denmark from 2007 to 2009 showed that in competitive athletes, the incidence in athletes aged 12 to 35 years is 0.47/100,000 AY; in those aged 36 to 49 years, it is 6.64/100,000 AY; in recreational athletes aged 12 to 35 years, the incidence is 0.43/100,000 AY, whereas in those recreational athletes aged 36 to 49 years, the incidence is 2.95/100,000 AY [148]. An extensive registry over 27 years (1980-2006) in 38 different sports found that the absolute number of SCD in young athletes is slightly higher than previous estimates but still relatively low, at a rate of less than 100 per year [149].



**Figure 13. Distribution by age of sports-related sudden death in the overall population (blue) and among young competitive athletes (red) [143]**

Moreover, the incidence of SCD in athletes is affected by sex. Indeed, SCD has been found to occur significantly more often in males than in females. According to the data from United States triathlon participants, nearly 85% of victims are males, and only 15% are females [14]. In Germany, the SCD is 0.2/100,000 AY in female participants compared with 3.6/100,000 AY in males [150]. Estimates in United States marathon runners showed that the incidence of SCA in male athletes is higher than in females (0.90/100,000 AY vs. 0.16/100,000 AY), the incidence of SCD that result from cardiac arrest is also high in the former ones (0.62/100,000 AY vs. 0.14/100,000 AY) [151]. Case reports of SCD in young athletes showed a female/male ratio of 1/9 [2]. A 20-year study of NCAA athletes from 2002 to 2022 found that the incidence in male athletes is 1/43,348 AY and in female athletes is 1/164,504 [152]. Similarly, a 4-year prospective study in young competitive athletes revealed that the incidence rate of SCD is lower in females than in males (1/203,786 AY vs. 1/43,932 AY) [153]. It is reported that the risk of sudden death in females is 5 to 33 times less common than in males, and

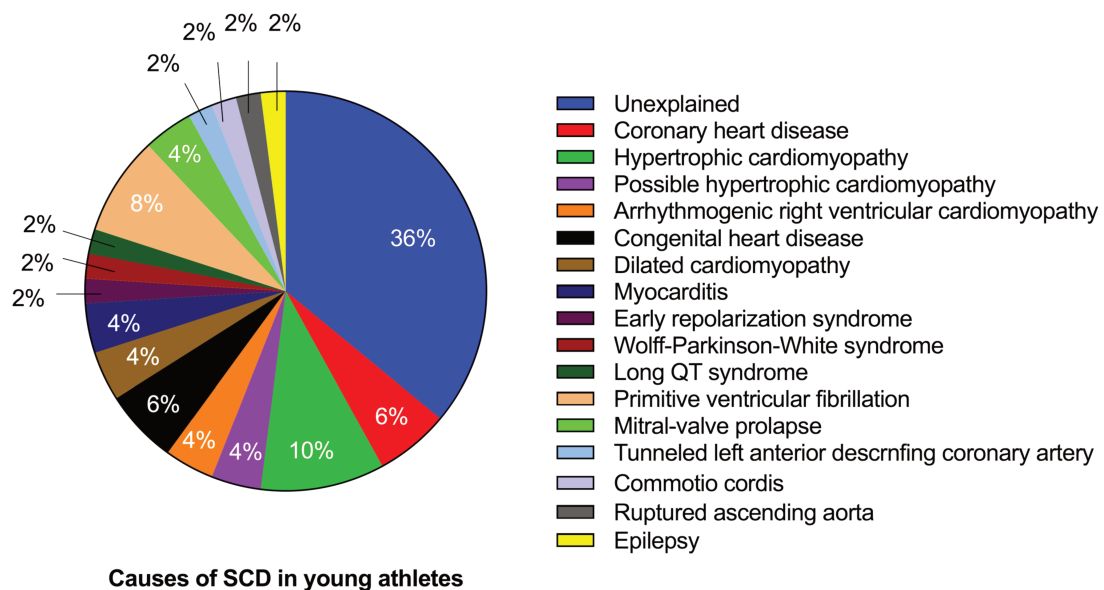
the sex differences persist despite a rapid increase in female participation in sports [8]. Studies of young competitive athletes in the United States showed that only 11% of SCD occurred in female athletes, despite the proportion of CVD reported in females has increased over time, reaching 12% between the years 2000 and 2006 [149], the incidence is still lower in females than in males. There is agreement among studies that women are less prone to sports-related SCD than men, but knowledge about the specific cause and precipitating circumstances is sparse [154]. Elucidating the role of female sex in the lower incidence of cardiac events may have implications for underlying mechanisms and, consequently, preventing SCD [8].

Overall, the estimated incidence of SCD in athletes is related to age, sex, and sports disciplines. Typically, old age, male athletes and basketball players have a higher incidence of SCD. The predisposing factors need to be identified to better understand the reasons for the higher incidence of SCD un athletes.

### **3.3 Etiology of sudden cardiac death in athletes**

The etiologies of SCD in athletes include various clinical conditions [155]. In young athletes, congenital heart disease predominates in this age group. The cardiac autopsy may reveal structural abnormalities, but the heart may be structurally normal in this setting, suggesting sudden arrhythmic death syndrome, with primary arrhythmia syndrome being the most likely underlying etiology [156]. HCM is the most common congenital heart disease and has been reported to cause SCD in approximately 2% to 50% of athletes [16, 157]. Some studies from the United States indicated that HCM is the most common cardiac cause in young athletes (36%) [149], and coronary artery anomalies are the second common cause of SCD in those populations, accounting for 17% of deaths [149]. Nevertheless, the attribution of SCD in young competitive athletes

has changed in the last two decades and is highly variable according to the methodology used [156]. Recent studies reported that the predominant cause in athletes older than 35 years is coronary artery disease (CAD) (76%), while in athletes younger than 35 years is sudden unexpected death (22%) [158]. Substantial studies showed that the most common autopsy finding in young people with SCD is a structurally normal heart [159]. SCD in young athletes is mainly due to clinically silent cardiomyopathies or primary electrical disorders (morphologically normal heart) [17]. A meta-analysis of the etiology of SCD in young athletes shows that HCM-caused SCD is only 10.3%, while SCD with structurally normal hearts at death is more common at 26.7% [11]. Similarly, a study of Italian competitive athletes showed that of the 49 cases of SCD (44 males, 5 females), 25% are associated with a structurally normal heart, and only one death (2%) is attributed to HCM [160]. In Denmark, in young athletes, 27% of SCD is caused by a structurally normal heart, while HCM accounted for only 7% of cases [161]. A prospective and comprehensive national survey throughout France found that in young competitive athletes, sudden unexplained death accounts for 36%, followed by HCM (10%), primitive ventricular fibrillation (8%), and CAD (6%) [143] (Figure 14).



**Figure 14. Causes of SCD in young competitive athletes [143]**

### 3.4 Objectives

Identifying a triggering event is complex because several factors increase the risk of cardiac death [162]. Most studies revealed that sudden unexplained death with a structurally normal heart is the leading cause of sudden death in young athletes. The absence of structural heart disease is a critical factor in the management and prognosis of athletes. Still, the best diagnostic work-up strategy to rule out structural heart disease has not been established [51]. As described previously, there are sex differences in the incidence of SCD in athletes. Despite the methodological challenges, studies have consistently reported a lower risk of SCD in female athletes than in males [8]. SCD is 5 to 33 times less likely to occur in female athletes than males, and the sex differences persist despite a rapid increase in female sports participation. However, little is known about the specific causes [154]. Unraveling the role of sex in the incidence of SCD may reveal the underlying mechanisms and, consequently, contribute to the prevention of SCD in athletes.

Existing knowledge on the incidence of SCD has been determined mainly based on studies conducted under specific circumstances using specific methodologies (such as the data are collected based on the national registry records or the assurance claims), often ignoring sex differences or considering only one sex (predominantly males) [9-12]. Although Harmon et al. [142] summarized the incidence in both sexes via a state-of-the-art review, new studies are not included. Moreover, the estimated incidence, potential causes, and pathogenic mechanisms of SCD in athletes have yet to be effectively addressed and thoroughly and systematically evaluated. Therefore, the study aimed to assess the sex differences in the incidence of SCA/D and etiologies in competitive athletes by systematic review and meta-analysis. Only studies with data on male and female athletes were included to avoid systematic bias in data aggregation.



## **4 Study 1: Sex differences in the incidence of sudden cardiac arrest/death in competitive athletes: a systematic review and meta-analysis**

### **4.1 Materials and methods**

This systematic review and meta-analysis were conducted under the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and recommendations [163]. They were registered in the International Prospective Register of Systematic Reviews (PROSPERO) (registration ID: CRD42023432022). Patient consent and ethics committee approval are not required.

#### *4.1.1 Search strategy*

Two investigators (LXL and FS) independently performed the systematic database searches. PubMed, Embase, Scopus, SPORTDiscus, and Cochrane Library were searched. The heading terms “sudden cardiac death” or (OR) “sudden cardiac arrest” combined with (AND) “athletes” were applied to identify the possible studies concerning SCA or/and SCD in athletes in published articles up to December 2023. Additionally, reference lists of eligible articles, relevant review articles, and meta-analysis reviews were manually searched to identify relevant articles further. Any disagreements were resolved by discussion with a third author (SLDL). The search strategies are available in the Appendix.

#### *4.1.2 Selection criteria*

The full text of identified articles was systematically assessed for eligibility after screening the title and abstract. The inclusion criteria for eligible studies in the meta-analysis were: (1) written in the English language; (2) published in peer-reviewed journals; (3) performed using prospective or retrospective cohort design; (4) observers included both sexes (a study was included when it reported events in both sexes but had 0 cases in one sex (usually in females)); (5) reported data including the incidence of SCA or SCD. Moreover, incidents that were not directly presented were generated based on existing data from the study; the rates were recalculated when the incidence was reported in a form other than per 100,000 AY; reported causes that were unrelated to cardiac disease (such as trauma or heat stroke) were excluded, and the incidence was recalculated using the actual cases. The formula follows the incidence rate per 100,000 AY = (number of events / total number of AY) × 100,000. When multiple reports were published on one dataset [14-16, 152, 153, 160, 164-173], studies with more extended observation periods or more data were selected [14, 16, 152, 153, 171, 173].

Studies were excluded when they (1) lacked sex-specific information, (2) had an absence of precise data to acquire the incidence, and (3) had duplicated observational years of the populations; supplementary materials were obtained when data were missing. Studies were discarded from subsequent analyses if there were missing data.

#### *4.1.3 Data collection process*

Data collection was separately conducted by two authors (LXL and FS). The following information was extracted: (1) study characteristics (first author's name, publication year, study country, study design, follow-up year, methods of case identification, and sample size of male and female participants); (2) participants'



information (onset age, type of events, and number of events in both sexes); and (3) clinical findings if available (e.g., autopsy reports).

#### *4.1.4 Quality assessment of eligible studies*

The Newcastle-Ottawa Quality Assessment scale [174] was used to assess the quality of each study included in the meta-analysis. The semi-quantitative principle of the star system was used in this scale. It consists of three elements with a total of 8 items (the item “comparability of cohorts based on design or analysis” was split into two sub-items, specifically “study controls for sex factor” and “study controls for other factors (e.g., type of sport and age)”). Each numbered item can be awarded a maximum of 1 star; thus, the total score was 9. Studies scored 0 to 3, 4 to 6, and 7 to 9 were determined as low, medium, and high quality, respectively [175].

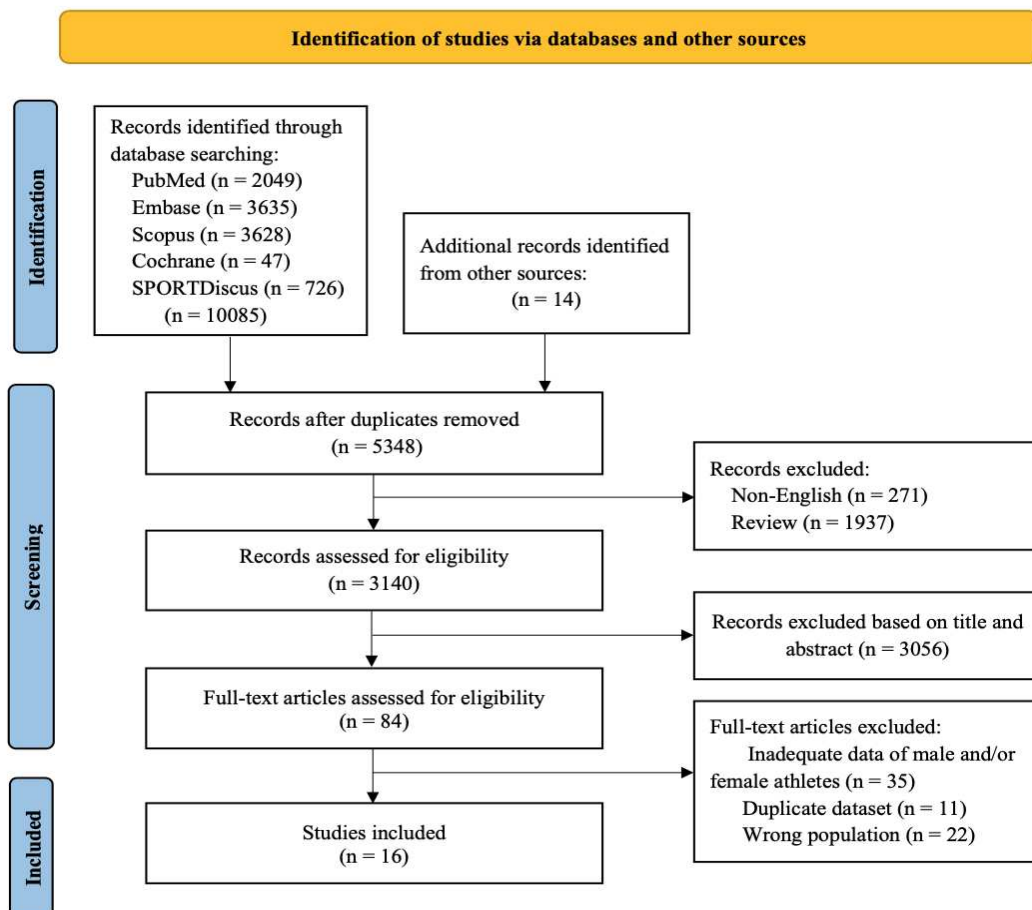
#### *4.1.5 Data synthesis and analysis*

The incidence of SCA/D with corresponding 95% confidence intervals (95% CI) was calculated for both sexes. The incidence rate ratio (IRR) was used to compare the risk of SCA/D between sexes. STATA (version 15.1; STATA Corp., USA) software was used for data analysis. A random-effects inverse-variance model was used for data pooling.  $I^2$  statistics assess heterogeneity. The magnitude of heterogeneity for  $I^2$  values less than 30%, 30% to 70%, and over 70% represent low, medium, and high heterogeneity, respectively [10].

## 4.2 Results

### 4.2.1 Study selection

A total of 10099 potential articles were identified from the combined systematic literature screen and other sources. After removing the duplicates, 5264 articles were excluded due to non-English language studies (271), review articles (1937), and unrelated titles and abstracts (3056). Eighty-four studies were assessed for eligibility based on their full texts. Sixty-eight studies were excluded due to insufficient data of sex-specific information, duplicate datasets, and the wrong population. Sixteen studies were included in the meta-analysis (Figure 15).



**Figure 15. PRISMA flow diagram of the search process for studies examining the incidence of sudden cardiac arrest/death in male and female athletes.** PRISMA, Preferred Reporting Item for Systematic Review and Meta-analysis

#### *4.2.2 Study characteristics*

Sixteen prospective or retrospective cohort studies were included, representing a combined sample of 268,729,566 participants per AY, including 154,928,991 AY males (57.65%) and 113,800,575 AY females (42.35%). Of the 1797 observed cases of SCA/D, 1578 occurred in male athletes (87.81%) and 219 in female athletes (12.19%). Age ranges from adolescent to adult. The follow-up duration ranged from 2 years [176] to 32 years [14, 177]. The observational years covered from 1979 [16] to 2022 [152]. Six studies assessed the events of both SCA and SCD [140, 151, 153, 178-180], while eight studies examined only SCD [16, 152, 161, 173, 177, 181-183], and two studies examined only SCA [14, 176]. In four studies, SCA/D occurs only in male athletes, with 0 events in female athletes [161, 173, 180, 183].

Eleven studies covered various sports [16, 140, 152, 153, 161, 173, 176, 177, 179, 181, 182], while five studies focused on a single type of sport, including running (marathon and half-marathon) [151, 178, 180], triathlon [14], and soccer [183]. The countries studied were the United States (62.5%) [14, 140, 151-153, 173, 176, 177, 182], Switzerland [181], Italy [16], France [180], Denmark [161], United Kingdom [183], and Japan [179]. Characteristics of the studies are summarized in Table 2.

#### *4.2.3 Quality assessment of the eligible studies*

All the eligible papers obtained at least have seven stars. Six studies scored 7 (37.50%), seven studies scored 8 (43.75%), and three scored 9 (18.75%). All these papers have high methodological quality (Table 3).

**Table 2. Characteristics of eligible studies**

Study (year, country)	Following year (y)	Study design	Methods of case identification	Sports category	Events	Occurred number	Onset age (y)	Person-years of population	Incidence per 100,000 athlete years (95% CI)
Bradley J et al. (2023, United States)	20y (2002-2022)	Retrospective and prospective	Database records, NCAA insurance claims, autopsy and media reports, and interviews	Multiple	SCD	M=119 F=24	20	M=5158412 F=3948096	M: 2.31 (1.89, 2.72) F: 0.61 (0.36, 0.85)
Maron BJ et al. (2016, United States)	32y (1980-2011)	Prospective	Combined National registry and databases records	Multiple	SCD	M=747 F=95	17.7±4.8	M=90903177 F=74802240	M: 0.82 (0.76, 0.88) F: 0.13 (0.10, 0.15)
Kim JH et al. (2012, United States)	10y (2000-2010)	Prospective and retrospective	Combined medical and postmortem records, and interview	Marathon and half-marathon	SCA/D	M=51 F=8	42±13	M=5666667 F=5189333	M: 0.90 (0.65, 1.15) F: 0.15 (0.05, 0.26)
Corrado D et al. (2003, Italy)	21y (1979-1999)	Prospective	Combined microscopic, histologic examination and immunohistochemistry	Multiple	SCD	M=47 F=5	23.1±7	M=1904490 F=464100	M: 2.47 (1.76, 3.17) F: 1.08 (0.13, 2.02)
Harmon KG et al. (2016, United States)	6y (2007-2013)	Prospective	Combined database registry and autopsy reports	Multiple	SCA/D	M=92 F=12	14-18	M=4124525 F=2850115	M: 2.23 (1.77, 2.69) F: 0.42 (0.18, 0.66)
Harris KM et al. (2017, United States)	32y (1985-2016)	Retrospective and prospective	Death registry records	Triathlon	SCA	M=9 F=3	41.8±8	M=967358 F=742199	M: 0.93 (0.32, 1.54) F: 0.40 (0.00, 0.86)
Holst AG et al. (2010, Denmark)	7y (2000-2006)	Retrospective	Death certificates report, cause of death registry, and autopsy records	Multiple	SCD	M=15 F=0	15-35	M=904830 F=334663	M: 1.66 (0.82, 2.50) F: 0.00 (0.00, 0.00)
Gerardin D et al. (2016, France)	7y (2006-2012)	Prospective	RACE Paris registry database	Running	SCA/D	M=12 F=0	43±10	M=2866528 F=716632	M: 0.42 (0.18, 0.66) F: 0.00 (0.00, 0.00)
Maron BJ et al. (2013, United States)	26y (1986-2011)	Prospective and retrospective	Database records, news media, Internet search, national registry, and personal interview	Multiple	SCD	M=11 F=0	12-18	M=2494226 F=1945935	M: 0.44 (0.18, 0.70) F: 0.00 (0.00, 0.00)
Malhotra A et al. (2018, United Kingdom)	21y (1996-2016)	Retrospective	Mandatory cardiovascular screening, and death reports	Soccer	SCD	M=8 F=0	15-17	M=112433 F=5918	M: 7.12 (2.18, 12.05) F: 0.00 (0.00, 0.00)
Peterson DF et al. (2021, United States)	4y (2014-2018)	Prospective	Combined autopsy and medical reports, and death certificates	Multiple	SCA/D	M=277 F=54	11-29	M=8849024 F=6568862	M: 3.13 (2.76, 3.50) F: 0.82 (0.60, 1.04)
Roberts WO et al. (2013, United States)	28y (1982-2009)	Retrospective	Combined race records, newspaper accounts, press, autopsy reports and interview	Marathon	SCA/D	M=13 F=1	28-60	M=379863 F=168230	M: 3.42 (1.56, 5.28) F: 0.59 (0.00, 1.76)

Suzuki-Yamanaka M et al. (2022, Japan)	10y (2009-2018)	Retrospective	Insurance claim	Multiple	SCA/D	M=51 F=4	15-18	M=9607259 F=4419729	M: 0.53 (0.39, 0.68) F: 0.09 (0.00, 0.18)
Toresdahl BG et al. (2014, United States)	2y (2009-2011)	Prospective	Combined National Registry for automated external defibrillators use, and interview	Multiple	SCA	M=16 F=2	13-19	M=924538 F=652828	M: 1.73 (0.88, 2.58) F: 0.31 (0.00, 0.73)
Van Camp SP et al. (1995, United States)	11y (1983-1993)	Retrospective	Combined autopsy records, death certificates, and medical reports	Multiple	SCD	M=92 F=8	13-24	M=19550662 F=10492917	M: 0.47 (0.37, 0.57) F: 0.08 (0.02, 0.13)
Asatryan B et al. (2017, Switzerland)	12y (1999-2010)	Retrospective	Forensic autopsy reports	Multiple	SCD	M=18 F=3	10-39	M=514999 F=498778	M: 3.50 (1.88, 5.11) F: 0.60 (0.00, 1.28)

M, male; F, female; SCA, sudden cardiac arrest; SCD, sudden cardiac death; NCAA, National Collegiate Athletic Association.

**Table 3. Results of quality assessment using the Newcastle-Ottawa Scale for observational cohort studies**

Study (year, country)	Selection				Comparability		Outcome			Scores
	Representative of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow-up long enough for outcome to occur	Adequate of follow up of cohorts		
Bradley J et al. (2023, United States)	☆	☆	☆	☆	☆	☆	☆	☆	☆	9
Maron BJ et al. (2016, United States)	☆	☆	☆	☆	☆	☆	☆	☆	☆	9
Kim JK et al. (2012, United States)	☆	☆	☆	☆	☆	☆	☆	☆	☆	9
Asatryan B et al. (2017, Switzerland)	☆	☆	☆		☆	☆	☆	☆	☆	8
Corrado D et al. (2003, Italy)	☆	☆	☆	☆	☆		☆	☆	☆	8
Harmon KG et al. (2016, United States)	☆	☆	☆	☆	☆		☆	☆	☆	8
Harris KM et al. (2017, United States)	☆	☆	☆		☆	☆	☆	☆	☆	8
Holst AG et al. (2010, Denmark)	☆	☆	☆		☆	☆	☆	☆	☆	8
Gerardin D et al. (2016, France)	☆	☆	☆		☆	☆	☆	☆	☆	8
Maron BJ et al. (2013, United States)	☆	☆	☆		☆	☆	☆	☆	☆	8
Malhotra A et al. (2018, United Kingdom)	☆	☆	☆		☆		☆	☆	☆	7
Peterson DF et al. (2021, United States)	☆	☆	☆	☆	☆		☆		☆	7
Roberts WO et al. (2013, United States)	☆	☆	☆		☆		☆	☆	☆	7
Suzuki-Yamanaka M et al. (2022, Japan)	☆	☆	☆		☆		☆	☆	☆	7
Toresdahl BG et al. (2014, United States)	☆	☆	☆	☆	☆		☆		☆	7
Van Camp SP et al. (1995, United States)	☆	☆	☆		☆		☆	☆	☆	7

One star represents one score. The follow-up year  $\geq 5$  years gets one score. Studies that address other factors that contribute to sex differences, such as sports, ethics, etiology, etc., with fewer than two are considered not to have taken other factors into account and are not scored.

#### 4.2.4 Synthesis of results

The initial random effects pooled analysis of the sixteen studies found that the incidence of SCA/D in male athletes varied from 0.42 to 7.12 per 100,000 AY. In contrast, the incidence in female athletes varied from 0.00 to 1.08 per 100,000 AY. The estimated incidence in male athletes was 1.42/100,000 AY (95% CI: [0.97, 2.09]), and in female athletes was 0.32/100,000 AY (95% CI: [0.17, 0.59]). There was high heterogeneity among the studies (male:  $I^2=97.8\%$ ; female:  $I^2=93.6\%$ ) (Figure 16-A). The IRR between the sexes was 5.55 (95% CI: [4.59, 6.70]), with low heterogeneity ( $I^2=0.0\%$ ) (Figure 16-B).

#### 4.2.5 Subgroup analysis

##### 4.2.5.1 Synthesis of the studies observed age $\leq 35$ years

Subgroup data synthesis of the eleven studies [16, 140, 152, 153, 161, 173, 176, 177, 179, 182, 183] in which the age of the subjects  $\leq 35$  years showed that the estimated incidence in male athletes was 1.46/100,000 AY (95% CI: [0.91, 2.34]), while in female athletes was 0.30/100,000 AY (95% CI: [0.14, 0.66]). There was high heterogeneity among the studies (male:  $I^2=98.4\%$ ; female:  $I^2=95.8\%$ ) (Figure 17-A). The IRR between sexes in athletes aged  $\leq 35$  years was 5.47 (95% CI: [4.42, 6.76]), and the heterogeneity was low ( $I^2=0.0\%$ ) (Figure 17-B).

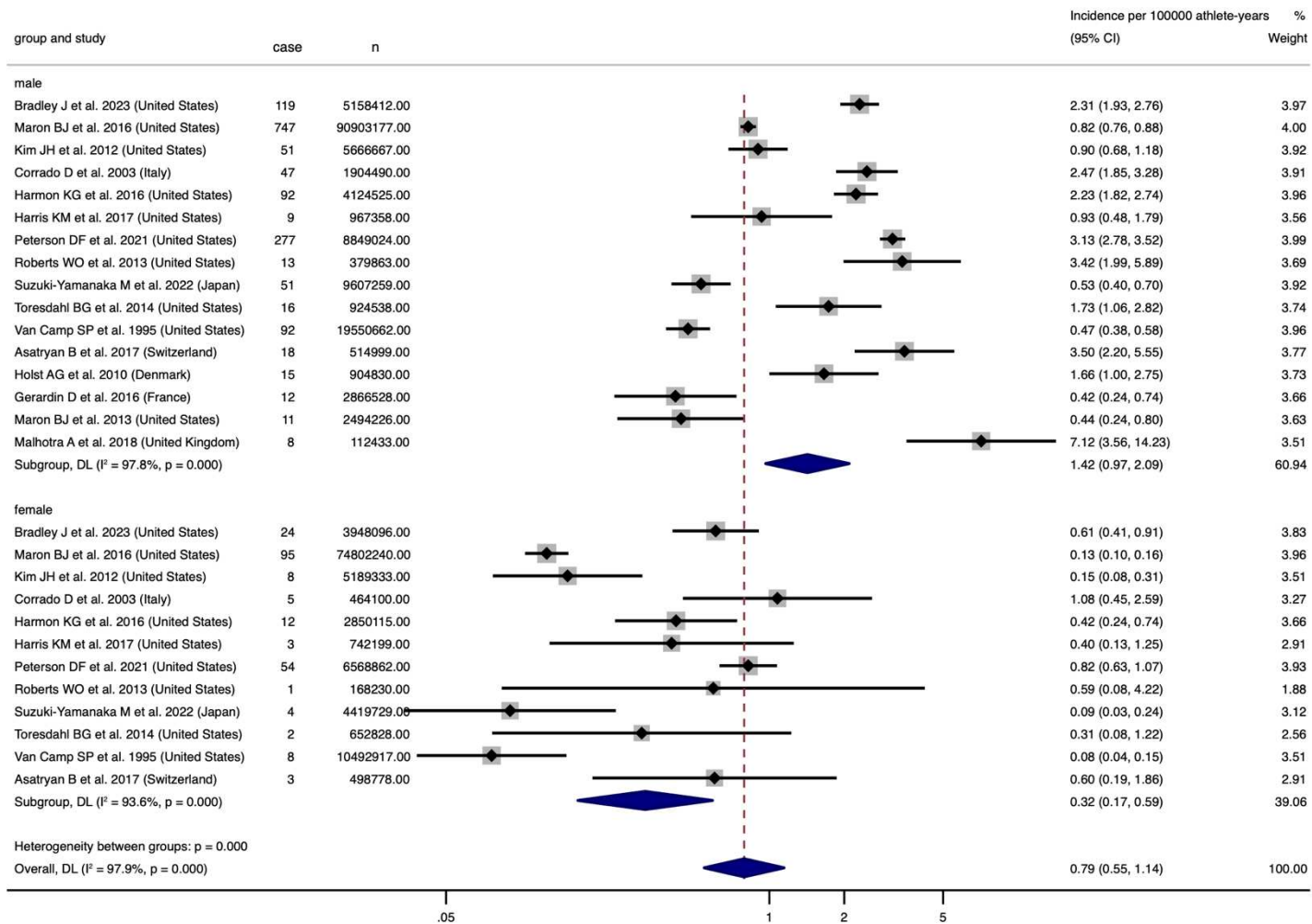


Figure 16-A. Incidence of SCA/D in male and female athletes



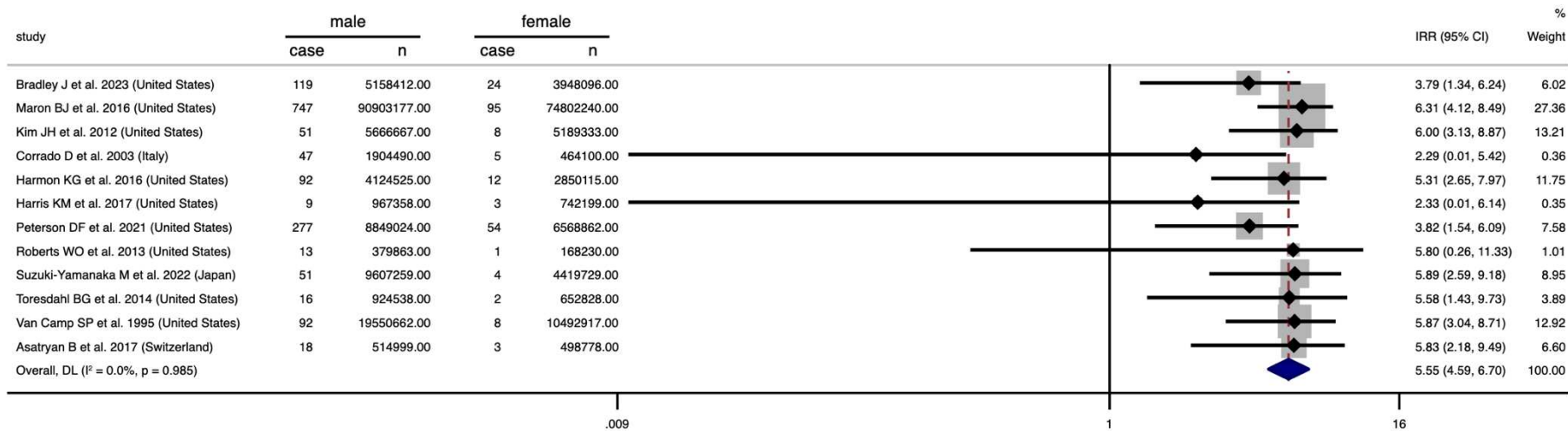


Figure 16-B. IRR in the incidence of male and female athletes

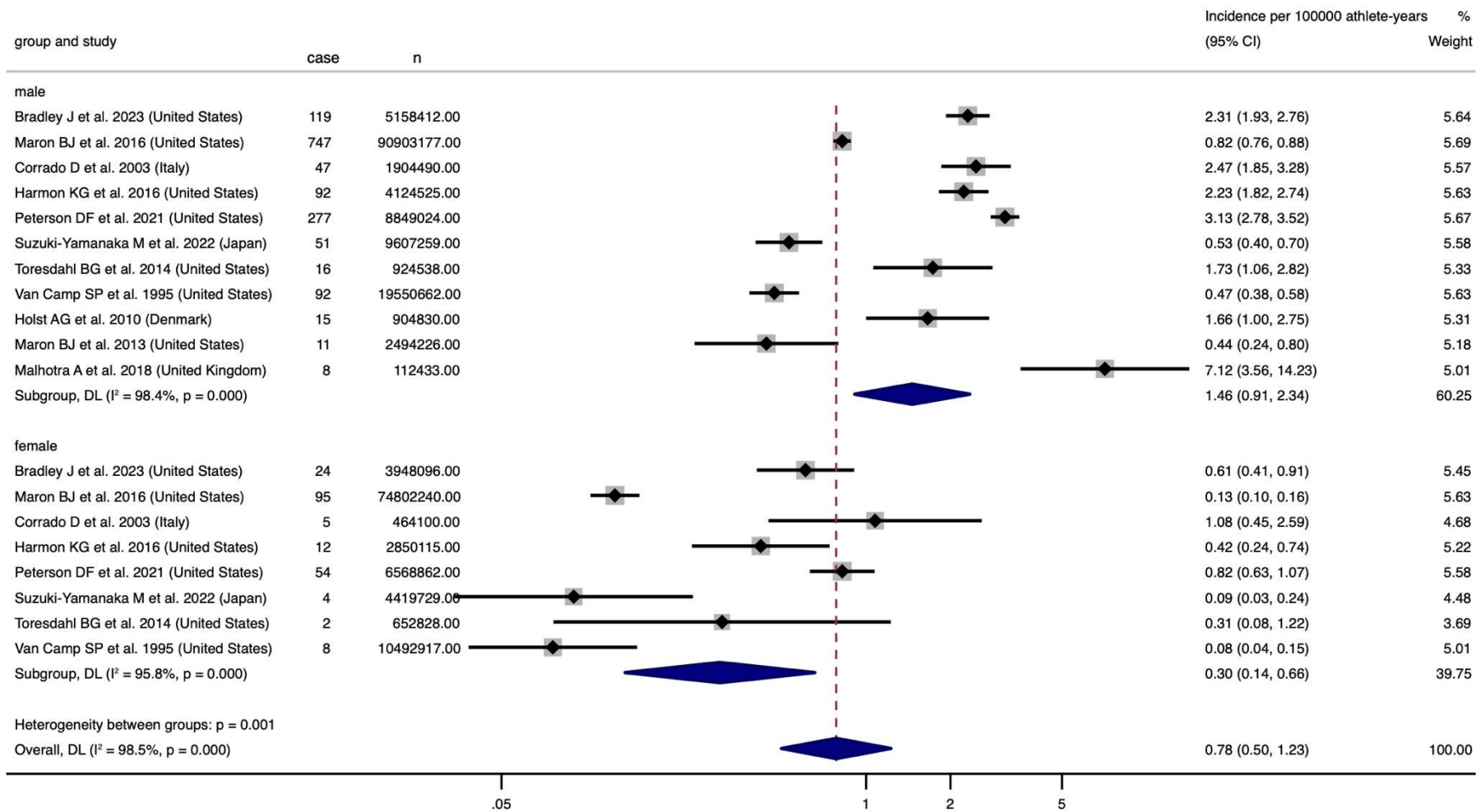


Figure 17-A. Incidence of SCA/D in male and female athletes aged  $\leq 35$  years

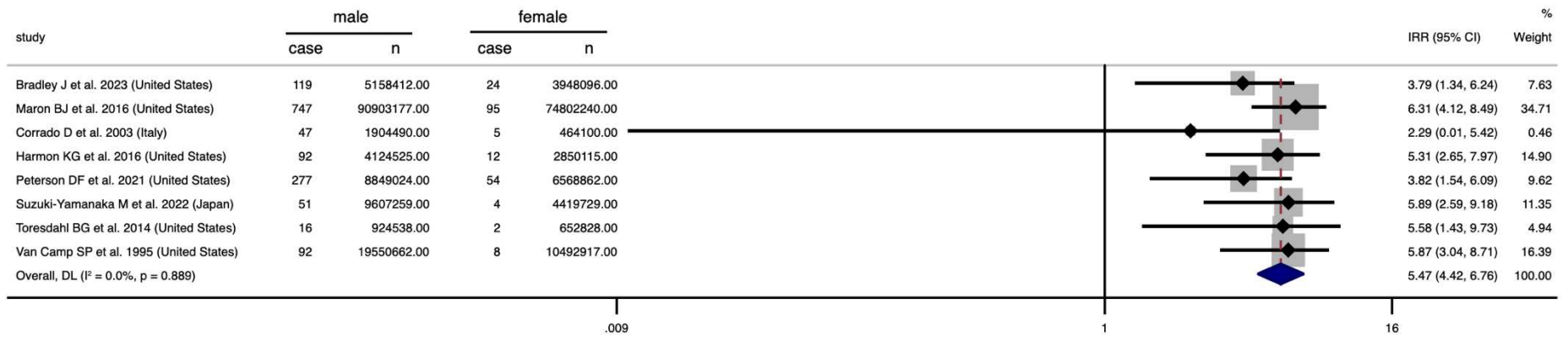


Figure 17-B. IRR in incidence of male and female athletes ≤ 35 years of age

#### 4.2.5.2 Synthesis of the data observed periods after the year 2000

Subgroup data analysis of the eight studies [140, 151-153, 161, 176, 179, 180] in which the observed periods after the year 2000 revealed that the incidence in males was 1.35/100,000 (95% CI: [0.84, 2.16]) and in females was 0.34/100,000 (95% CI: [0.18, 0.63]). The heterogeneity was high (males:  $I^2=96.7\%$ ; females:  $I^2=86.3\%$ ) (Figure 18-A). The IRR in studies of observed periods including all years was 6.02 (95% CI: [4.59, 7.90]), while the IRR in observed periods after the year 2000 was 5.13 (95% CI: [3.94, 6.67]), with low heterogeneity ( $I^2=0.0\%$ ) (Figure 18-B).

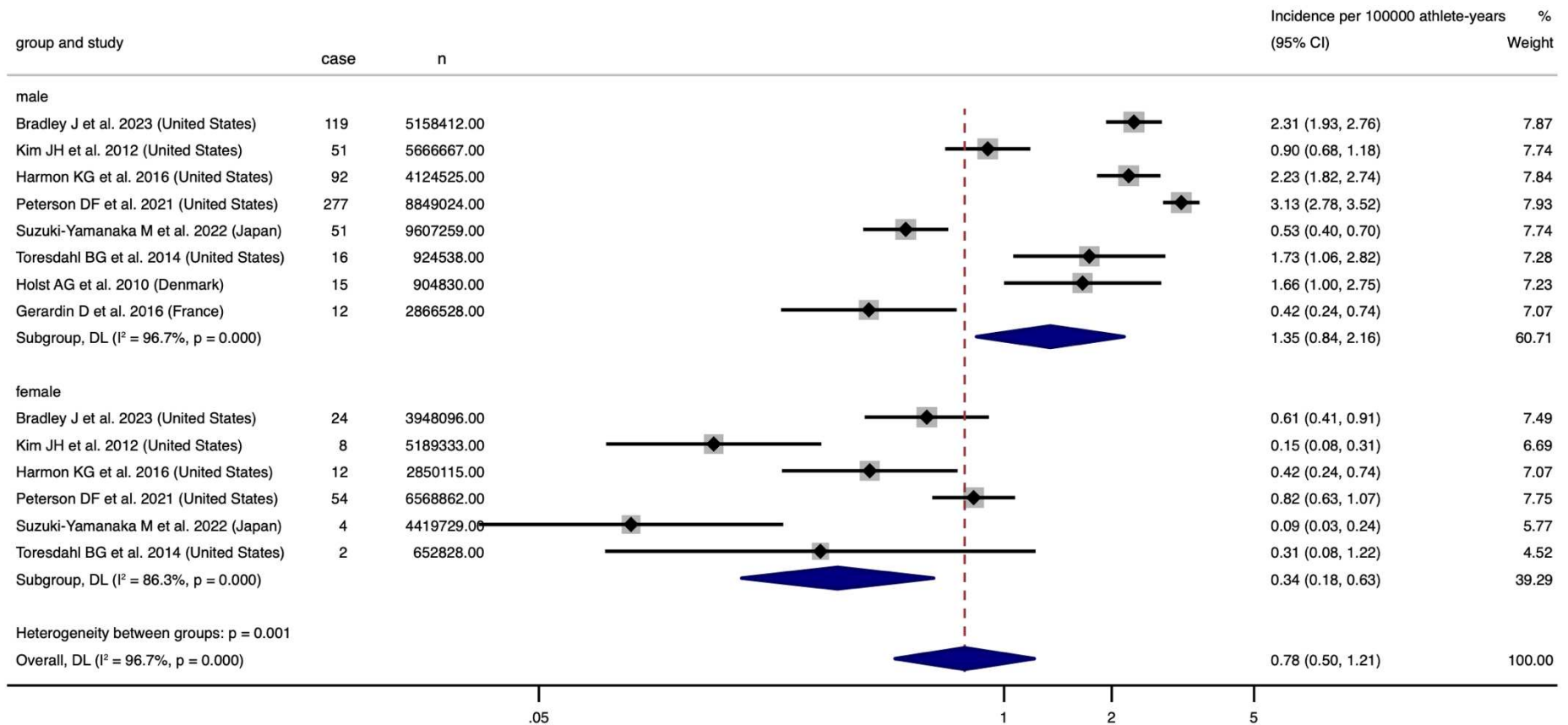
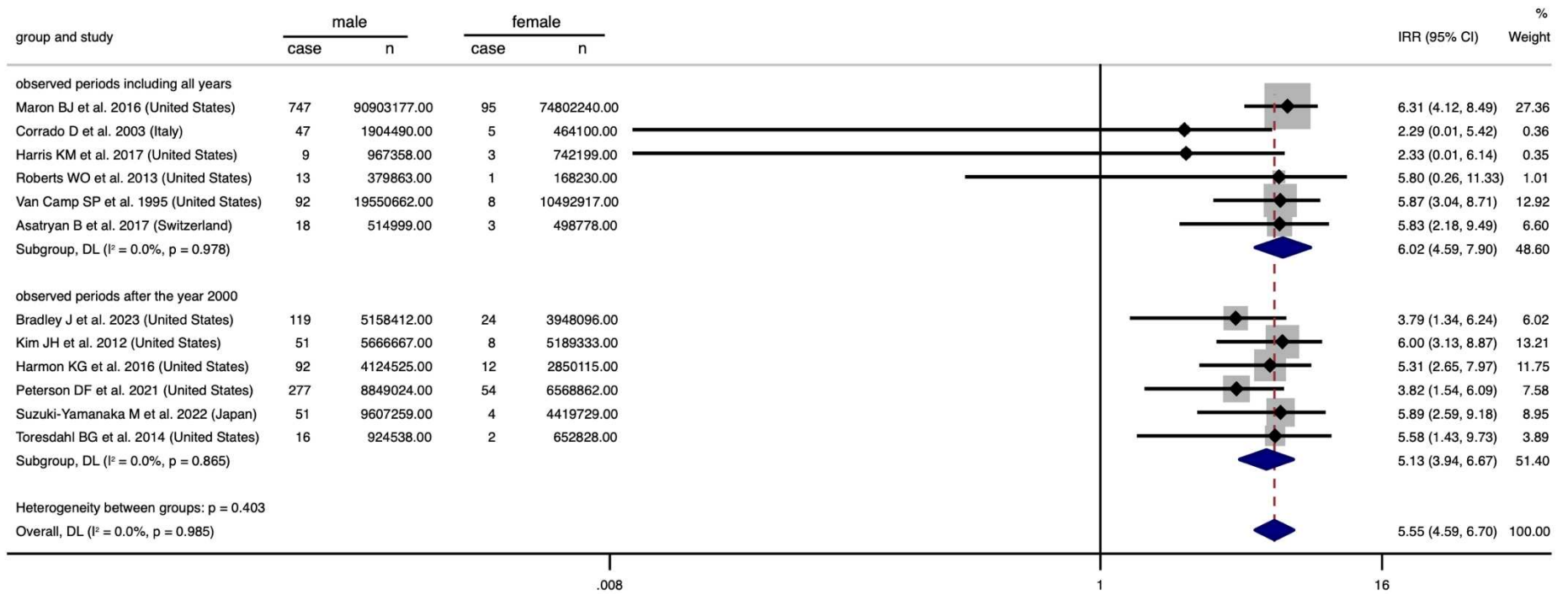


Figure 18-A. Incidence of SCA/D in male and female athletes observed after the year 2000



**Figure 18-B. IRR in the incidence of SCA/D in male and female athletes observed after the year 2000 and observed including the years before and after the year 2000**

#### 4.2.6 Etiologies of SCA/D

Of the sixteen studies, the etiologies of SCA/D were reported in 1119 cases. The availability in male athletes was 63.62% (1004/1578), and 52.51% (115/219) in female athletes. The most common cause of SCA/D in male athletes was HCM (453/1004, [45.12%]), followed by a congenital coronary anomaly (161/1004, [16.04%]), and coronary artery disease (CAD) (103/1004, [10.26%]). The most common cause in females was a congenital coronary anomaly (38/115, [33.04%]), followed by HCM (16/115, [13.91%]), and ARVC (14/115, [12.17%]) (Figure 19).

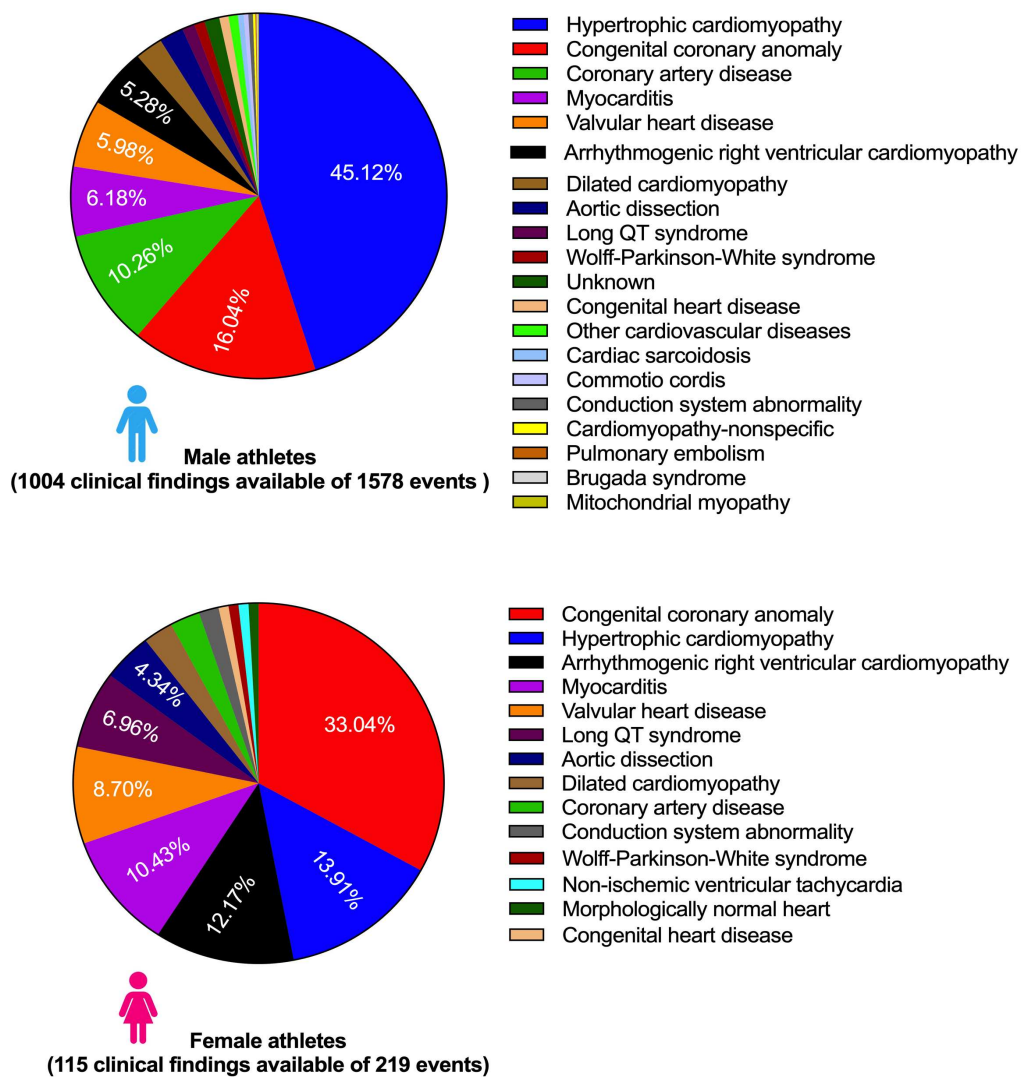


Figure 19. Clinical findings of the cause of SCA/D in male and female athletes

### 4.3 Discussion

This meta-analysis assessed the sex differences in the incidence of SCA/D in competitive athletes. Previous studies have explored the incidence of SCA or SCD in athletes under specific circumstances, but they often ignore the sex differences. Of the sixteen studies included in the present meta-analysis, we found that (1) the incidence in female athletes was 5.55 times lower than in males; (2) considering the athletes  $\leq 35$  years of age, the incidence in females was 5.47 times lower than in male; (3) the IRR in studies of observed periods after the year 2000 was 5.13 (95% CI: [3.94, 6.67]), while the observed periods including all years was 6.02 (95% CI: [4.59, 7.90]); (4) the cause of SCA/D were different as regards to the sex: in male athletes the most common cause was HCM, while in females was congenital coronary anomaly.

#### *4.3.1 Sex differences in the incidence of SCA/D*

Women represent an increasing proportion of sports participants. However, there was still a lack of original data on the incidence of SCA/D in female athletes [184]. Consistent with previous studies [8], the present study found that female athletes had a lower estimated incidence of SCA/D than males. The estimated incidence in male athletes was 1.42/100000 AY (95% CI: [0.97, 2.09]), and in female athletes was 0.32/100,000 AY (95% CI: [0.17, 0.59]), which was approximately six times lower in females than in males. Considering the athletes  $\leq 35$  years of age, the estimated incidence in males was 1.46/100,000 AY (95% CI: [0.91, 2.34]), while in females was 0.30/100,000 AY (95% CI: [0.14, 0.66]), which was 5.47 times lower in females than in males. Studies of young Swedish orienteers between 1979 and 1992 found that of the 16 cases of unexpected SCD, 15 were male athletes, and only one was female athletes [185]; a large regional registry in the United Kingdom found that of the 748



cases of SCD in people who exercise regularly, only 13% were women, demonstrating a lower incidence of SCD in female athletes [154]. Despite the similar subject characteristics, the average annual incidence from European registries of SCA in females was 0.19/100,000, more than ten times lower than in male athletes [184]. A prospective study conducted in France between 2005 and 2010 found that the estimated incidence rate in female athletes was only 0.51/100,000 AY (95% CI: [0.34, 0.68]), while in male athletes reached 10.1/100,000 AY (95% CI: [9.3, 10.8]) [186]. One explanation frequently provided was the lower prevalence of females in the athlete population. Nevertheless, in the prospective Race Paris registry on cardiac events in long-distance running, collecting data on 1,000,000 participants over ten years, only one life-threatening cardiac event occurred in a female athlete. However, females accounted for 22% of all runners [187].

In subgroup analysis on the studies covering the periods after the year 2000, the estimated incidence in males was 1.35/100,000 AY (95% CI: [0.84, 2.16]), and in females was 0.34/100,000 AY (95% CI: [0.18, 0.63]), the IRR was 5.13 (95% CI: [3.94, 6.67]), while the IRR in studies in the observed periods including all years was 6.02 (95% CI: [4.59, 7.90]). A previous publication reported that the incidence of SCD increased at a rate of 6% per year from 1994 to 2006 compared with 1980 to 1993 and that the proportion of all deaths in females has increased over time [149]. Another study showed that the incidence of sports-related SCA remained relatively stable over time, with a decrease in SCD only due to a significant improvement in on-field resuscitation (essential life support and public AED use) [188]. However, in this meta-analysis, there were several challenges in comparing incidence rates across trials since the estimates vary depending on the age of the athletes, the source of the sampling population, the sports activity, and the definition of sudden death [139].

#### *4.3.2 Sex differences in etiologies of SCA/D*

In male athletes, the most common cause of SCA/D was HCM (45.12%), followed by a congenital coronary anomaly (16.04%), CAD (10.26%), myocarditis (6.2%), valvular heart disease (5.98%) and ARVC (5.28%). This is consistent with the literature on a population of young athletes [150, 189]. In female athletes, CAD was considerably less common, and the other etiologies were encountered in a different order of frequency. Congenital coronary anomaly was the most frequent (33.04%), followed by HCM (13.91%), ARVC (12.17%), myocarditis (10.43%), and valvular heart disease (8.7%). The difference in the prevalence of CAD was the same as in the general non-athlete population. Women generally develop CAD at an older age, which is linked to the hormonal protection provided by Estrogen in pre-menopausal women [190]. It was demonstrated that CAD mortality was up to 5 times higher in middle-aged men than women [191]. As regards the other etiologies encountered, there was no difference in the prevalence of HCM as regards sex; nevertheless, male sex was a risk factor for SCA/D in HCM [192]. The explanations were still unclear; some authors have suggested that the greater intensity of training and participation in the competition in male subjects may partly explain the difference. Nevertheless, this explanation was not convincing in our population of athletes [193]. Females have significant cardiac remodeling compared to sedentary controls but rarely reach absolute LV dimensions or LV wall thickness that overlap with DCM or HCM [194]. Whether this might have any incidence on the risk of SCD was still unclear. Therefore, identifying the protective mechanism of the cardiovascular system in female athletes may help find a switch to mitigate the risk of SCD in athletes.

### *4.3.3 Limitations*

The narrow inclusion criteria (each study included involving data relevant to both sexes) reduced the risk of bias. However, this was a limitation at the same time. Several studies of SCA/D in athletes had large samples and data but were excluded due to a lack of information on sex-specific information [150]. This reduced the amount of data included in the meta-analysis and weakened the evidence base. In addition, data synthesis revealed high heterogeneity within groups, suggesting some moderators influenced sex-specific variability. However, due to the limited number of studies included in this meta-analysis, only sub-group analysis of athletes aged  $\leq 35$  years and the observational periods after the year 2000 were conducted, and it is not possible to examine factors such as ethnicity, type of sports, and sports levels in sex differences.

### *4.3.4 Perspectives*

Since in most patients, SCA occurs without warning symptoms [195], cardiovascular pre-participation screening attempts to identify pre-existing cardiac abnormalities, ensuring optimal management and thereby reducing the potential for adverse events and sports-related fatalities [18]. The incidence of SCD in young competitive athletes has substantially decreased in the Veneto region of Italy since implementing a systematic screening [20]. However, the low incidence in female athletes challenges the cost-effectiveness of screening in female athletes [196]. A better comprehension of the sex differences in the rate of SCA/D might help us to perform a better pre-participation screening strategy in both male and female athletes [8].

#### **4.4 Conclusion**

The meta-analysis provides evidence for the sex differences in the incidence of SCA/D in competitive athletes. The incidence of SCA/D in female athletes was approximately six times lower than that in males (the heterogeneity was low). Identifying the reasons for the differences may have implications for targeting the prevention of SCD. More attention should be paid to athletes, especially male athletes, who invest in intensive endurance exercise practice.

#### **4.5 Summary and perspectives**

Traditionally, female sports participation has lagged far behind that of males. In the last half-decade, however, female athletes have increased by more than 1000% [8]. Faced with this increase in the sports participation of female athletes, we would expect an increase in cardiac events in this population, as in the male population. Although substantial studies have reported SCD in male participants, the underlying pathogenesis remains unclear. Therefore, the surge in female athletes provides an opportunity to better understand the mechanisms of sudden death in athletes. This meta-analysis provided evidence for sex differences in the incidence of SCA/D in competitive athletes. The study found that the incidence of SCA/D in females was approximately six times lower than in males, and the etiology of SCA/D varied by sex. In male athletes, the most common cause was HCM, whereas in females, it was congenital coronary artery anomalies. This reminds us that investigating sex differences may have implications for targeting the prevention of SCD in athletes. Increased attention should be directed to athletes during intensive endurance exercise, especially male athletes.

In addition to the sex profile of athletes in the context of SCD research, sports disciplines also play a role in the occurrence of SCD during exercise. It has been reported that endurance athletes were more susceptible to CVD [41]. Indeed, a previous retrospective study on 30 Olympic sports found that when compared to other sports, endurance athletes, especially short-distance triathletes, have a relatively unexpectedly high prevalence of cardiac events [13]. This study caught our attention because triathlon has become an increasingly popular sport worldwide in recent decades [14]. The United States Triathlon reported that more than 460,000 participants participated in more than 3,200 sanctioned adult events in 2015 [14]. Over the years, the number of race-related deaths has raised concerns about the safety of athletes in this competitive sport [15]. Therefore, to investigate the cardiac risk in triathletes, the specific objective of the second study was to determine the prevalence of CVD in elite triathletes according to sex, sports disciplines, and formats.



## **5 Study 2: The prevalence of cardiovascular disease in elite triathletes: an Internet-based retrospective study**

### **5.1 Materials and methods**

#### *5.1.1 Study methods*

The present retrospective study investigated the prevalence of CVD in elite athletes of eleven triathlon disciplines identified on the website between 2006 and 2019 via a previously published methodology [13]. We chose this methodology because one of the major challenges of studying the outcomes of elite athletes was that no single center was involved in the follow-up of all these athletes from all over the world. In our connected world, and given the medical transparency currently imposed in top-level sports, most injuries or medical problems in athletes were immediately reported in social, sports, and popular media, and all this information was accessible on the Internet. This methodology may underestimate the exact number of cardiac events, but the underreported risk affects all the sports disciplines similarly.

#### *5.1.2 Triathlon sport disciplines and selection of athletes*

To identify the cardiac diseases of elite triathletes, we focused on eleven triathlon sport disciplines, which were involved in three race formats, including (1) short/medium distance (International Triathlon Union (ITU) Aquathlon World Championships, ITU Duathlon World Championships, ITU Triathlon World Championships, ITU Cross Triathlon World Championships, ITU Winter Triathlon World Championships); (2) long distance (ITU Long Distance Duathlon World

Championships, ITU Long Distance Triathlon World Championships, Ironman 70.3 World Championships); (3) and ultra-long distance (Ironman World Championships, Norseman Xtreme World Championships, Ötillö Swimrun World Championships) (Table 4). No events were organized for the ITU Long Distance Duathlon World Championships in 2009 and 2010, the ITU Winter Triathlon World Championships in 2015 and 2017, and Ötillö Swimrun World Championships of elite females from 2006 to 2008; the first ITU Cross Triathlon World Championship was held in 2011; therefore, no events were organized from 2006 to 2010. Each discipline's yearly internationally top 10 athletes of both sexes were involved from the World Triathlon (<https://www.triathlon.org/>), Wikipedia (<https://www.wikipedia.org/>), and other relevant websites.

All the included athletes ranked in the yearly top 10 at least once during the interest period. The inclusion year of the athlete was defined by the first year of being in the top 10 between 2006 and 2019; the exclusion year was defined by the last year of being in the top 10 between 2006 and 2019. Athletes who made multiple entries in the top 10 of the same triathlon sport discipline during the observation period were registered only once; athletes who made multiple entries in the top 10 of the different disciplines were recorded several times. Of the 1545 elite triathletes registered, 169 (male 88, female 81) athletes participated in at least two types of triathlon sport disciplines. Therefore, the overall population of the athletes included was 1329 (male 639, female 690).



**Table 4. Triathlon sport disciplines of the World Championships studied**

<b>Format</b>	<b>Triathlon event</b>	<b>Sport disciplines and official distances</b>		
<b>Short/medium distance</b>	ITU Aquathlon World Championships	2.5km run	1km swim	2.5km run
	ITU Duathlon World Championships	10km run	40km cycle	5km run
	ITU Triathlon World Championships	1.5 km swim	40 km cycle	10 km run
	ITU Cross Triathlon World Championships	1km swim	20-30km mountain bike	6-10km trial run
	ITU Winter Triathlon World Championships	6.2km run	11.8km mountain bike	10km ski
<b>Long distance</b>	ITU Long Distance Duathlon World Championships	10 km run	150 km cycle	30 km run
	ITU Long Distance Triathlon World Championships	4 km swim	120 km cycle	30 km run
	Ironman 70.3 World Championships	1.9 km swim	90 km cycle	21.1 km run
<b>Ultra-long distance</b>	Ironman World Championships	3.86 km swim	180.25 km cycle	42.2 km run
	Norseman Xtreme World Championships	3.8 km swim	180 km cycle	42 km run
	ÖTILLÖ SWIMRUN World Championships	10 km swim	\	65 km run

### *5.1.3 Identification of cardiovascular disease*

After establishing the list of triathletes, the media reported CVD was identified on the website via the Google search engine. Multiple searches were conducted on the same athletes using different terms. More precisely, the name of each athlete was correlated along with the keywords related to their sport (e.g., “triathlon” for triathletes) and the keywords related to cardiovascular diseases (“heart/cardiovascular problem /disorder/disease,” “heart/cardiac injury,” “cardiac arrest/death,”) in Google searches. Subsequently, a cardiologist further confirmed the results based on the information available. The athletes who died or stopped their sports careers due to sports-related cardiac abnormalities were identified as having severe outcomes.

Considering that the data are publicly available on the Internet, based on public declarations of the athletes, and that the athletes in this study were anonymous, thus it was unnecessary to ask for the subjects’ consent. The research protocols were approved by the local ethics comity of Rennes (n°21.64).

### *5.1.4 Statistical analysis*

The prevalence of CVD was calculated according to the sex, sports disciplines, and formats of the athletes included. Except for the isolated bicuspid aortic valve (BAV), all the other conditions observed in the present study theoretically have the potential for instantaneous outbreaks when stimulated by a high amount of exercise. Therefore, the hazard function was then calculated. Statistical differences were compared using Fisher’s exact tests or  $\chi^2$  tests. Data were expressed as mean  $\pm$  SD. Significance levels were defined by  $p < 0.05$ . Statistical analyses were conducted with Python (version 3.10).

## 5.2 Results

### *5.2.1 The prevalence of cardiovascular disease identified in the whole population*

The mean age of 1329 athletes at inclusion was  $30\pm 6$  years, and at exclusion, it was  $31\pm 6$  years. Twelve cardiac diseases were observed (prevalence 0.90%). The mean age of their occurrence was  $29\pm 7$  years (range 17 to 39) (Table 5). Cardiac abnormalities include SCD (n=1), “arrhythmia” (n=1), AF (n=2), supraventricular tachycardia (n=2), aortic root dilation (n=1), right ventricular outflow tachycardia (n=1), BAV with aortic dilation (n=2), and isolated BAV (n=2). Of the whole population, one death occurred from cardiac arrest (0.08%). Among the 11 athletes who survived, 4 of them stopped their sports practice (36.36%), while 7 continued their athletic training and competitions (63.64%), sometimes after an interventional cardiology procedure/ablation (Table 6).

**Table 5. Characteristics and cardiovascular disease of athletes observed**

Distance	Triathlon event	Male (n = 748)		Female (n = 797)		Overall (n = 1545*)	
		Screened athletes (cases of CVD)	Age at inclusion/exclusion	Screened athletes (cases of CVD)	Age at inclusion/exclusion	Screened athletes (cases of CVD)	Age at inclusion/exclusion
<b>Short/medium</b>	ITU Aquathlon World Championships	90 (1)	26 ± 6 / 27 ± 6	88 (1)	24 ± 5 / 25 ± 5	178 (2)	25 ± 6 / 26 ± 6
	ITU Duathlon World Championships	77 (0)	29 ± 5 / 30 ± 6	72 (0)	28 ± 5 / 30 ± 6	149 (0)	29 ± 5 / 30 ± 6
<b>Long</b>	ITU Triathlon World Championships	55 (3)	27 ± 4 / 29 ± 3	63 (3)	27 ± 4 / 29 ± 4	118 (6)	27 ± 4 / 29 ± 4
	ITU Cross Triathlon World Championships	47 (1)	30 ± 5 / 31 ± 6	52 (0)	31 ± 6 / 32 ± 6	99 (1)	30 ± 5 / 32 ± 6
	ITU Winter Triathlon World Championships	51 (0)	29 ± 5 / 31 ± 6	61 (0)	30 ± 7 / 31 ± 7	112 (0)	29 ± 6 / 31 ± 7
	ITU Long Distance Duathlon World Championships	66 (0)	31 ± 5 / 32 ± 5	57 (0)	33 ± 5 / 35 ± 5	123 (0)	32 ± 5 / 34 ± 5
	ITU Long Distance Triathlon World Championships	91 (1)	30 ± 5 / 31 ± 5	99 (1)	31 ± 4 / 32 ± 4	190 (2)	31 ± 4 / 32 ± 5
<b>Ultra-long</b>	Ironman 70.3 World Championships	71 (0)	30 ± 4 / 32 ± 5	72 (0)	30 ± 4 / 32 ± 4	143 (0)	30 ± 4 / 32 ± 5
	Ironman World Championships	57 (1)	32 ± 3 / 34 ± 3	62 (0)	34 ± 4 / 35 ± 4	119 (1)	32 ± 3 / 34 ± 4
	Norseman Xtreme World Championships	96 (0)	32 ± 8 / 33 ± 7	108 (0)	34 ± 9 / 34 ± 9	204 (0)	33 ± 8 / 34 ± 8
	ÖTILLÖ SWIMRUN World Championships	47 (0)	32 ± 7 / 34 ± 8	64 (0)	36 ± 8 / 36 ± 8	111 (0)	34 ± 8 / 35 ± 8

The number marked with “\*” means that some athletes were accounted for more than one time since those athletes engaged in at least two sports disciplines during the observational years. Age at inclusion means the age of athletes when they succeeded in Top 10 for the first time between 2006 and 2019; age at exclusion means the age of athletes when they succeeded in Top 10 for the last time between 2006 and 2019.

**Table 6. The descriptions of the reported cardiovascular diseases in athletes**

<b>Name</b>	<b>Sex</b>	<b>Country</b>	<b>Cardiac diseases</b>	<b>Descriptions</b>	<b>Timetable (Succeed in top10 during the WCS and the years of success)</b>	<b>Sports distance</b>	<b>Types of disciplines participated</b>	<b>Outcomes (Stopped or not)</b>
①	M	France	Sudden cardiac death	“During a swimming training session, he suffered from a heart rhythm disorder followed by cardio-ventilatory arrest which resulted in him being plunged in an artificial coma. Several months later, he died following cardiac arrest.”	1) ITU triathlon WCS, 2011-2013 2) Suffered heart rhythm disorder, 2014	Short	1	Y (death)
②	F	New Zealand	Right ventricular outflow tract tachycardia	“Her heart condition, diagnosed as right ventricular outflow tract tachycardia.”	1) First noticed the problem, 2011 2) ITU Aquathlon WCS, 2012 3) ITU triathlon WCS, 2014	Short★	2	N
③	F	New Zealand	Supraventricular tachycardia	“Her heart rate would be as high as 230 beats per minutes. This arrhythmia problem became worse as her career progressed in triathlon and was particularly bothersome in the season and especially during the run portions of the races. With careful evaluation, she was found to have a supraventricular tachycardia and underwent a successful ablation procedure.”	1) ITU Triathlon WCS, 2008 2) ITU Duathlon WCS, 2009 3) ITU Aquathlon WCS, 2009 4) Problem became worse, 2010	Short	3	N
④	F	Australia	Supraventricular tachycardia	“Her difficulties with as arrhythmia were very evident when she had to be rescued from the water at the Triathlon. She was found to have supraventricular tachycardia and underwent a successful ablation procedure.”	1) Diagnosed, 2009 2) ITU triathlon WCS, 2012	Short★	1	N
⑤	M	New Zealand	Atrial fibrillation	“He was diagnosed with atrial fibrillation, an arrhythmia estimated to cause 15 percent of all strokes”. The appearance of his condition comes as scientists are finding a possible link between extreme endurance sport and dangerous heart arrhythmias.”	1) Diagnosed, 2005 2) ITU Triathlon WCS, 2006	Short★	1	Y
⑥	M	Canada	Atrial fibrillation	“During a routine fitness test, he could not complete a lap around the gym without panting. Later that evening, he was diagnosed with atrial fibrillation.” At that point, I was already competing in	1) Diagnosed, 2010 2) ITU Cross Triathlon WCS, 2017	Short★	1	N

7	F	Australia	Arrhythmia	<p>triathlons in the elite class, he recalls. I remember laying in the hospital bed, stressed and crying. My heart was peaking at 220 beats per min, then dropping to 50.”</p> <p>“There is an arrhythmia, but it doesn’t appear dangerous as it’s so infrequent. A heart problem forced her onto the roadside during the dying stages of the triathlon race.”</p>	<p>1) ITU Triathlon WCS, 2009 2) ITU Ironman70.3 WCS, 2013-2017 3) Diagnosed, 2016 4) Long-Distance Triathlon WCS, 2018</p>	Short	4	N
8	M	USA	Aortic root dilation	<p>“The diameter of his aortic root (located at the base of the aortic valve) was 5.9 cm.”</p>	<p>1) ITU Aquathlon WCS, 2015 2) Diagnosed, 2016</p>	Short	1	Y
9	M	German	Bicuspid aortic valve with aortic dilation	<p>“He was bothered by chest seemingly mild breathing difficulty and an unexplained fall-off in performance and sought evaluation. He was found to have a bicuspid aortic valve, severe aortic valve regurgitation (leaking), and a large (7 cm) aortic aneurysm of the ascending aorta.”</p>	<p>1) Ironman WCS, 2006 2) Diagnosed, 2011</p>	Ultra-long	1	Y
10	M	Denmark	Bicuspid aortic valve with aortic dilation	<p>“He has a bicuspid aortic valve. He has a moderate leak. It is possible that further hard training and racing would increase the risk of progression so that heart valve replacement would be needed in the near future. His aorta is moderately dilated, which markedly increases the risk of dissection under heavy workloads”</p>	<p>1) Ironman WCS, 2006 2) Diagnosed, 2011</p>	Long	2	Y
11	F	New Zealand	Isolated bicuspid aortic valve	<p>“She was found to have a bicuspid aortic valve, a congenital condition where the aortic valve has 2, rather than the normal 3 cusps.”</p>	<p>1) ITU Long Distance Triathlon WCS, 2007 2) Ironman WCS, 2008-2014 3) Diagnosed, 2009</p>	Long & Ultra-long	2	N
12	M	Spain	Isolated bicuspid aortic valve	<p>“The National Sports Council ruled that the heart disorder he was suffering from congenital aortic valve disease. Made him unsuitable for top-level competition and his licence was revoked. However, he did not give in and, after obtaining reports from a number of specialists that refuted the CSD’s ruling, had his licence reinstated.”</p>	<p>1) His career suffered a setback, 2000 2) ITU Triathlon WCS, 2006 3) Long-Distance Triathlon WCS, 2019</p>	Short	3	N

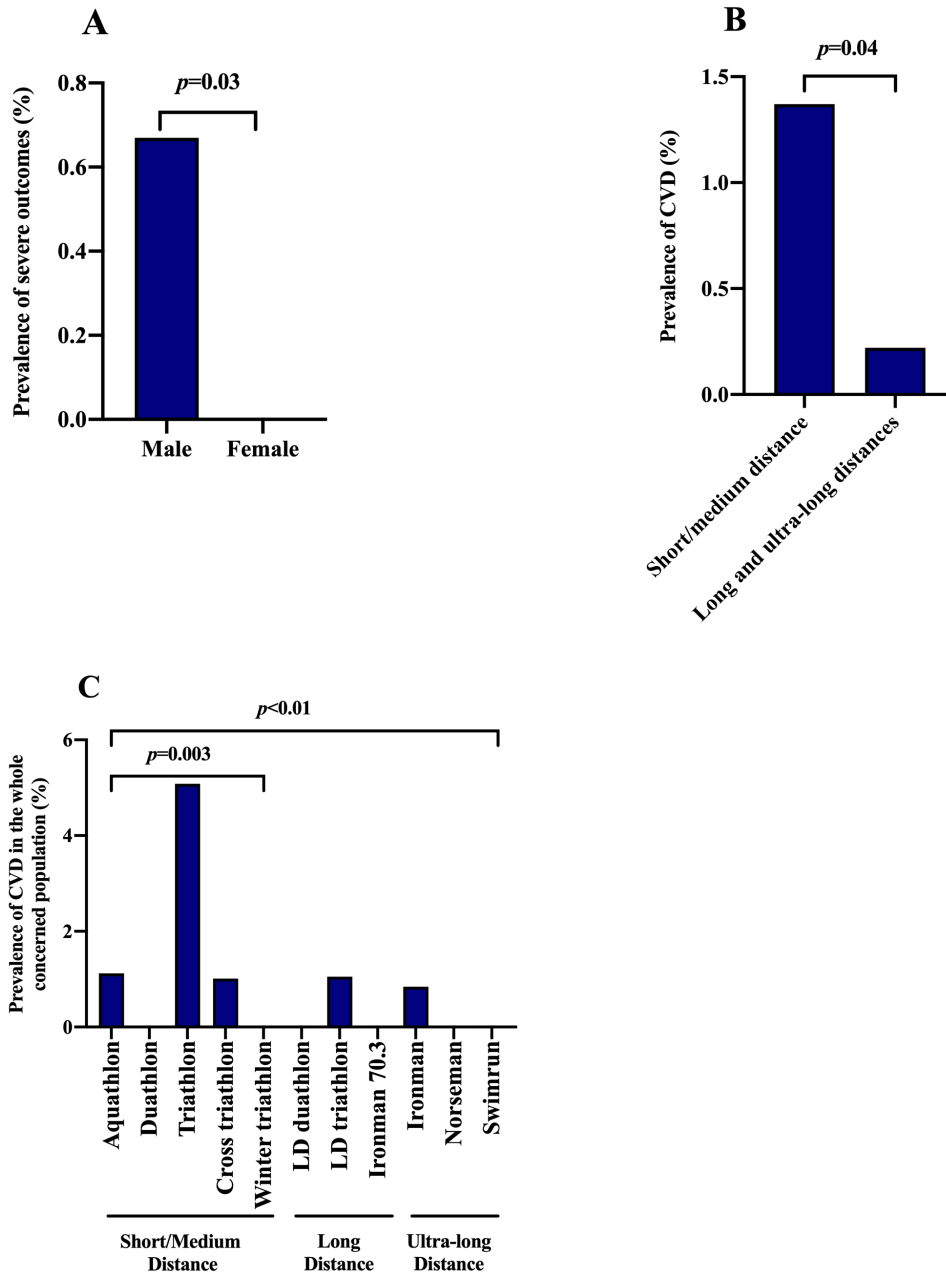
WCS, World Championships. “★” means that the athletes who suffered from cardiovascular diseases before succeeding in the Top 10 during the World Championships during the observed years. M, male; F, female. N, continued their sports training and competition; Y, stopped their sports careers for cardiac reasons.

### 5.2.2 *The prevalence of cardiovascular disease related to sexes, disciplines, and formats*

Seven CVD were reported in males (1.10%), including SCD (n=1), AF (n=2), aortic root dilation (n=1), BAV with aortic dilation (n=2), and isolated BAV (n=1). In comparison, five were reported in females (0.72%), including “arrhythmia” (n=1), supraventricular tachycardia (n=2), right ventricular outflow tachycardia (n=1), and isolated BAV (n=1). No significant difference was found between males and females in the occurrence of CVD ( $p>0.05$ ). The severe outcomes (the athletes who suffered from SCD and those who had to stop their sports careers for cardiac reasons) are all in males (0.38%). A significant difference was found between males and females in the severe outcomes ( $p=0.03$ ) (Figure 20-A). However, due to the small number of these events, no statistical difference was found according to sex in the occurrence of SCD ( $p>0.05$ ).

Considering the prevalence of CVD in the three different formats of triathlon sports disciplines, a significant difference was found between short/medium distance (1.37%) vs. long- and ultra-long distances (0.22%) ( $p=0.04$ ) (Figure 20-B). Three severe outcomes occurred in short/medium distance sport disciplines, while two were in long- and ultra-long distances. No statistical difference was found in severe outcomes when comparing the short/medium vs. long- and ultra-long distances ( $p>0.05$ ).

When comparing the prevalence of CVD in short/medium distance sport disciplines, a significant difference was found ( $p=0.003$ ), and the prevalence in short-distance triathlon (5.08%) was higher than others. When comparing the prevalence of CVD among all the eleven triathlon sport disciplines, the prevalence in short-distance triathlon was significantly higher than in others ( $p<0.01$ ) (Figure 20-C).



**Figure 20-A-C. Prevalence of CVD in elite triathletes (1).** (A) Prevalence of severe cardiac outcomes in males and females.  $p=0.03$  means a significant difference in the prevalence of severe outcomes between males and females. (B) Prevalence of CVD in athletes engaged in short/medium distance sports vs. those in long- and ultra-long distances.  $p=0.04$  means a significant difference between the athletes engaged in short/medium distances vs. those in long- and ultra-long distances. CVD, cardiovascular diseases. (C) Prevalence of CVD in different formats and disciplines.  $p=0.003$  and  $p<0.01$  means a significant difference among the sports disciplines in short/medium distance formats and among all the concerned sports disciplines.



5.2.3 *The prevalence of cardiovascular disease in athletes who participated in one or multiple types of triathlon disciplines/formats*

Of the population, 87.28% were engaged in one type of triathlon sport discipline, and 12.71% were involved in more than one type of sport (Table 7).

**Table 7. Populates participated in different types of sports discipline**

<b>Types of sport disciplines participated</b>	<b>Male (cases) (n=639)</b>	<b>Female (cases) (n=690)</b>	<b>Overall (cases) (n=1329)</b>
One	551 (5)	609 (1)	1160 (6)
Two	70 (1)	62 (2)	132 (3)
Three	15 (1)	13 (1)	28 (2)
Four	3 (0)	4 (1)	7 (1)
Five	0 (0)	2 (0)	2 (0)

Cases, cases of cardiovascular diseases observed

Considering the athletes engaged in one type of triathlon sport discipline, 6 cardiac diseases were identified (0.52%), of which 4 with severe outcomes (0.34%). When comparing the prevalence of CVD and the prevalence of severe outcomes in the three formats, no significant difference was found among the short/medium distance and long- and ultra-long distance ( $p>0.05$ ). A significant difference was found in the prevalence of CVD when comparing all the sports disciplines ( $p=0.01$ ) in those athletes who participated in one type of sports discipline (Figure 20-D), with a higher prevalence in short-distance triathlon (3.53%).

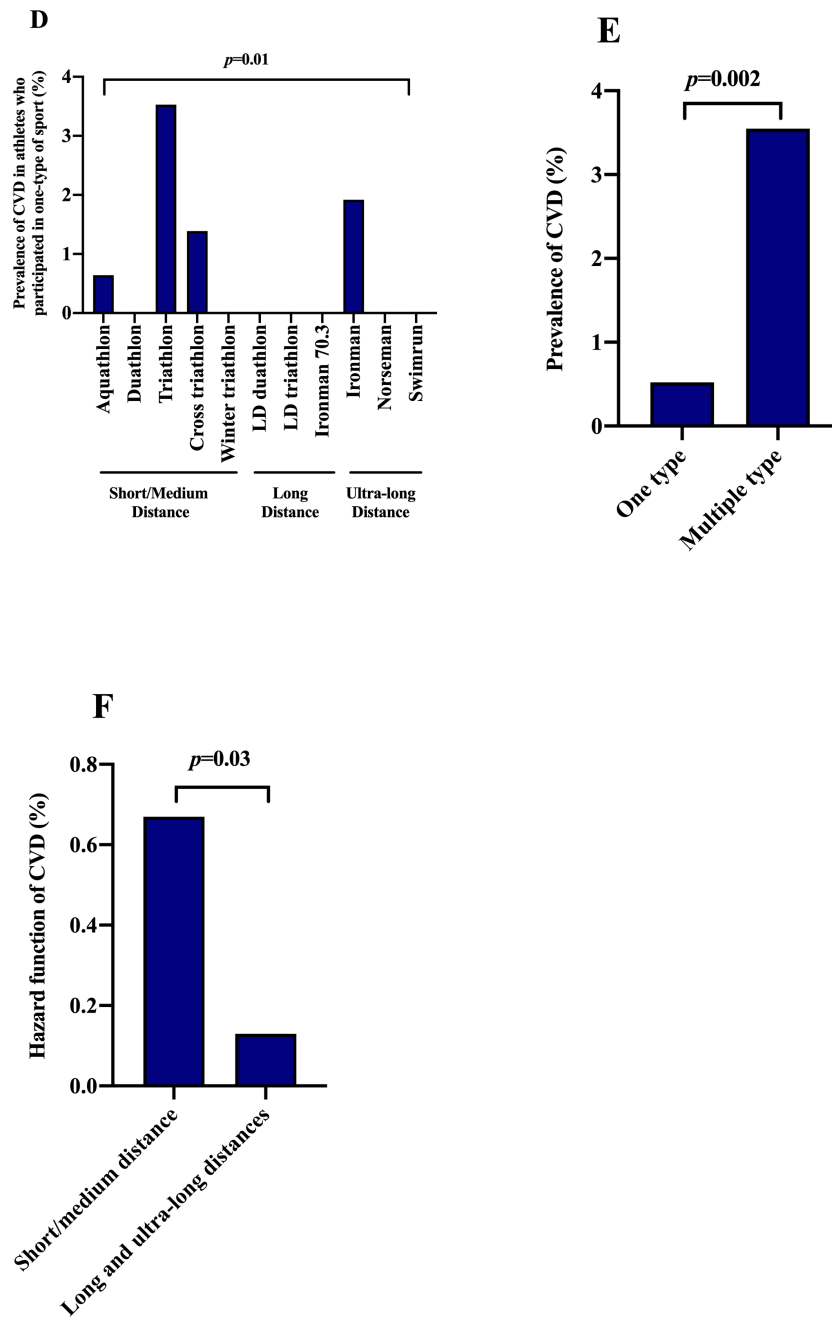
When comparing the athletes engaged in one type of sports discipline and those in more than one type, the prevalence in the athletes engaged in multiple types of sports disciplines (3.55%) was significantly higher than those who merely succeeded in one type of sport (0.52%) ( $p=0.002$ ) (Figure 20-E).

#### 5.2.4 Hazard function

After excluding 2 cases of isolated BAV, the overall hazard function of CVD and severe outcomes was 0.36% and 0.18%, respectively. There was no significant difference between the sexes in CVD hazard function and severe outcomes ( $p>0.05$ ).

Considering the hazard function of CVD in different formats, the hazard function in short/medium distances (0.67%) was higher vs. in long- and ultra-long distances (0.13%) ( $p=0.03$ ) (Figure 20-F). No significant difference was found in severe outcomes in short/medium distance format compared to long and ultra-long ( $p=0.66$ ).

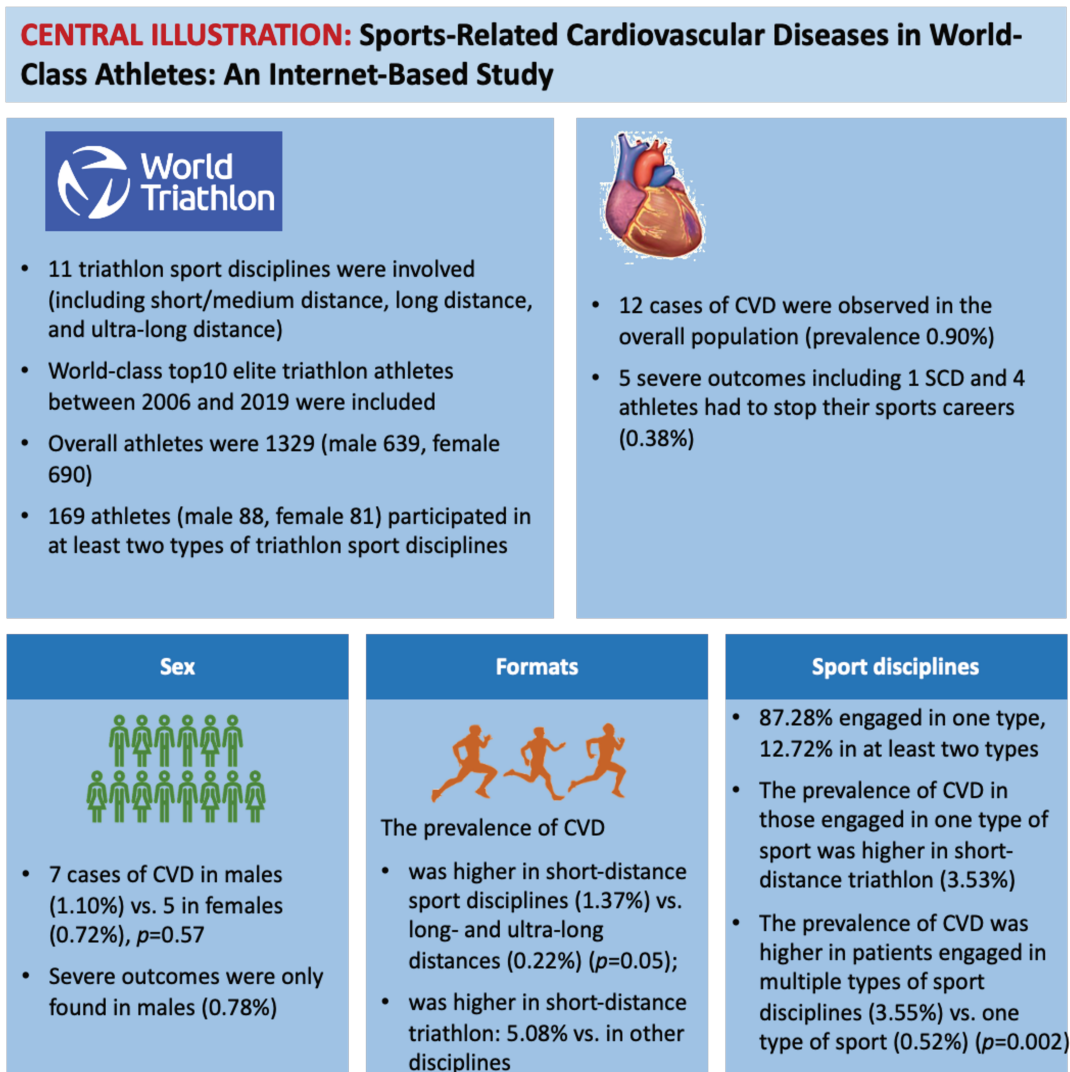
When comparing the athletes engaged in one type of sport and those in at least two sports, no significant difference was found between the two in the hazard function of CVD ( $p=0.29$ ) and the hazard function of severe outcomes ( $p=1.0$ ).



**Figure 20-D-F. Prevalence of CVD in elite triathletes (2).** (D) Prevalence of CVD in athletes engaged in one type of sport.  $p=0.01$  means a significant difference when comparing all the sports disciplines in those athletes engaged in one type of sport. (E) Prevalence of CVD in athletes engaged in one-type and multi-type of sports.  $p=0.002$  means a significant difference when comparing the athletes engaged in one type of sport and those engaged in multiple. (F) Hazard function of CVD in different formats.  $p=0.03$  means a significant difference in short/medium distance sports format vs. long- and ultra-long distances

### 5.3 Discussion

The present study aimed to estimate the prevalence of CVD in elite triathletes and determine the effects of sex, sports disciplines, and formats on CVD. The study found that (1) the overall prevalence of CVD in elite triathletes was 0.90%; (2) severe outcomes were merely observed in male athletes; (3) the prevalence and the hazard function of CVD in short/medium distance were higher than long- and ultra-long distances ( $p=0.04$  and  $0.03$ ); (4) the prevalence in athletes engaged in multiple types of sports disciplines (3.55%) was significantly higher than those merely succeed in one-type of sport (0.52%) ( $p=0.002$ ) (Figure 21. central illustration).



**Figure 21. Central illustration**

### *5.3.1 The prevalence of sudden cardiac arrest/death in athletes*

Sports-related cardiac fatalities have generated widespread concern about the safety of endurance athletes [151]. However, the risk of SCD has yet to be systematically investigated in triathletes [15]. Since participation has increased and become increasingly popular worldwide in recent decades [22]. Triathlon is a complex sporting event that requires cross-training and then competing in swimming, followed by cycling and running, which imposes extremely high cardiac constraints [197]. Therefore, the potential sports-related cardiac disabilities in those engaged in triathlon sports disciplines should not be ignored.

Studies from Minneapolis Heart Institute found that the cardiac arrests and deaths during the triathlon were unexpectedly high [14]. The incidence of cardiac events in United States Triathlon participants ranged from 1.5 per 100,000 [15] to 1.74 per 100,000 [14], higher than that reported in marathon runners (0.8 per 100,000 participants) [198]. Using the same methodology, we found that the prevalence of CVD (0.90%) in elite triathlon athletes was higher than that in the Olympic sports of the same class (0.61%) [13]. In these two studies, the prevalence of cardiac abnormalities was much lower than that observed among Olympic athletes (3.90%), which could be partly explained by the methodological difference (Internet-based study vs. Italian Olympic medical program).

### *5.3.2 Sex differences in the prevalence of cardiovascular disease in athletes*

Sports-related SCD has been found to occur 5 to 33 folds higher in male athletes than in females, and the sex differences persist despite the growing number of athletes [8]. Studies of the United States Triathlon found that 85% of the victims were males,

and the risk was increased with age [14]. The average annual incidence of SCA from the European Union in women was 0.19 per 100,000 AY, more than 10 times lower than in males with similar subject characteristics (2.63 per 100,000 AY). Following previous studies, the present study found that the severe cardiac outcomes in elite triathletes were higher in males when compared to females ( $p=0.03$ ). Hormones may play an essential role in lowering cardiovascular risk in female athletes [199]. Indeed, the modulation of the central and peripheral estrogen levels was able to suppress sympathetically but elevate parasympathetic tone in the cardiovascular system [200]. Sympathetic hyperactivity triggers the onset of malignant arrhythmias; on the contrary, augmented parasympathetic tone exerts protective effects [200, 201].

### *5.3.3 Impacts of triathlon disciplines/formats on cardiovascular disease*

Concerning the effects of triathlon sport discipline formats, Harrys et al. found that the risk of death or cardiac arrest was similar for short, intermediate, and long-distance races (1.61 vs. 1.41 vs. 1.92 per 100000) in triathletes in the United States [14]. In the present study, we found that the prevalence of CVD in short/medium distance sports format was higher than in long- and ultra-long distances ( $p=0.04$ ). Which was in accordance with the previous studies [13]. Despite the discrepancy in the results, the association between short/medium distance format and CVD might be, in part, related to the high intensity of sports practice. Indeed, compared to long and ultra-long formats, the effort intensity was more remarkable in short/medium distance ones due to less time required. Cardiac function can be altered following prolonged high-volume and high-intensity endurance exercise [108, 202]; those alterations in cardiac function were more related to the intensity rather than the duration of exercise [203]. Intensity was more related to all-cause mortality and CAD mortality than exercise duration [204]. Extremely intense exercise exposes cardiac chambers to a disproportionate increase in

afterload and wall stress that can induce myocardial fatigue [205]. Serum cardiac troponin increased during heavy- (90 min) and moderate- (120 min) intensity cycling but only exceeded healthy reference limits in 90 min of heavy intensity exercise [206].

Many athletes are not defined by just one triathlon discipline/format. They engaged in several different triathlon disciplines/formats during their careers because of the highly identical characteristics of some triathlon events. In the present study, we found that the prevalence of CVD in athletes who participated in several different types of sports was higher than in those who participated only in one type ( $p=0.002$ ). Nevertheless, we must recognize the bias between the base size of the population participating in one sports discipline and those participating in multi-type sports disciplines (1160 vs. 169). The mechanism underlying this finding must be clearly understood, and further investigations should be fully elucidated.

#### *5.3.4 Limitations and Perspectives*

The limitations of the present study were primarily due to the Internet research methodology. Previous studies on the outcome of elite athletes were conducted by searching only the causes of death obtained in National Death Registries and not focusing on cardiac diseases. Nevertheless, triathlon is a young discipline, making it unlikely that many death events will be collected on young athletes. Indeed, the first modern swim/bike/run events were held in San Diego, United States, in 1974; the first European Triathlon was held in Pilson, Czechoslovakia, in 1980; the first international triathlon structure was founded in 1985.

We cannot exclude that our search, based on the Internet, underestimates the actual number of events. Indeed, concerned about contractual and selection issues, some athletes may have deliberately hidden the diagnosis from the media. However, this potential limit applies equally to all athletes, regardless of sport triathlon disciplines or sexes. Thus, these limitations can be acceptable with the main observations of our study.

Furthermore, we had no access to the medical reports of the athletes and had to rely on their declaration on the Internet. Thus, the possibility of inaccurate diagnoses cannot be ruled out. However, we were surprised by the detailed description of symptoms and diagnoses reported.

#### **5.4 Conclusion**

The prevalence of severe cardiac outcomes was higher in male than in female triathletes. Athletes in short/medium distance formats were more prone to be affected by cardiac diseases. These results should attract our attention and encourage us to conduct prospective triathlete studies. Given the growing number of individuals participating in triathlon programs, it is imperative to enhance the screening and monitoring for potential CVD risks in these populations.



## 5.5 Summary and perspectives

As it was reported, elite athletes, despite the absence of symptoms or astonishing performances, were not immune to cardiovascular disorders and may be exposed to unforeseen high risks during sporting activity [109]. Athletes in intensive endurance exercise were more susceptible to CVD [41]. Indeed, studies revealed that when compared to other sports, endurance athletes, especially short-distance triathletes, have a relatively unexpectedly high prevalence of cardiac events [13]. Consistent with previous studies [14], although the prevalence of severe cardiovascular events in elite triathletes was relatively low, the study showed that the prevalence of severe cardiac outcomes was higher in male triathletes than in females. Athletes in short/medium distance formats were more prone to be affected by cardiac diseases. Although there were several possible cardiovascular causes [207], the mechanisms of the occurrence of cardiac events in those elite triathletes remain uncertain. Little was known about the specific causes and predisposing conditions of the occurrence of cardiovascular risks in these populations [154]. These results should attract our attention and encourage us to carry out prospective studies on triathletes to better understand their specific cardiovascular risks, which could help in improving the screening and monitoring and thus, better prevent them.







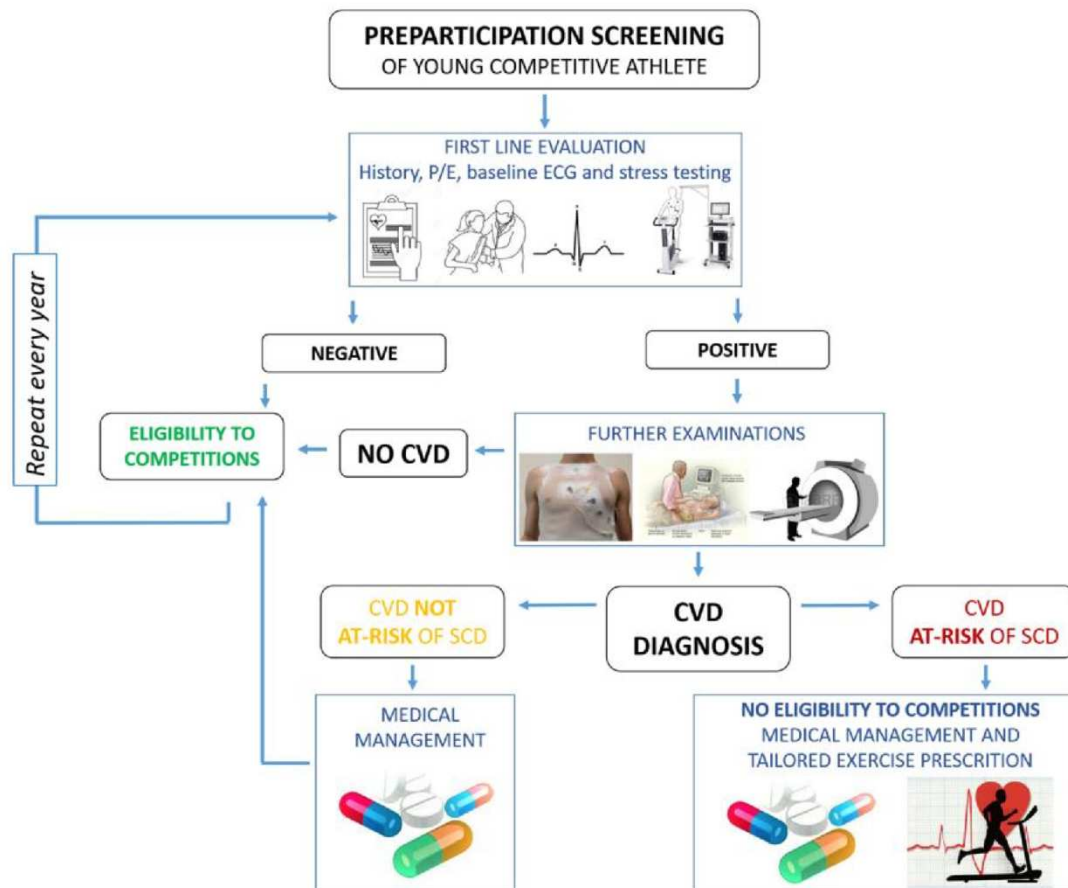
## **PART 3. CARDIAC SCREENING OF ATHLETES**

Intensive endurance exercise training and participation in competitive sports can trigger the onset of ominous ventricular tachyarrhythmias in predisposed individuals [16]. However, over 80% of cases lack antecedent symptoms and family history [17]. Therefore, there is considerable interest in the early identification of at-risk populations [18]. Cardiovascular pre-participation screening is the systematic practice of medical evaluation of large populations of athletes before participating in sports to identify (or raise suspicion of) abnormalities that could lead to disease progression or sudden death [208]. In some countries, the law requires every athlete to undergo a clinical evaluation for eligibility. An interesting study conducted by Italian researchers reported that the incidence of SCD in young competitive athletes has decreased significantly in the Veneto region of Italy since the introduction of nationwide systematic screening [20]. Indeed, data analysis revealed that during the study period (1982-2004), the annual incidence of SCD decreased by 89% in screened athletes [20]. A more recent study in a large population of Italian children revealed that the cardiovascular pre-participation screening led to the identification of CVD at risk of SCD over the whole study age range and more often on repeat evaluations [209]. These favorable outcomes and survival data provide compelling evidence that early detection by pre-participation screening and appropriate management of CVD at risk of SCD in the athlete population is life-saving [210].

However, there are significant differences in the consensus guidelines for pre-participation screening protocols used by European and American cardiologists/sports medicine physicians. The complex debate concerns the methods and rationale for pre-participation screening, including using 12-lead ECG [93]. The panel of experts from

the American Heart Association recommends personal and family history and physical examination as potentially effective strategies for raising the suspicion of CVD in both large and small screening populations of high school and college athletes [93]. At the same time, pre-participation screening by history and physical examination alone (without non-invasive testing) is not sensitive enough to guarantee the detection of all cardiovascular abnormalities associated with sudden death in young athletes [93]. Therefore, the European Society of Cardiology and the International Olympic Committee recommend combining non-invasive testing (e.g., 12-lead ECG) with standard medical history and physical examination. The premise of this screening strategy is that the ECG is a powerful tool for detecting or raising suspicion of many CVDs that cause sudden death in young athletes [19].

The Italian screening program (Figure 22) has successfully detected cardiovascular abnormalities, particularly HCM and other cardiomyopathies, leading to many athletes being disqualified from competitive sports to reduce their risk of SCD [20]. Researchers attribute this reduction in the rate of SCD to their long-standing systematic national pre-participation screening program, which routinely includes a 12-lead ECG [20]. According to long-term experience in Italy, cardiac pre-participation screening of competitive athletes, mainly by ECG, seems to be a life-saving strategy. This is because (1) the risk of SCD in sports is a serious health problem; (2) asymptomatic athletes with high-risk CVD can be detected by ECG screening; (3) effective management strategies can be developed based on limiting life-threatening training/competition and subsequent clinical treatment; most importantly, (4) early detection and management of athletes can be an effective way to improve the treatment outcome of underlying diseases and reduce the incidence of SCD [145].



**Figure 22.** Flow diagram illustrating the Italian protocol of preparticipation cardiovascular screening [210]. CVD, cardiovascular disease; ECG, electrocardiogram

Although cardiovascular pre-participation testing offers the potential to identify athletes with life-threatening cardiovascular abnormalities before the onset of symptoms and may reduce their risk of SCD, there is considerable cardiologists debate regarding the efficacy, impact of false-positive results, and cost-effectiveness of routine screening [208]. In particular, the false-positive rate for ECG screening can be as high as 5% to 10%, leading to unnecessary secondary investigations or physical activity restrictions [211]. However, in a study of 42,386 athletes initially screened, 3,914 (9%) were referred for further testing, and 879 (2%) were ultimately disqualified for cardiovascular reasons. Therefore, the percentage of false-positive results (e.g., athletes with a normal heart but positive screening findings) requiring additional testing is 7%, with a modest proportionate cost effect [20]. Similarly, studies indicated that in a large

and unselected population of young people undergoing cardiovascular screening, the prevalence of markedly abnormal ECG patterns suggestive of structural heart disease is low (<5%) and should not preclude the use of 12-lead ECG in pre-participation screening [212]. Notably, the false-positive rate for ECG screening is strongly influenced by the criteria used to define “abnormalities” [18]. Modern standards have been proposed to differentiate physiological cardiac adaptations in athletes from findings suggestive of an underlying pathology, namely the criteria of the ESC or, more recently, the “Seattle Criteria” [213]. Studies using these modern ECG criteria have resulted in significantly lower false positive rates [214], and new proposals are being made to refine the interpretation of the athlete’s ECG [215]. Therefore, ECG may be a necessary strategy for cardiovascular pre-participation screening for the prevention of SCD risk in athletes.

As previously described, the incidence of SCD in triathletes was unexpectedly high. Thus, we believe that cardiovascular pre-participation screening, especially ECG-based cardiac assessment, could play a role in the identification of potential CVD that might induce SCD in elite athletes. Besides, the fact that ECG patterns vary considerably between sexes [21]. Until now, the sex differences in the ECG characteristics in triathletes remain unknown. Therefore, the aim of the following study was to investigate the cardiovascular status of elite male and female triathletes by ECG evaluation.



## **1 Study 3: Electrocardiogram-based cardiac screening in male and female triathletes**

### **1.1 Materials and methods**

#### *1.1.1 Study population*

Male and female triathletes registered on the French ministerial lists of high-level athletes between 2015 and 2021 were involved in this study. The athletes' clinical information (such as basic information and training volumes) and ECG results were obtained from MediSharp, a platform supporting the mandatory longitudinal medical monitoring of high-level triathletes, organized by the French Federation of Triathlon. The platform is secure and respects General Data Protection regulations. The patient consent is not required as the results are publicly available on request.

#### *1.1.2 ECG patterns*

Standard 12-lead ECG was obtained from the MediSharp. ECGs were performed in a supine position under quiet breathing conditions and were recorded at 25 mm/s. The results of the ECG were interpreted by a cardiologist (TL) blinded to the clinical data. All the ECG results were evaluated according to the clinical criteria [64, 80]. Quantitative measurements were collected and confirmed by visual inspection, including HR, RR interval, P wave, PR or PQ interval, QRS complex, QRS axe, QT interval, and QTc.

### 1.1.3 Statistical analysis

Continuous variables were presented as mean±SD. Statistical differences were assessed using two-tailed unpaired t-tests for normally distributed continuous data and Fisher's exact test for dichotomous variables. A significant difference was defined as  $p<0.05$ . GraphPad Prism 8.0 (GraphPad Prism Software Inc.) was used for data analysis.

## 1.2 Results

### 1.2.1 Study population

Eighty six triathletes (male=50, female=36) were involved in this study, average age was 19.9±4.8 years (male 20.2±5.2, female 18.7±4.1,  $p>0.05$ ), average height was 173.1±9.1 cm (male 178.2±7.5, female 165.8±5.6,  $p<0.001$ ), average weight was 61.0±8.9 kg (male 66.1±6.9, female 53.9±5.9,  $p<0.001$ ), average body mass index was 20.3±1.7 kg/cm<sup>2</sup> (male 20.8±1.5, female 19.6±1.7,  $p=0.001$ ). Training volumes were determined for 66 of the 86 triathletes (76.7%) (male=38, female=28). Training volume was 21±6 hours/week in males and 19±6 hours/week in females ( $p>0.05$ ) (Table 8).

**Table 8. Basic information of the triathletes involved (mean ± SD)**

	Overall	Male	Female	Male vs Female
<b>Athletes</b>	86	50	36	
<b>Age (years)</b>	19.9±4.8	20.2±5.2	18.7±4.1	$p=0.15$
<b>Height (cm)</b>	173.1±9.1	178.2±7.5	165.8±5.6	$p<0.0001$ **
<b>Weight (kg)</b>	61.0±8.9	66.1±6.9	53.9±5.9	$p<0.0001$ **
<b>Body mass index (kg/cm<sup>2</sup>)</b>	20.3±1.7	20.8±1.5	19.6±1.7	$p=0.001$ **
<b>Training volume (h/week)</b>	20.4±5.8	21.2±5.9	19.3±5.6	$p=0.18$

### *1.2.2 Standard ECG measurements*

ECG measurements revealed that males had relatively larger P waves than females ( $96.0\pm 12.0$  vs.  $89.9\pm 11.5$  ms,  $p=0.02$ ). Similarly, males had a significantly longer QRS complex than females ( $96.6\pm 11.1$  vs.  $90.3\pm 8.6$  ms,  $p=0.005$ ). No significant statistical difference was found in HR, RR interval, PR or PQ interval, QRS axis, QT interval, and QTc between sexes ( $p>0.05$ ). Whether there was a statistical difference or not between the sexes, all indicators were within the normal range (Table 9).

### *1.2.3 ECG manifestations in triathletes*

The ECG results revealed that the most common electrical manifestations in triathletes were early repolarization (46.5%) and incomplete RBBB (39.5%). The prevalence of early repolarization was 48.0% (24/50) in males and 44.4% (16/36) in females ( $p>0.05$ ), and the prevalence of incomplete RBBB was 42.0% (21/50) in male athletes and 36.1% (13/36) in females ( $p>0.05$ ). No statistical difference among the electrical manifestations between sexes ( $p>0.05$ ) (Table 9).

**Table 9. Description of electrocardiogram patterns (mean ± SD)**

	Overall (86)	Male (50)	Female (36)	Male vs Female
<b>ECG patterns</b>				
Heart rate (bpm)	54.1±9.2	53.8±8.7	54.6±10.0	<i>p</i> =0.71
RR interval (ms)	1132±186.1	1131±179.5	1133±197.0	<i>p</i> =0.97
P wave (ms)	93.4±12.1	96.0±12.0	89.9±11.5	<i>p</i> =0.02 *
PR or PQ interval (ms)	154.1±25.6	158.8±26.2	147.8±23.7	<i>p</i> =0.05
QRS complex (ms)	94.0±10.6	96.6±11.1	90.3±8.6	<i>p</i> =0.005 **
QRS axe (°)	69.9±25.0	71.2±27.1	68.1±21.9	<i>p</i> =0.57
QT interval (ms)	427.6±31.1	424.9±29.3	431.3±33.5	<i>p</i> =0.35
QTc (ms)	406.2±26.6	402.7±25.3	411.0±27.9	<i>p</i> =0.15
<b>Percentage of present</b>				
Ectopic atrial rhythm	3.5%	2.0%	5.6%	<i>p</i> =0.21
Junctional rhythm	1.2%	2.0%	0.0%	<i>p</i> =0.73
PR short	8.1%	6.0%	11.1%	<i>p</i> =0.39
Primary balloon aortic valvuloplasty	3.5%	6.0%	0.0%	<i>p</i> =0.13
Secondary balloon aortic valvuloplasty (mobitz1)	0.0%	0.0%	0.0%	<i>p</i> >0.99
Right axial deviation	1.2%	2.0%	0.0%	<i>p</i> =0.39
Left axial deviation	1.2%	2.0%	0.0%	<i>p</i> =0.39
Left atrial hypertrophy	1.2%	2.0%	0.0%	<i>p</i> =0.39
Right atrial hypertrophy	3.5%	6.0%	0.0%	<i>p</i> =0.13
Incomplete right bundle branch block	39.5%	42.0%	36.1%	<i>p</i> =0.58
Complete right bundle branch block	1.2%	2.0%	0.0%	<i>p</i> =0.39
Early repolarization	46.5%	48.0%	44.4%	<i>p</i> =0.74
Atypical early repolarization	0.0%	0.0%	0.0%	<i>p</i> >0.99
Abnormal Q wave	0.0%	0.0%	0.0%	<i>p</i> >0.99
Abnormal T wave inversion	3.5%	2.0%	5.6%	<i>p</i> =0.38

### 1.3 Discussion

ECG measurements were evaluated to investigate the cardiovascular conditions in male and female triathletes. This study found that the most common ECG manifestations in triathletes were early repolarization and incomplete RBBB, no matter for sexes. Nevertheless, under almost similar training volumes (about 20 hours/week), male triathletes had relatively longer P wave duration and higher QRS voltage than females, but all the ECG patterns were within the normal limits. This indicated that male triathletes were more susceptible to physiological changes than females.

Intensive endurance training over the years leads to adaptations in the cardiovascular system (athlete's heart), which are associated with ECG changes. Sinus bradycardia, incomplete RBBB, first-degree atrioventricular block, and voltage criteria for ventricular hypertrophy are commonly found in electrical manifestations in endurance athletes [216]. In recreational long-distance triathletes, six months of endurance training increases the risk of "training-related" changes, including bradycardia, shorter P wave duration, reduced QTc, and increased LV Sokolow-Lyon index [217]. Long-distance triathlon competition can acutely affect ECG findings in asymptomatic athletes, with common pathological findings being increased QRS voltage, early repolarization, and incomplete RBBB [218]. However, in most cases, these changes were attributed to physiological adaptations of the heart as a result of systematic physical training [21]. In this study, despite approximately 40% of male and female athletes presenting with early repolarization and incomplete RBBB, all the ECG patterns were within normal ranges, indicating a benign adaptation to training.

Nevertheless, in some conditions, the magnitude of these benign adaptations is increased. Indeed, studies showed that it is not always the best triathletes who have the most significant structural adaptations of the heart, questioning the "athlete's heart" syndrome as a physiological entity [219]. According to some researchers, the "athlete's

heart” in triathletes is not a specific “physiological entity”, but could be a transition phase to dilated HCM [220]. When compared to healthy non-athletes with similar anthropometric and general physical characteristics, triathletes showed significant signs of mixed eccentric and concentric hypertrophy. In contrast to the findings of pathological LVH, triathletes had completely normal LV diastolic function [220]. Whereas in some highly trained triathletes, exercise-induced physiological stress results in reduced LV systolic contractility and altered diastolic filling coupled with minimal cardiac damage [221]. Some studies show signs of eccentric and concentric LVH with evidence of supernormal LV diastolic function. This has important hemodynamic adaptations and implications for the resting ECG. This suggested that the ventricular premature beats during peak exercise could be the first expression of pathological cardiac changes to exercise [222]. These changes would no longer merely physiological. They might be an indication of an evolution of pathologically hypertrophic and DCM [222].

To date, most of the studies on ECG-based cardiac screening, including studies in triathletes, have focused mainly on the male sex. Therefore, there is a lack of sufficient evidence to explain sex differences in ECG specificity in triathletes. Fortunately, there are some studies in other sports. Cardiac screening in elite dancers showed that 83% of dancers had a normal axis, 31% had incomplete RBBB, and 17% had sinus bradycardia; there were significant sex differences in almost all the ECG parameters studied [223]. Accordingly, observational cross-sectional findings in student athletes [224] and in competitive rowers [225], revealed that males were more likely than females to have sinus bradycardia, incomplete RBBB, early repolarization, and isolated QRS voltage criteria for LVH. In correspondence with those studies, the present study revealed that male triathletes were more susceptible to physiological changes than females. Proposed mechanisms include sex-specific differences in hormones, blood pressure, and autonomic tone. Consequently, these biological differences influence the degree of

cardiac hypertrophy, dilatation, and thus the development of arrhythmias during prolonged intensive endurance exercise [8].

#### **1.4 Limits**

The present study exits some limitations. A significant statistical difference in body mass index between male and female triathletes increased the heterogeneity between sexes. In the absence of echocardiographic data, the interpretation of the results has to be based on the electrical manifestations in the heart, which may reduce the sensitivity to detect abnormal findings. Besides, in the present study, only training volumes were obtained, and training intensity was not known, which might play a role in the development of exercise-related cardiac modification.

#### **1.5 Conclusion**

At almost similar training volumes (about 20 hours/week), male triathletes had a relatively longer P wave duration and higher QRS voltage than females, but all the ECG patterns were within normal limits. The most common ECG manifestations in triathletes were early repolarization and incomplete RBBB, no matter sexes. Findings from the study suggest that male triathletes are more susceptible to physiological changes than females. Large samples are needed to confirm these findings and to better understand cardiac remodeling in triathletes to determine the reasons for the increased risk of SCD in male triathletes.

## **1.6 Summary and perspectives**

As we have seen previously, triathlon appears to be at risk of cardiovascular pathologies. Although normal, their ECG presents particularities such as the high proportion of pronounced early repolarization and incomplete RBBB. Moreover, male triathletes seem more affected than females. Still, with the aim of better understanding the cardiac remodeling of the triathletes and from a prevention perspective, it seemed interesting to us to compare the triathlon with one of the three sports constituting it, cycling, in terms of cardiac remodeling. The objective of our 4th study was, therefore, to compare the ECG characteristics between elite triathletes and cyclists.



## **2 Study 4: Electrocardiogram-based cardiac screening in elite triathletes and cyclists**

### **2.1 Materials and methods**

#### *2.1.1 Study population*

To compare the electrical characteristics of triathlon and cycling sports, elite male triathletes and cyclists were involved in this study. All were registered on the French ministerial lists of high-level. The list of athletes and routine physical examination records, including ECG results, were obtained from the French Triathlon Fédération and French Cycling Fédération, and the MediSharp, with it, health data from different practitioners is centralized. The patient's consent was not required.

#### *2.1.2 ECG patterns*

Standard 12-lead ECG performed in supine under well-controlled conditions and recorded at 25 mm/s were obtained. The ECG was interpreted by a cardiologist (TL). ECG patterns were evaluated in accordance with generally accepted clinical criteria [64, 80]. Quantitative measurements, including HR, RR interval, P wave, PR or PQ interval, QRS complex, QRS axe, QT interval, and QTc, were automatically calculated and confirmed by visual inspection.

### 2.1.3 Statistical analysis

Continuous variables were presented as mean±SD. Statistical differences between athletes were assessed using a two-tailed unpaired t-test for normally distributed continuous data and Fisher's exact test for dichotomous variables. A significant difference was defined as  $p<0.05$ . GraphPad Prism 8.0 was used for data analysis.

## 2.2 Results

### 2.2.1 Study population

All the 105 athletes included in the study were males, 42 of them from short-distance triathlon (40%), and 63 from road cycling (60%). Average age was 22.1±4.2 years (triathletes aged 21.1±5.1 years, cyclists aged 22.8±3.4 years,  $p=0.07$ ). Average height was 178.5±6.9 cm (triathletes 178.7±8.0 cm, cyclists 178.4±6.2 cm,  $p=0.81$ ). Average weight was 68.5±7.1 kg (triathletes 67.0±6.7 kg, cyclists 69.4±7.3 kg,  $p=0.09$ ). Average body mass index was 21.5±1.6 kg/cm<sup>2</sup> (triathletes 21.0±1.5 kg/cm<sup>2</sup>, cyclists 21.8±1.6 kg/cm<sup>2</sup>,  $p=0.009$ ) (Table 10).

**Table 10. Basic information of the athletes involved (mean ± SD)**

	Overall (n=105)	Triathlon (n=42)	Cycling (n=63)	Triathlon vs Cycling
Age (years)	22.1±4.2	21.2±5.1	22.8±3.4	$p=0.07$
Height (cm)	178.5±6.9	178.7±8.0	178.4±6.2	$p=0.81$
Weight (kg)	68.5±7.1	67.0±6.7	69.4±7.3	$p=0.09$
Body mass index (kg/cm <sup>2</sup> )	21.5±1.6	21.0±1.5	21.8±1.6	$p=0.009$ **

### 2.2.2 Standard ECG measurements

ECG assessments revealed that the P wave amplitude was significantly lower in triathletes than in cyclists ( $95.5\pm 11.6$  vs  $102.1\pm 11.4$  ms,  $p=0.005$ ). No significant statistical difference was found in HR, RR interval, PR or PQ interval, QRS complex, QRS axis, QT interval, and QTc ( $p>0.05$ ). All indicators were within the normal ranges (Table 11).

### 2.2.3 ECG manifestations in triathletes

The ECG assessment revealed that the most common electrical manifestations in athletes were early repolarization (60.95%, 64/105) and incomplete RBBB (43.81%, 46/105). The prevalence of early repolarization in triathletes was 52.38% (22/42) and in cyclists was 66.67% (42/63); the prevalence of incomplete RBBB in triathletes was 42.86% (18/42) and in cyclists was 44.444% (28/63). Of all the indicators, no statistical difference was found between triathletes and cyclists ( $p>0.05$ ) (Table 11).

**Table 11. Description of electrocardiogram patterns (mean ± SD)**

	Overall (n=105)	Triathlon (n=42)	Cycling (n=63)	Triathlon vs Cycling
<b>ECG patterns</b>				
Heart rate (bpm)	53.5±8.8	52.3±7.5	54.3±9.5	<i>p</i> =0.26
RR interval (ms)	1146±200.3	1143±174.6	1147±216.7	<i>p</i> =0.92
P wave (ms)	99.5±11.9	95.5±11.6	102.1±11.4	<i>p</i> =0.005 **
PR or PQ interval (ms)	158.8±25.4	159.0±27.7	158.7±24.0	<i>p</i> =0.95
QRS complex (ms)	99.0±10.4	96.9±11.3	100.3±9.5	<i>p</i> =0.09
QRS axe (°)	67.9±31.2	68.3±26.8	67.6±34.0	<i>p</i> =0.91
QT interval (ms)	428.3±33.3	427.4±29.3	428.9±35.9	<i>p</i> =0.82
QTc (ms)	402.8±27.6	401.2±25.2	403.8±29.2	<i>p</i> =0.64
<b>Percentage of present (case)</b>				
Ectopic atrial rhythm	0.00% (0)	0.00% (0)	0.00% (0)	<i>p</i> >0.99
Junctional rhythm	1.90% (2)	2.38% (1)	1.59% (1)	<i>p</i> >0.99
Primary balloon aortic valvuloplasty	4.76% (5)	7.14% (3)	3.23% (2)	<i>p</i> =0.39
Secondary balloon aortic valvuloplasty (mobitz1)	0.00% (0)	0.00% (0)	0.00% (0)	<i>p</i> >0.99
Right axial deviation	0.95% (1)	0.00% (0)	1.59% (1)	<i>p</i> >0.99
Left axial deviation	1.90% (2)	2.38% (1)	1.59% (1)	<i>p</i> >0.99
Right atrial hypertrophy	4.76% (5)	7.14% (3)	3.23% (2)	<i>p</i> =0.39
Left atrial hypertrophy	5.71% (6)	2.38% (1)	7.94% (5)	<i>p</i> =0.40
Incomplete right bundle branch block	43.81% (46)	42.86% (18)	44.44% (28)	<i>p</i> >0.99
Complete right bundle branch block	3.81% (4)	2.38% (1)	4.76% (3)	<i>p</i> =0.65
Early repolarization	60.95% (64)	52.38% (22)	66.67% (42)	<i>p</i> =0.16
Atypical early repolarization	0.00% (0)	0.00% (0)	0.00% (0)	<i>p</i> >0.99
Anormal T-wave inversion	1.90% (2)	2.38% (1)	1.59% (1)	<i>p</i> >0.99

## 2.3 Discussion

The study compared the ECG patterns between elite triathletes and cyclists. Findings revealed that the P wave amplitude was lower in triathletes than in cyclists. Despite this, all indicators were within normal limits. Early repolarization and incomplete RBBB were the most common ECG manifestations in both triathletes and cyclists. However, there was no difference in indicators between the two populations.

Early repolarization and incomplete RBBB are typically considered as training-related normal variants in athletes [41]. In this study, the variant changes were presented in both triathletes and cyclists, indicating that the ECG manifestations were normal in both populations, reinforcing the physiological adaptations of prolonged exercise training in these athletes. Early repolarization was defined as J-point elevation  $\geq 0.1$  mV in at least two leads within a non-anterior territory (inferior [II, III, aVF] or lateral territory [I, aVL, V4-V6]). However, an early repolarization pattern in inferior leads of a standard ECG was associated with an increased risk of death from cardiac causes in the middle-aged general population [226]. A multicenter study showed an unexpectedly high incidence of early repolarization (in inferior lateral leads) in patients younger than 60 years with syncope and cardiac arrest due to idiopathic ventricular fibrillation, which suggested that SCA may be associated with early repolarization patterns [227]. Early repolarization patterns in professional athletes without clinical markers of pathology and presented in isolation are normally considered benign variants in athletes [228], and have been shown to be a direct result of exercise training [229]. However, recent studies in professional basketball players with criteria for an early repolarization pattern revealed different results in cardiopulmonary exercise testing and cardiac remodeling compared to athletes without an early repolarization pattern [228]. This suggests that ECG findings, especially present with early repolarization patterns, must be interpreted in the context of the athlete's status (e.g., sports levels and sex) [228].

The right bundle branch block obstructs the right bundle branch, making the heartbeat signal late and out of sync with the left bundle branch, causing an irregular heartbeat. Unlike a completely right bundle branch block, an incomplete or partial block means that electrical signals are partly disrupted. Studies revealed that the prevalence of incomplete RBBB in athletes was approximately 7%, which should be attributed to normal, long-term adaptation to intense, repeated exercise [230]. However, evidence showed that incomplete RBBB was associated with lower HR, increased QRS voltage, QTc duration, precordial Q wave voltage, indices of RV hypertrophy, and negative T waves. These findings were typical of RV hypertrophy and suggested a close relationship between incomplete RBBB and RV hypertrophy [231]. However, evidence showed that the cardiovascular adaptations associated with endurance training include RV ECG and imaging changes that may overlap with clinical features of several inherited (e.g., ARVC) and acquired (e.g., sarcoidosis) heart diseases. However, their diagnosis relies on the demonstration of pathological changes (e.g., TWI, ventricular aneurysms, late enhancement), which, when present in athletes, should be considered abnormal and refused as an adaptation to exercise [232]. These findings suggest that, even though these ECG changes may be normal physiological adaptations in triathletes and cyclists involved in the present study, athletes should be taken seriously when they present with other pathological conditions. Thus, we suspect that even though triathlon and cycling are two different sports (multiple disciplines vs. individual sports), they both place high demands on athletes' cardiovascular systems, and undoubtedly, long-term participation in those high-intensity endurance exercises may result in pronounced cardiac remodeling, which might increase the risk of maladaptation of the heart in athletes. Indeed, a previous study of 30 Olympic athletes revealed that although short-distance triathletes had the highest rates of cardiac events, cyclists are not “far behind”, coming in second to short-distance triathletes [13].

Early studies of cardiac screening in athletes are mainly on single-discipline sports, primarily endurance or strength-trained subjects. Studies of cyclists and runners who compete regularly showed that runners have a slightly lower resting HR than cyclists, while echocardiographic data comparison revealed no difference in morphological functional changes between the two groups of athletes [233]. Another study of cyclists and long-distance runners with matched age, height, and weight showed that runners develop an increase in LV wall thickness that was proportional to the internal diameter, but that in cyclists, the increase was disproportionate because of the isometric work of the upper body during cycling [234]. The discrepancy may be due to the fact that the athletes involved have different characteristics as well as different training regimens [233]. Simultaneously, the evidence reminds us that the impact of sports components on an athlete's heart cannot be ignored. Echocardiographic studies in multisport athletes showed that, compared with age- and sex-matched controls, elite triathletes had significantly increased LV wall thickness and cavity dimensions as well as LV mass, whereas elite modern pentathletes (running, swimming, shooting, fencing, and showjumping) showed significantly increased LV wall thickness but a non-significant increase in LV internal diameter [235]. This suggests that the stimulus leading to LV enlargement in triathletes is associated with prolonged endurance activity, together with an isometric component associated with cycling; in contrast, elite modern pentathletes have a reduced endurance component combined with a high isometric component associated with fencing [235]. The above evidence showed that the sports components are closely linked to the cardiovascular remodeling in athletes. Given that isotonic and isometric components are commonly present simultaneously in some sports, do different proportions of the two components affect cardiac remodeling differently in athletes who train equally hard? Since the sports constraints are different between cycling and triathlon, the answer to this question might help to explain the greater risk observed in triathletes compared to cyclists [13].

## **2.4 Conclusion**

Early repolarization and incomplete RBBB were the most common ECG manifestations in both triathletes and cyclists, indicating a physiological adaptation to prolonged intensive endurance exercise. However, no significant differences of ECG parameters were observed between both populations. Thus, ECG adaptations fail to explain higher cardiac risk in triathletes compared to cyclists. Further studies are needed to explore the effect of the proportions of sports components on pronounced cardiac remodeling in elite athletes.







# PART 4. GENERAL DISCUSSION AND PERSPECTIVES

## 1 General discussion

SCD is a tragic event in athletes with far-reaching implications that attracted widespread attention. However, the occurrence and specific causes of SCD in competitive athletes remain unclear. To better understand this phenomenon and prevent the occurrence of tragic events in those active individuals, four studies were conducted in this thesis. In study 1, sex differences in the incidence of SCA/D in competitive athletes were explored by a systematic review and meta-analysis. This study revealed that the incidence of SCA/D in female athletes was lower than in males. However, the clinical findings between the sexes were different. The most common cause in female athletes was congenital coronary anomaly, while in males, it was HCM. In study 2, the prevalence of CVD in elite triathletes was investigated by an Internet-based retrospective study. This study revealed that although the prevalence of CVD in elite triathletes was relatively low, severe outcomes were only observed in male athletes. The prevalence in short-distance triathletes was more susceptible than that in long- and ultra-long-distance triathlons. In study 2, ECG-based cardiac screening in male and female triathletes was assessed. This study revealed that prolonged intensive endurance exercise induced physiological changes in those athletes, manifested by early repolarization and incomplete RBBB in both sexes. Despite this, male athletes were more susceptible to physiological changes than females. In study 4, we conducted an ECG-based cardiac screening between triathletes and cyclists. The study revealed that athletes in both triathlon and cycling sports were highly cardiac demanding, manifested by early repolarization and incomplete RBBB, which suggested the cardiac physiological adaptations to prolonged endurance exercise training.

## **1.1 Sex differences and the occurrence of cardiovascular disease in athletes**

For years, studies have consistently shown that the risk of SCD in female athletes was lower than that in males. In study 1, through a systematic review and meta-analysis, we concluded that the estimated incidence of SCA/D was about six times lower in female athletes than in males. In study 2, we concentrated on elite triathletes and found that the more severe cardiac outcomes mostly occurred in male athletes, and female athletes were less prone to be affected. Hence, understanding the potential mechanisms of the lower risk of CVD in female athletes may provide evidence for the prevention of cardiac death in athletes. Although the literature on the etiology of SCD in female athletes is limited, proposed mechanisms include sex-specific differences in hormones, blood pressure, and autonomic tone. Consequently, these biological differences influence the degree of cardiac hypertrophy, dilatation, and thus, the development of arrhythmias during prolonged intensive endurance exercise [8].

### *1.1.1 Hormones and sex differences of cardiovascular disease in athletes*

It seems that consistent sex disparities in the risk of CVD in athletes must derive from sex itself [236]. The spotlight has largely been on estrogens; studies showed that premenopausal women have a lower risk of CVD, while in postmenopausal women, the risk increases with age, and the gap with men is narrowing. This suggested that estrogen plays an important role in maintaining cardiovascular health [237]. However, in some studies, postmenopausal estrogen supplementation did not reduce the cardiac risk, and estrogen supplementation in men showed significantly worse outcomes [237]. While in some other studies, six months of hormone replacement therapy improved the parameters that associated with cardiac autonomic function and at least may partly explain the potential cardioprotective effects of hormone replacement therapy [238].

In recent years, androgens have attracted significant interest in explaining the sex differences in CVD [239]. Testosterone is the most important endogenous androgen, which exerts its effects in a variety of ways. Evidence of age-related declines in testosterone levels in men and increasing cardiovascular events with age led to the postulation of the idea of “andropause” or male menopause. Unfortunately, in the last few decades, androgens have been highlighted as being abused by athletes worldwide. There are numerous reports of their association with SCD and adverse cardiovascular outcomes when abused. Observational studies suggested that lower androgen levels predict a poor cardiovascular risk profile [239]. Nevertheless, the regulatory effects of endogenous and exogenous estrogens and androgens on CVD need to be further investigated to elucidate the sex-specific effects in athletes.

### *1.1.2 Autonomic tone and sex differences of cardiovascular disease in athletes*

The predominant occurrence of cardiac arrests and the increasing incidence of CVD in male athletes have been explained by an elevated adrenergic tone as an additional risk factor [240]. Indeed, in contrast to cholinergic (parasympathetic) branches, which may have a protective effect, adrenergic (antagonistic sympathetic) tone, particularly in the presence of myocardial ischemia, may trigger malignant arrhythmias [241]. Generally, the adrenergic level in females is low, and vagal indicators of autonomic tone are high [242]. Evidence showed that athletes of both sexes show a different circadian pattern of exercise-induced increases in indicators of vagal tone. Female athletes maintained higher markers of vagal tone at comparable training volumes; these regulation patterns may produce a cardioprotective effect and indicate superior protection against exercise-induced ventricular arrhythmias [240].

Heart rate variability (HRV), systolic blood pressure variability, and spontaneous baroreflex sensitivity are indirect measures of autonomic regulation of the cardiovascular system. By measuring the parameters of these dimensions, studies showed differences in cardiovascular parameters between sexes [243]. HRV is commonly used in clinical practice to assess the physiological status of cardiac autonomic activity and is a widely used marker that reflects the interplay between the sympathetic and parasympathetic branches of the autonomic nervous system and the modulation of normal cardiac rhythm. Sex is an influential determinant of cardiac autonomic tone. All HRV parameters, except for high frequency power, are higher in men, and these sex differences are limited to age categories below 40 and 50 years. The lower sympathetic tone (low frequency power) in women may protect against arrhythmias and the development of CAD [244]. The decline in standard deviation of the averages of NN intervals for all 5-minute segments is significantly steeper (time domine) in female subjects over 40 years of age, suggesting a possible reduction in the moderating effect of female sex hormones on long-term fluctuations in cardiac autonomic control after menopause [245]. Studies in junior cross-country skiers (16 to 19 years) showed that there is a general increase in HRV after intensive training; although males and females do not differ in the HRV response (at rest) to training, the level of parasympathetic activity is higher in females than in males, as reflected by consistently higher high frequency power and total HRV in female athletes [246]. This evidence indicated that the alterations in the balance of ovarian hormones might be responsible for the changes in cardiac autonomic activity [244].

## 1.2 Sports disciplines and the occurrence of cardiovascular disease in athletes

Triathlon are defined as “one sport, two transitions, and three disciplines” [247]. As an endurance sport, triathlon apparently shares much with long-distance running but also claims its own specificity due to the three disciplines and two transitions [248]. Triathlon involves several specific aspects that make the physiological demands different from those of individual sports such as swimming, cycling, and running [249]. Studies showed that the key requirements for successful triathlon performance are high  $\dot{V}O_{2\max}$ , lactate thresholds, maximum sustainable percentage of  $\dot{V}O_{2\max}$ , as well as low energy costs of exercise for each discipline [247]. As with other individual endurance athletes, triathletes possess a high  $\dot{V}O_{2\max}$  value [249]. Compared to cycling alone, drafting allows triathletes to save significant amounts of energy during the bike section and creates the conditions for improved running performance [250]. However, less-trained triathletes have less developed technical skills specific to the transition phase. They may experience a greater drop in performance in the first kilometer of the run than their more successful counterparts. Athletes with good transition skills may also avoid the common mistake of starting the run at a faster pace than they can sustain [247]. Certainly, elite athletes, especially those who have achieved outstanding results in major competitions, must have trained extensively and demandingly; compared to athletes competing in an individual sport, triathletes must simultaneously master the techniques of three sports, which greatly increases the difficulty of the sport and the amount of training required. It is, therefore, theorized that exercise training in triathlon sports may have a more profound effect on cardiac remodeling in high-level triathletes.

In study IV, we compared the ECG characteristics between triathletes and cyclists. Although all the ECG parameters are within the normal ranges, both triathletes and cyclists showed significant early repolarization and incomplete RBBB, suggesting that the hearts of cyclists and triathletes alike responded physiologically to prolonged

endurance training. This suggested that both cyclists and triathletes have developed benign physiological adaptations to prolonged training. Notably, these athletes were young and at the height of their youth and vigor, so we were not surprised by this result. However, in study 2, we investigated the prevalence of cardiac events in elite triathletes; although the exact number of triathletes with CVD was relatively small, some athletes do develop severe cardiac outcomes, suggesting that prolonged triathlon training and competition could be, in some cases, detrimental to the cardiovascular health.

Considering the relatively high prevalence of cardiac events in short-distance triathletes [13], evidence showed that competitors during triathlon races experience a range of environmental conditions and physiological demands that exceed those found in individual sports of comparable duration [251]. Although the triggers of cardiovascular abnormalities cannot be excluded in some cases, logistical factors and adverse environmental conditions may have been responsible for these events, as about 95% of fatalities in triathletes occurred during the swimming segment [15]. The tragic events are more frequent in triathlons with a larger number of participants. As triathlons begin with chaotic, high-density mass starts, with up to 2000 largely inexperienced competitors entering the water at the same time, there is an opportunity for physical contact and exposure to cold, turbulent water [251], and the inherent barriers to identifying athletes in distress and initiating timely resuscitation in open water [15]. Some studies showed a higher rate of SCD in triathletes, but study 4 found that triathletes and cyclists appear to have similar changes in cardiac remodeling. The complex environment in which triathletes compete may explain this inconsistency. However, there is no definitive conclusion to date on whether the effects of triathlon on the cardiovascular system are related to the combination of multiple sports. Therefore, much remains to be investigated regarding this issue.



### **1.3 Cardiac risk factors and the occurrence of cardiac disease in athletes**

Exercise may provoke cardiac events in susceptible individuals. So, understanding the risk factors of sports-related cardiac events may identify opportunities for the prevention of SCD [252]. It was reported that approximately 70% of CVD deaths were attributed to modifiable risk factors [253]. The modifiable risk factors of CVD include a cluster of behavioral, metabolic, socioeconomic, and psychosocial factors and household and ambient pollution [253]. Evidence showed that physical work, psychological stress, heat stress, dehydration, personal protective equipment, smoke exposure as well as cardiovascular risk factors, such as smoking, hypertension, obesity, and dyslipidemia, were all associated with a higher risk of on-duty CVD in firefighters [254]. An observational, cross-sectional study of Gaelic Athletic Association athletes demonstrated the presence of hypertension and negative lifestyle behaviors in this population [255]. A case-control study in athletes indicated that prior CVD, smoking, and a recent episode of fatigue or flu-like symptoms were associated with an increased risk of exercise-related acute cardiac events [252]. A retrospective assessment of 1,500 forensic autopsies showed that 80 sports-related SCD were due to inadequate training [256]. However, the changes in physical fitness and physical activity were related to the absolute levels of risk factors for CVD in young adulthood, especially in men [257]. On the contrary, seniors without major chronic diseases with consistent and stable physical activity for over 25 years showed that a lifetime history of consistent physical activity, regardless of dose, ranging from sedentary to competitive marathon running, was not associated with the development of CVD [258]. Identification of CVD risk factors remains an important goal of overall disease prevention and management [259]. Control of multiple risk factors was associated with a reduction in CVD events of more than 50% [260]. Therefore, athletes and physicians should pay careful attention when these factors exist.

Although it would be ridiculous to discourage people from competitive endurance training, such as triathlons or ultra-endurance events, for fear of developing CVD, it is equally inappropriate to argue that extraordinary endurance training can never be harmful [101]. Perhaps we should be prepared to accept that too much prolonged intensive endurance exercise may promote abnormal alterations in athletes [79]. However, the potential mechanism of the detrimental effects of prolonged intensive endurance exercise on cardiovascular health remains unclear. Uncovering the potential triggering factors may help to prevent tragic events in athletes. Since the majority of the cases are absent of antecedent symptoms and family history, ECG-based cardiac pre-participation screening really needs to be encouraged in athletes with vigorous training according to (1) the individual's current level of physical activity, (2) the presence of signs or symptoms and/or known cardiovascular, metabolic, or renal disease, and (3) desired exercise intensity, as these variables have been identified as risk modulators for sports-related cardiac events [259].

## 2 Perspectives

At present, there remain some issues that need to be resolved: (1) The upper limit to the health benefits of physical activity and the “optimal dose” are not clear; (2) The specific causes and circumstances in athletes should be further clarified according to sex, sport disciplines, age, ethics, and training levels; (3) Whether there is a relationship between the proportion of sports components and the occurrence of CAD during prolonged intensive endurance training; (4) The interpretation of an athlete’s ECG is often delegated to personal experience and is usually based on traditional ECG criteria used in general population [64], thus, there is a critical need for physician training in modern ECG interpretation that distinguishes normal physiological adaptations from distinctly aberrant patterns that may indicate underlying pathology [80]; (5) Although the resting ECG can detect most causes of SCD in athletes [153], the ECG has limitations in both sensitivity and specificity. Specifically, ECG fails to identify coronary anomalies, premature coronary atherosclerosis, and aortopathies [65], and false-positive ECG results are common in the detection of HCM [261]. Therefore, exercise ECG testing, echocardiographic assessment, and cardiac magnetic resonance imaging should be considered to narrow the differential diagnosis, especially for athletes with “grey zone” hypertrophy [65]; (6) Although cardiac pre-participation screening in athletes plays an important role in the prevention of tragic events, it is important to note that most athletes, particularly in amateur and recreational sports, do not undergo regular screening. Furthermore, it is estimated that 10% of SCA cannot be prevented by pre-participation screening. Considering all these effects, the measures of secondary prevention and “rescue on the field” are of paramount importance [262]. Thus, the best strategy is to synergistically combine primary prevention by identifying athletes with cardiac risk before participating in sports and secondary prevention by providing AED in the event of unpredictable arrhythmic cardiac arrest [208]; (7) The survival from SCA can be significantly improved by involving lay and non-professional

rescuers in cardiopulmonary resuscitation and the use of AED through public access defibrillation programs specifically designed to reduce the time from SCA to shock delivery [263]. However, numerous areas are deficiency in cardiovascular safety programs. For example, 28% of participating clubs did not have an AED in their stadium, and 36% did not have a documented medical action plan outlining cardiovascular safety procedures. Additionally, 41% of clubs reported a transport time of more than 5 minutes from the stadium to the nearest hospital [262]. From above, it is conceivable that the facilities for ADE may also be inadequate at venues for other sports. Therefore, the immediate availability of an AED could be potentially lifesaving for asymptomatic athletes, providing a safety net for the imprecision of the proactive strategy in athletes. In addition, about 81% of delayed cardiopulmonary resuscitation is due to misinterpretation or lack of awareness of symptoms [158], Therefore, regular cardiopulmonary resuscitation training of athletes and staff with direct access to an AED is also recommended to make SCA a more common survivable event [263].





## PART 5. REFERENCE

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# PART 6. RÉSUMÉ EN FRANÇAIS

## ● INTRODUCTION GÉNÉRALE

### 1 Les bénéfices de l'exercice physique

#### *1.1 Les bénéfices de l'exercice physique dans la population générale*

L'activité physique est une série de mouvements corporels produits par les muscles squelettiques qui entraînent une dépense d'énergie supérieure au métabolisme de repos. Elle englobe l'exercice, les sports et les activités physiques. L'activité physique peut être bénéfique pour la santé notamment en réduisant le risque de maladies chroniques, en favorisant un vieillissement en bonne santé et en augmentant l'espérance de vie. Les lignes directrices de l'Organisation Mondiale de la Santé recommandent aux adultes de pratiquer chaque semaine 150 à 300 minutes d'activité physique d'intensité modérée ou 75 à 150 minutes d'activité physique d'intensité vigoureuse, ou une combinaison d'activité physique d'intensité modérée et vigoureuse. Il a été rapporté que le fait d'atteindre et de maintenir au moins les recommandations minimales de santé publique permettrait d'éviter 46% des décès liés à l'inactivité physique. Pour chaque tranche de 15 minutes d'activité physique en plus de la quantité quotidienne minimale recommandée, on observe une réduction de 4% de toutes les causes de mortalité et une réduction de 1% de la mortalité par cancer.

Le système cardiovasculaire est l'un des plus grands bénéficiaires de l'activité physique. Les avantages cardiovasculaires comprennent une baisse de la tension artérielle et des taux de triglycérides ainsi qu'une amélioration des marqueurs inflammatoires et de la résistance à l'insuline. L'activité physique est donc considérée

comme une stratégie efficace pour la prévention primaire et secondaire des maladies cardiovasculaires (CVD). Bien que la quantité maximale d'activité physique nécessaire pour promouvoir la fonction cardiaque et réduire le risque cardiaque reste inconnue, la plupart des études montrent un déclin graduel avec l'augmentation des niveaux d'activité.

### ***1.2 Les bénéfices de l'exercice physique chez les athlètes***

Les athlètes ont toujours suscité un grand intérêt de la part du public et des médias et sont souvent considérés comme des modèles de santé optimale. Mais qui est réellement un athlète ? En règle générale, un athlète est défini comme une personne qui pratique un sport organisé nécessitant un entraînement régulier en vue de compétitions. Il accorde une grande importance à l'excellence et aux performances physiques. Les effets bénéfiques de l'exercice physique sur les athlètes sont bien décrits. Il a été démontré que l'exercice régulier favorise un vieillissement en bonne santé en améliorant de manière significative la fonction cardiovasculaire. Les athlètes bien entraînés ont une meilleure capacité fonctionnelle que leurs homologues sédentaires, celles-ci étant souvent comparables aux jeunes non sportifs. Si l'on considère les recommandations européennes et américaines actuelles, les athlètes de compétition (et certains sportifs de loisir) dépassent généralement les recommandations en matière d'activité physique avec plus de 20 heures d'exercice intensif par semaine. Cette forme de pratique intensive induit une augmentation soutenue du débit cardiaque sur une longue période, obtenue grâce à divers changements électriques, structurels et fonctionnels uniques dans le cœur, regroupés sous le nom de "cœur d'athlète".

## 2 Le cœur du sportif

### *2.1 Définition, base physiologique et facteurs déterminants*

L'exposition répétée et prolongée à l'exercice contribue à une série de modifications du système cardiovasculaire, appelées "cœur d'athlète" ou remodelage cardiaque induit par l'exercice (EICR). Les caractéristiques du cœur d'athlète comprennent des changements structuraux, fonctionnels et électriques tels que l'hypertrophie ventriculaire, une amélioration de la fonction et de la compliance cardiaques et un remodelage électrique. Le cœur d'athlète est un phénomène bénin, représentant une adaptation physiologique à l'exercice physique régulier.

L'EICR est stimulé par les conditions hémodynamiques et neurohumorales induites par l'exercice. La conséquence de ce remodelage cardiaque induit par l'exercice est l'augmentation de la consommation maximale d'oxygène ( $\dot{V}O_{2\max}$ ) de l'athlète.

L'EICR résulte de nombreux facteurs, tels que les caractéristiques de la discipline sportive, le volume et l'intensité de l'entraînement ou encore l'âge, le sexe, l'origine ethnique et la taille de l'athlète. En ce qui concerne le type de sport, l'exercice isotonique (caractéristique des sports d'endurance) implique une augmentation soutenue du débit cardiaque avec une résistance vasculaire périphérique normale ou réduite. Ce type d'exercice isotonique entraîne une surcharge en volume au niveau du cœur, ce qui se manifeste avec le temps par une hypertrophie harmonieuse excentrique avec une augmentation de l'épaisseur de la paroi et une dilatation de toutes les cavités cardiaques. De l'autre côté, l'exercice isométrique (caractéristique des sports de résistance) induit des augmentations courtes mais conséquentes de la résistance vasculaire périphérique associées à une augmentation normale ou faible du débit cardiaque. Cette augmentation de la résistance vasculaire périphérique provoque une

hypertension systolique transitoire mais potentiellement marquée et une “surcharge de pression” du ventricule gauche (VG), qui se manifeste par un épaissement de la paroi du VG avec une légère dilatation de sa cavité. Cela entraîne une hypertrophie concentrique. En règle générale, les sports présentant des caractéristiques physiologiques mixtes impliquant des composantes statiques et dynamiques, comme l’aviron et le triathlon, entraînent une dilatation des 4 chambres avec des augmentations équilibrées de la taille et de l’épaisseur de la paroi du VG ou une hypertrophie excentrique.

Outre les disciplines, les caractéristiques du cœur de l’athlète sont également affectées par la durée et l’intensité de l’exercice physique. L’EICR nécessite un stimulus d’exposition à l’exercice répété et soutenu, mais l’intensité et la durée minimales de l’exercice nécessaires pour stimuler ce processus restent largement inexplorées. Chez les athlètes d’endurance, l’EICR suit une réponse diphasique avec une augmentation de la taille de la chambre du VG, de la fonction diastolique et de la torsion systolique au cours d’une phase d’augmentation aiguë d’entraînement. Cette phase est suivie d’une phase d’adaptation chronique caractérisée par une augmentation de l’épaisseur de la paroi et une régression de la torsion du VG. Cela suggère que la durée de l’entraînement est un déterminant essentiel de l’EICR et a des implications pour l’évaluation de la structure et de la fonction myocardiques.

Globalement, le développement du cœur de l’athlète est le résultat de plusieurs facteurs. Les effets combinés de ces facteurs sur les aspects électriques, structuraux et fonctionnels du cœur de l’athlète peuvent être déterminés électrocardiographie et électrocardiogramme.



## ***2.2 Spécificités du cœur d'athlète***

### **2.2.1 Spécificité de l'électrocardiographie (ECG)**

L'ECG est une méthode utilisée pour enregistrer l'activité électrique des cardiomyocytes. Les modifications de l'ECG chez les sportifs sont courantes et reflètent généralement le remodelage structurel et électrique du cœur en adaptation à l'exercice régulier. En effet, les athlètes entraînés présentent souvent des modifications de l'ECG telles qu'une bradycardie sinusale, un bloc auriculo-ventriculaire du premier degré, et un bloc de branche droit incomplet (BBDI), qui sont dues à l'adaptation physiologique du système nerveux autonome à l'exercice régulier en augmentant le tonus vagal et en atténuant l'activité du système nerveux sympathique.

Les modifications électriques cardiaques chez les athlètes entraînés varient en fonction de différents facteurs, tels que le sexe, l'âge, l'origine ethnique, le niveau de forme physique et le type de sport. Par exemple, les modifications de l'ECG liées au sport sont plus fréquentes chez les athlètes d'endurance que dans les populations non sportives. Les athlètes d'endurance présentent les modifications ECG les plus profondes, comme la bradyarythmie et la repolarisation précoce. En ce qui concerne le sexe, la littérature récente a mis en évidence une nette différence entre les hommes et les femmes. Par exemple, les athlètes féminines sont plus susceptibles de présenter une inversion antérieure de l'onde T, tandis que les hommes sont plus susceptibles de présenter un voltage QRS élevé et une repolarisation précoce.

### 2.2.2 Spécificité de l'échocardiographie

L'échocardiographie est un moyen non invasif et sensible permettant d'évaluer les dimensions et la fonction cardiaques, ce qui permet de comprendre en profondeur la physiologie cardiovasculaire au repos et à l'effort. L'EICR est associée à une hypertrophie ventriculaire, à une augmentation de la masse du VG et à une modeste hypertrophie de la racine aortique pour répondre aux exigences physiologiques accrues de l'exercice. Les athlètes présentent généralement une épaisseur de paroi du VG supérieure de 10 à 20%, une taille de cavité VG et VD supérieure de 10 à 15% et un volume systolique et de fin de diastole (VG-VD) supérieur à celui de leur homologues sédentaires en bonne santé.

Les adaptations à l'exercice dépendent également du type d'entraînement effectué. Les entraînements d'endurance et de résistance entraînent des modifications nettement différentes de la fonction cardiaque. Normalement, les athlètes de résistance présentent une augmentation de l'épaisseur de la paroi et de l'épaisseur relative de la paroi. En revanche, la volume VG et les diamètres de fin de diastole VG-VD sont plus importants chez les athlètes d'endurance.

L'EICR est observé aussi bien chez les athlètes masculins que féminins, mais il est généralement moins prononcée chez les femmes que chez les hommes. En règle générale, les athlètes féminines présentent une taille absolue de la chambre du VG inférieure d'environ 10%, une épaisseur de la paroi du LV inférieure de 10% à 20% et une masse absolue du VG inférieure de 20% à 55% par rapport aux athlètes masculins. Bien que la géométrie se situe généralement dans les limites de la normale, les femmes ont tendance à développer une hypertrophie excentrique, alors que les hommes présentent souvent un remodelage concentrique. Il est donc nécessaire d'adopter une approche sexospécifique pour interpréter les caractéristiques uniques du cœur de l'athlète.

Tous ces éléments suggèrent qu'une participation régulière et soutenue à un entraînement intensif d'endurance est typiquement associée à des modifications électriques et structurelles du cœur. Si toutes ces modifications apparaissent généralement comme des adaptations physiologiques bénignes dans une minorité de cas, le phénotype cardiaque peut ressembler à celui de maladies cardiaques spécifiques, ce qui traduit une incertitude diagnostique représentée par ce qu'on appelle la "zone grise".

### **3 La zone grise dans l'évaluation du cœur d'athlète**

#### ***3.1 Zone grise et électrocardiogramme***

Les modifications de l'ECG chez les athlètes sont généralement utilisées pour refléter le remodelage du cœur en tant qu'adaptation à l'exercice physique régulier. Cependant, les anomalies dans les résultats de l'ECG des athlètes peuvent être le signe d'une maladie cardiovasculaire sous-jacente qui les expose à un risque de décès pendant l'exercice. Il est donc essentiel de distinguer les anomalies de l'ECG causées par un exercice intense régulier de celles potentiellement liées à un risque cardiaque accru. Le consensus international pour l'interprétation de l'ECG chez les athlètes suggère que lorsque les résultats obtenus chez les athlètes sont considérés comme des adaptations physiologiques à un exercice répétitif, il n'est pas nécessaire de procéder à une évaluation plus poussée. Toutefois, pour les résultats limites, lorsque ces résultats sont présents individuellement, ils ne nécessitent pas d'examen supplémentaire, alors que lorsque deux résultats ou plus sont présents simultanément, un examen supplémentaire est nécessaire.

### ***3.2 Zone grise et échocardiographie***

L'échocardiographie fonctionnelle, y compris le Doppler tissulaire et l'imagerie de déformation par speckle tracking, est un autre outil essentiel pour diagnostiquer les athlètes. L'EICR peut donner lieu à des résultats d'échocardiographie qui se recourent avec les formes courantes de maladies myocardiques associées à des événements indésirables dans la CVD. Par conséquent, différencier l'EICR de la pathologie myocardique est l'une des tâches les plus critiques pour les cliniciens. Le terme "zone grise" a été utilisé pour décrire le chevauchement clinique entre l'EICR et la pathologie. Selon la recherche et le cadre clinique, combinés aux résultats des échocardiogrammes, il existe quatre variantes de base de la "zone grise": (1) épaissement de la paroi du VG, (2) dilatation de la chambre du VG, (3) dilatation du VG, et (4) hypertrabéculatation du VG. Chacune de ces variantes donne lieu à des diagnostics différentiels différents.

### ***3.3 Chevauchement entre le remodelage cardiaque induit par l'exercice et la cardiomyopathie génétique***

Les changements physiologiques électriques et structuraux observés chez les athlètes sont généralement réversibles après une période de désentraînement; cependant, une petite proportion d'athlète peut présenter des changements plus profonds qui se chevauchent avec ceux observés chez les individus présentant des expressions morphologiquement légères de cardiomyopathies génétiques. Les cardiomyopathies génétiques constituent une famille complexe de maladies comprenant la cardiomyopathie hypertrophique (HCM), la cardiomyopathie dilatée, la cardiomyopathie arythmogène du VD et la cardiomyopathie de non-compaction du VG. L'évaluation doit donc être effectuée avec prudence, car un diagnostic erroné de cardiomyopathie peut entraîner un arrêt de la pratique sportive. Inversement, un

diagnostic erroné d'un cœur d'athlète chez une personne atteinte de cardiomyopathie peut mettre en danger. Dans certains cas, malgré des investigations approfondies, le dilemme diagnostique n'est pas résolu et une période de désentraînement de 6 à 8 semaines est recommandée pour surveiller la régression des anomalies électriques et structurelles et minimiser le risque cardiaque. Bien qu'une telle approche semble sensée et pragmatique, il est difficile de persuader les athlètes de compétition de faire une pause, car cela affecte la condition physique.

En conclusion, nous pouvons dire que, dans la plupart des cas, les adaptations qui se produisent dans le cœur d'un athlète sont physiologiques et positives pour l'amélioration des performances cardiovasculaires. Néanmoins, des événements tragiques de mort cardiaque pendant la compétition ont été rapportés chez certains athlètes d'élite apparemment en bonne santé. Par exemple, un footballeur espagnol, Antonin Puerta, est décédé d'un arrêt cardio-respiratoire lors d'un match en 2007, et un cycliste belge, Michael Goolaerts, a été victime d'un décès cardiaque après un SCD lors de la course Paris-Roubaix en 2018. Ces cas suggèrent qu'une maladie cardiovasculaire sous-jacente a pu être subtilement oubliée lors du dépistage de ces athlètes, ce qui a conduit à des événements tragiques. Ainsi, les athlètes pourraient rester exposés au risque de CVD malgré les avantages bien documentés d'une activité physique régulière sur la santé et la morbidité cardiaque.

## ● RISQUES CARDIAQUES CHEZ LES ATHLÈTES

### 1 Paradoxe du sport

Si les bienfaits de l'exercice physique sur la santé sont indéniables, les bienfaits des exercices d'endurance intensifs sur la santé cardiovasculaire sont désormais remis en question par certains chercheurs. Le maintien de la condition physique par une activité physique régulière peut contribuer à réduire la fréquence des événements, car un nombre disproportionné d'événements survient chez les personnes les moins actives physiquement qui pratiquent une activité physique inhabituelle. En revanche, la pratique d'un sport peut temporairement augmenter le risque d'événements cardiaques indésirables, en particulier chez les personnes souffrant de certaines pathologies cardiaques. Ce phénomène est connu sous le nom de "paradoxe du sport".

Des données récentes ont révélé une relation en U entre l'intensité de l'exercice et la santé cardiovasculaire ; un exercice modéré est préférable à un mode de vie sédentaire, mais un exercice d'endurance intensif peut être délétère pour certaines personnes. Des études de cohortes prospectives sur la participation à la course à pied ont montré que l'augmentation de la dose de course à pied est susceptible d'apporter des avantages significatifs en termes de santé publique et de longévité. Toute quantité de course à pied, même une fois par semaine, est préférable à l'absence de course à pied, mais une quantité plus importante de course à pied n'est pas nécessairement associée à des bénéfices plus importants en termes de mortalité. En effet, les résultats ont montré que les personnes qui déclaraient être vigoureusement actives tous les jours avaient un risque de CVD plus élevé que celles qui déclaraient être vigoureusement actives 2 à 3 fois par semaine, ce qui suggère que les avantages d'un mode de vie actif pourraient avoir atteint un plateau ou même être en déclin chez les athlètes engagés dans une pratique intensive.

## **2 Risques cardiovasculaires d'un entraînement intensif et prolongé**

L'entraînement intensif de longue durée peut entraîner des manifestations cardiovasculaires potentiellement néfastes susceptibles d'atténuer les bienfaits d'un mode de vie physiquement actif pour la santé. Des preuves substantielles ont suggéré qu'une activité physique intense peut non seulement déclencher des événements cardiaques chez des individus sensibles, mais aussi favoriser le développement de maladies cardiovasculaires chez des athlètes n'ayant pas d'antécédents cardiovasculaires. En effet, chez les athlètes olympiques robustes et en bonne santé, on observe une prévalence relativement élevée d'anomalies cardiaques, y compris une proportion faible mais non négligeable de pathologies à risque, ce qui suggère que malgré l'absence de symptômes ou de performances étonnantes, ils ne sont pas immunisés contre les CVD et peuvent être exposés à un risque élevé et imprévisible de SCD. Une calcification accélérée des artères coronaires, une fibrose myocardique, une fibrillation auriculaire et même un risque accru de décès par crise cardiaque ont été rapportés chez ces athlètes en bonne santé.

## **3 La mort subite d'origine cardiaque chez les athlètes**

### ***3.1 Une réalité chez les athlètes***

La mort subite liée au sport est l'événement le plus tragique chez les athlètes. Cet épisode tragique fait généralement l'objet d'une couverture médiatique importante et suscite d'intenses discussions au sein des communautés scientifiques et médicales. La mort subite d'origine cardiaque, connue sous le nom de SCD, est la principale cause médicale (plus de 90 %) de décès chez les athlètes. Un effondrement inattendu dû à une cause cardiaque, au cours duquel une réanimation cardio-pulmonaire ou un

défibrillateur externe automatisé est administré (ADE) aux athlètes qui ont survécu, est défini comme un arrêt cardiaque soudain (SCA). Dans certaines études, des exercices d'endurance intensifs ont été décrits comme un facteur déclenchant de la SCA chez les athlètes. De manière cohérente, les personnes habituellement actives présentaient un risque de mort subite associé à un épisode d'exercice d'endurance intensif beaucoup plus faible que celles qui faisaient de l'exercice moins d'une fois par semaine ; cependant, dans toutes les analyses, le risque restait significativement élevé pendant et après un exercice d'endurance intensif chez les personnes les plus actives. Par conséquent, l'exploration du risque et de l'étiologie de la mort subite d'origine cardiaque chez les athlètes est nécessaire pour participer au développement de stratégies de surveillance et de prévention cardiovasculaire.

### ***3.2 Incidence de la mort cardiaque subite chez les athlètes***

Malgré la grande visibilité et l'attention considérable accordée par le public et les médias à la mort subite du cœur chez les athlètes, l'incidence exacte de la mort subite d'origine cardiaque dans ces populations reste controversée. Les estimations varient considérablement en fonction de la définition de l'athlète, des méthodes de collecte des données, de l'absence de déclaration obligatoire dans de nombreux pays, de l'inclusion ou de l'exclusion des cas en fonction du moment et du lieu de l'événement, de l'inclusion de tous les événements cardiaques (y compris les survivants) par rapport à ceux qui entraînent la mort ou encore de la population étudiée.

Des études réalisées à partir d'un registre national en Allemagne ont montré que l'incidence globale chez les athlètes se situe entre 1.2/100 000 années-athlètes (AY) et 1.5/100,000 AY.



En outre, l'incidence de la SCD chez les athlètes dépend du sexe. En effet, il a été constaté que les hommes étaient plus touchés que les femmes. Par exemple chez des triathlètes aux Etats-Unis, près de 85 % des victimes sont des hommes pour seulement 15 % des femmes. En Allemagne, le SCD est de 0.2/100,000 AY chez les femmes, contre 3.6/100,000 AY chez les hommes. Les rapports de cas de SCD chez les jeunes athlètes montrent un ratio femme/homme de 1/9. Le risque de mort subite serait 5 à 33 fois moins élevé chez les femmes que chez les hommes, et les différences entre les sexes persistent malgré l'augmentation rapide de la participation des femmes au sport. Des études portant sur de jeunes athlètes de compétition aux États-Unis ont montré que seuls 11% des cas de mort subite d'origine cardiaque survenaient chez des athlètes féminines; bien que la proportion de maladies cardiovasculaires signalées chez les femmes ait augmenté au fil du temps, atteignant 12% entre 2000 et 2006, l'incidence reste plus faible chez les femmes que chez les hommes. Les études s'accordent sur le fait que les femmes sont moins sujettes aux SCD que les hommes, mais les connaissances sur la cause spécifique et les circonstances de survenue sont rares.

Dans l'ensemble, l'incidence estimée de la mort subite d'origine cardiaque chez les athlètes est liée à l'âge, au sexe et aux disciplines sportives. En règle générale, les athlètes masculins présentent une incidence plus élevée de SCD.

### ***3.3 Étiologie de la mort cardiaque subite chez les athlètes***

Les étiologies de la mort cardiaque subite chez les athlètes comprennent diverses conditions cliniques. Chez les jeunes athlètes, les cardiopathies congénitales prédominent. L'autopsie cardiaque peut révéler des anomalies structurelles, mais le cœur peut être structurellement normal dans ce contexte, suggérant un syndrome de mort subite arythmique, le syndrome d'arythmie primaire étant l'étiologie sous-jacente

la plus probable. La cardiomyopathie hypertrophique (CMH) est la cardiopathie congénitale la plus fréquente. Il a été rapporté qu'elle provoque une mort subite chez environ 2 à 50% des athlètes. Certaines études menées aux États-Unis indiquent que la CMH est la cause cardiaque la plus fréquente chez les jeunes athlètes (36%), et que les anomalies des artères coronaires sont la deuxième cause de SCD dans ces populations, représentant 17% des décès. Néanmoins, l'attribution des décès par crise cardiaque chez les jeunes athlètes de compétition a changé au cours des deux dernières décennies et varie fortement en fonction de la méthodologie utilisée. Des études approfondies ont montré que le résultat le plus fréquent de l'autopsie chez les jeunes foudroyé par une SCD est un cœur structurellement normal. Les SCD chez les jeunes athlètes sont principalement dus à des cardiomyopathies cliniquement silencieuses ou à des troubles électriques primaires (cœur morphologiquement normal). Une enquête nationale prospective et exhaustive menée dans toute la France a révélé que chez les jeunes athlètes de compétition, la mort subite inexplicée représente 36%, suivie de la CMH (10%), de la fibrillation ventriculaire primitive (8%) et de la maladie coronarienne (6%).

## **4 Étude 1 : Différences inter-sexes dans l'incidence de la mort subite d'origine cardiaque : une revue systématique et une méta-analyse**

### ***4.1 Objectifs de l'étude***

L'identification d'un événement déclencheur est complexe car plusieurs facteurs augmentent le risque de décès d'origine cardiaque. La plupart des études ont révélé que la mort subite inexpliquée avec un cœur structurellement normal est la principale cause de mort subite chez les jeunes athlètes. L'absence de cardiopathie structurelle est un facteur essentiel dans la prise en charge et le pronostic des athlètes. Cependant, la meilleure stratégie de diagnostic pour exclure une cardiopathie structurelle n'a pas encore été établie. Comme décrit précédemment, il existe des différences entre les sexes en ce qui concerne l'incidence de la SCD chez les athlètes. Malgré les difficultés méthodologiques, les études ont toujours fait état d'un risque plus faible de décès par SCD chez les athlètes féminines par rapport à leurs homologues masculins. Cependant, on sait peu de choses sur les causes spécifiques.

Les connaissances actuelles sur l'incidence des SCD ont été déterminées principalement sur la base d'études menées dans des circonstances spécifiques à l'aide de méthodologies spécifiques (telles que les données collectées sur la base des registres nationaux ou des demandes d'assurance), en ignorant souvent les différences entre les sexes ou en ne considérant qu'un seul sexe (principalement les hommes). Bien que Harmon et al. aient résumé l'incidence de la SCD dans les deux sexes à l'aide d'une revue de l'état de l'art, les nouvelles études sur ce sujet n'y sont pas incluses. En outre, l'incidence estimée, les causes potentielles et les mécanismes pathogènes du SCD chez les athlètes n'ont pas encore été abordés de manière efficace ni évalués de manière approfondie et systématique. C'est pourquoi cette étude visait à évaluer les différences

inter-sexes en ce qui concerne l'incidence et l'étiologie de la SCA/D chez les athlètes de compétition par le biais d'une analyse systématique et d'une méta-analyse. Seules les études comportant des données sur des athlètes masculins et féminins ont été incluses afin d'éviter tout biais systématique dans l'agrégation des données.

#### ***4.2 Matériel et méthodes***

Cette étude systématique et cette méta-analyse ont été réalisées conformément aux lignes directrices et aux recommandations PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis). Elles ont été enregistrées dans l'International Prospective Register of Systematic Reviews (ID: CRD42023432022). Deux chercheurs (LXL et FS) ont indépendamment effectué des recherches systématiques dans les bases de données selon les termes de l'intitulé. L'échelle d'évaluation de la qualité de Newcastle-Ottawa a été utilisée pour évaluer la qualité de chaque étude incluse dans la méta-analyse.

#### ***4.3 Résultats***

Seize études de cohortes prospectives ou rétrospectives ont été sélectionnées sur un total de 10099 articles potentiels, représentant un échantillon combiné de 268,729 566 participants par AY, dont 154,928,991 AY masculins (57.65%) et 113,800,575 AY féminins (42.35%). Sur les 1,797 cas observés de SCA/D, 1,578 sont survenus chez des athlètes masculins (87.81%) et 219 chez des athlètes féminines (12.19%). L'incidence estimée chez les athlètes masculins était de 1,42/100 000 AY (IC 95% : [0.97, 2.09]), et chez les athlètes féminines de 0.32/100,000 AY (IC 95% : [0.17, 0.59]). La cause la plus fréquente de SCA/D chez les athlètes masculins était la CMH (453/1004,

[45.12%]), suivie d'une anomalie coronarienne congénitale (161/1004, [16.04%]) et d'une coronaropathie (103/1004, [10.26%]). La cause la plus fréquente chez les femmes était une anomalie coronarienne congénitale (38/115, [33,04 %]), suivie de la CMH (16/115, [13.91%]) et de la CVAR (14/115, [12.17%]).

#### ***4.4 Conclusion***

La méta-analyse fournit des preuves des différences entre les sexes dans l'incidence du SCA/D chez les athlètes de compétition. L'incidence du SCA/D chez les femmes athlètes était environ six fois plus faible que chez les hommes. L'identification des raisons de ces différences peut avoir des implications pour cibler la prévention de l'SCA/D. Une plus grande attention devrait être accordée aux athlètes, en particulier aux athlètes masculins, qui s'investissent dans la pratique intensive d'exercices d'endurance.

## **5 Etude 2 : Prévalence des maladies cardiovasculaires chez des triathlètes Elite : étude rétrospective basée sur Internet**

### ***5.1 Objectifs de l'étude***

Outre le profil sexuel des athlètes, les disciplines sportives jouent également un rôle dans la survenue de SCD. Il a été rapporté que les athlètes d'endurance étaient plus susceptibles de souffrir de CVD. En effet, une étude rétrospective antérieure portant sur 30 sports olympiques a révélé que, par rapport à d'autres sports, les athlètes d'endurance, en particulier les triathlètes de courte distance, présentent une prévalence relativement élevée et inattendue d'événements cardiaques. Cette étude a attiré notre attention parce que le triathlon est devenu un sport de plus en plus populaire dans le monde entier au cours des dernières décennies. L'United States Triathlon a rapporté que plus de 460 000 participants ont pris part à plus de 3 200 événements sanctionnés pour adultes en 2015. Au fil des ans, le nombre de décès a suscité des inquiétudes quant à la sécurité des athlètes dans ce sport de compétition. Par conséquent, pour étudier le risque cardiaque chez les triathlètes, l'objectif spécifique de la deuxième étude était de déterminer la prévalence des maladies cardiovasculaires chez les triathlètes Elite en fonction du sexe, des disciplines triathlétiques et des formats.

### ***5.2 Matériel et méthodes***

La présente étude rétrospective a examiné la prévalence des CVD chez des triathlètes Elite de onze disciplines du triathlon entre 2006 et 2019, à partir de données internet. Après avoir établi la liste des triathlètes (Top 10 mondial dans chaque discipline du triathlon), les CVD rapportées par les médias ont été identifiées sur le web

via le moteur de recherche Google. Plusieurs recherches ont été effectuées sur les mêmes athlètes en utilisant des termes différents. Un cardiologue a ensuite confirmé les résultats sur la base des informations disponibles. Les athlètes décédés ou ayant interrompu leur carrière sportive en raison d'anomalies cardiaques liées au sport ont été identifiés comme ayant des conséquences graves.

### **5.3 Résultats**

Le nombre total d'athlètes était de 1329 (hommes 639, femmes 690). L'âge moyen à l'inclusion était de  $30 \pm 6$  ans, et à l'exclusion de  $31 \pm 6$  ans. Douze maladies cardiaques ont été observées, la prévalence globale des CVD chez les triathlètes d'élite était de 0.90%. Les résultats les plus graves sont tous des hommes (0.38%). La prévalence et la fonction de risque des CVD sur les distances courtes/moyennes étaient plus élevées que sur les distances longues et ultra-longues ( $p=0.04$  et  $0.03$ ). La prévalence des athlètes pratiquant plusieurs types de disciplines sportives (3.55%) était significativement plus élevée que celle des athlètes ne pratiquant qu'un seul type de sport (0.52%) ( $p=0.002$ ).

### **5.4 Conclusion**

La prévalence du risque cardiaque était plus élevée chez les triathlètes hommes que chez les triathlètes femmes. Les athlètes des formats courte/moyenne distance étaient plus enclins à souffrir de maladies cardiaques. Ces résultats doivent attirer notre attention et nous encourager à mener des études prospectives sur les triathlètes. Compte tenu du nombre croissant d'individus participant à des triathlons, il est impératif d'améliorer le dépistage et le suivi des risques potentiels de maladies cardiovasculaires dans cette population.

## ● DÉPISTAGE CARDIAQUE DES ATHLÈTES

De part le risque cardiaque non négligeable auquel sont confrontés les athlètes, l'identification précoce des sujet à risque suscite un intérêt considérable. Le dépistage cardiovasculaire préalable est une pratique systématique d'évaluation médicale des athlètes avant la pratique d'un sport, afin d'identifier (ou de suspecter) des anomalies susceptibles d'entraîner une progression de la maladie ou une mort subite. Dans certains pays, la loi exige que chaque athlète subisse une évaluation clinique pour être éligible. Une étude intéressante menée par des chercheurs italiens a révélé que l'incidence de la SCD chez les jeunes athlètes de compétition a diminué de manière significative dans la région de Vénétie, en Italie, depuis l'introduction d'un dépistage systématique à l'échelle nationale. En effet, l'analyse des données a révélé qu'au cours de la période d'étude, l'incidence annuelle des SCD a diminué de 89 % chez les athlètes dépistés. Une étude plus récente portant sur une large population d'enfants italiens a révélé que le dépistage cardiovasculaire préalable à la participation permettait d'identifier les maladies cardiovasculaires à risque de mort subite sur l'ensemble de la tranche d'âge étudiée et plus souvent lors d'évaluations répétées. Ces résultats favorables et ces données de survie prouvent de manière irréfutable que la détection précoce par le dépistage avant la compétition et la prise en charge appropriée des maladies cardiovasculaires à risque de mort subite dans la population d'athlètes peuvent sauver des vies.

Cependant, il existe des différences significatives dans les lignes directrices consensuelles pour les protocoles de dépistage pré-participatif utilisés par les cardiologues/médecins du sport européens et américains. Le débat porte sur les méthodes et la raison d'être du dépistage pré-participatif, y compris l'utilisation de l'ECG à 12 dérivation. Le groupe d'experts de l'American Heart Association recommande que les antécédents personnels et familiaux ainsi que l'examen physique



soient des stratégies potentiellement efficaces pour lever les soupçons de maladies cardiovasculaires. La Société européenne de cardiologie et le Comité international olympique recommandent quant à eux de combiner les tests non invasifs (par exemple, l'ECG à 12 dérivations) avec les antécédents personnels et familiaux et l'examen physique standard. Cette stratégie de dépistage repose sur le fait que l'ECG est un outil puissant pour détecter ou suspecter de nombreuses maladies cardiovasculaires à l'origine de la mort subite chez les jeunes athlètes.

Le programme de dépistage italien a permis de détecter avec succès des anomalies cardiovasculaires, en particulier la CMH et d'autres cardiomyopathies, ce qui a conduit à la disqualification de nombreux athlètes afin de réduire le risque de décès par SCD. Les chercheurs attribuent cette réduction du taux de décès à leur programme national systématique de dépistage avant la compétition, qui comprend systématiquement un ECG à 12 dérivations. D'après l'expérience à long terme de l'Italie, le dépistage cardiaque préalable à la participation des athlètes de compétition, principalement par ECG, semble être une stratégie qui permet de sauver des vies.

Bien que les tests cardiovasculaires préalables à la participation offrent la possibilité d'identifier les athlètes présentant des anomalies cardiovasculaires potentiellement mortelles avant l'apparition des symptômes et de réduire leur risque de mort subite, l'efficacité, l'impact des résultats faussement positifs et le rapport coût-efficacité du dépistage systématique font l'objet d'un débat considérable chez les cardiologues. En particulier, le taux de faux positifs pour le dépistage par ECG peut atteindre 5 à 10%, ce qui conduit à des examens secondaires inutiles ou à des restrictions de l'activité physique. Toutefois, dans une étude portant sur 42 386 athlètes soumis à un dépistage initial, 3,914 (9%) ont été orientés vers des examens complémentaires et 879 (2%) ont finalement été disqualifiés pour des raisons cardiovasculaires. Par conséquent, le pourcentage de résultats faussement positifs (par exemple, les athlètes

dont le cœur est normal mais dont les résultats du dépistage sont positifs) nécessitant des tests supplémentaires est de 7%, avec un effet proportionnel modeste sur les coûts. De même, des études ont indiqué que dans une vaste population non sélectionnée de jeunes gens soumis à un dépistage cardiovasculaire, la prévalence de schémas ECG nettement anormaux suggérant une cardiopathie structurelle est faible (<5%) et ne devrait pas empêcher l'utilisation de l'ECG à 12 dérivation dans le cadre d'un dépistage avant la participation. Notamment, le taux de faux positifs pour le dépistage par ECG est fortement influencé par les critères utilisés pour définir les "anomalies". Des normes modernes ont été proposées pour différencier les adaptations cardiaques physiologiques chez les athlètes des résultats suggérant une pathologie sous-jacente, à savoir les critères de l'ESC ou, plus récemment, les "critères de Seattle". Les études utilisant ces critères ECG modernes ont abouti à des taux de faux positifs nettement inférieurs, et de nouvelles propositions sont faites pour affiner l'interprétation de l'ECG de l'athlète. Par conséquent, l'ECG peut être une stratégie nécessaire pour le dépistage cardiovasculaire avant la participation afin de prévenir le risque de SCD chez les athlètes.

## **1 Étude 3 : Dépistage cardiaque basé sur l'électrocardiogramme chez les triathlètes masculins et féminins**

### ***1.1 Objectifs de l'étude***

Comme nous l'avons décrit précédemment, l'incidence de la mort subite d'origine cardiaque chez les triathlètes est étonnamment élevée. Nous pensons donc que le dépistage cardiovasculaire avant la participation, en particulier l'évaluation cardiaque basée sur l'ECG, pourrait jouer un rôle dans l'identification des maladies cardiovasculaires potentielles susceptibles d'induire un décès par crise cardiaque chez les athlètes Elite. En outre, les schémas ECG varient considérablement d'un sexe à l'autre. Jusqu'à présent, les différences entre les sexes dans les caractéristiques de l'ECG chez les triathlètes restent inconnues. Par conséquent, l'objectif de l'étude suivante était d'étudier les caractéristiques ECG des triathlètes Elite en fonction du sexe.

### ***1.2 Matériel et méthodes***

Les triathlètes masculins et féminins inscrits sur les listes ministérielles françaises de sportifs de haut niveau entre 2015 et 2021 ont été impliqués dans cette étude. Les informations cliniques des athlètes (telles que les informations de base et les volumes d'entraînement) et les résultats de l'ECG ont été obtenus à partir de MediSharp. Les résultats de l'ECG ont été interprétés par un cardiologue en aveugle des données cliniques selon les critères cliniques. Les mesures quantitatives ont été collectées et confirmées par inspection visuelle, notamment la FC, l'intervalle RR, l'onde P, l'intervalle PR ou PQ, le complexe et l'axe QRS, l'intervalle QT et le QTc.

### **1.3 Résultats**

Quatre-vingt six triathlètes (homme  $n=50$ , femme  $n=36$ ) ont participé à cette étude, l'âge moyen était de  $19.9\pm 4.8$  ans (homme  $20.2\pm 5.2$ , femme  $18.7\pm 4.1$ ,  $p>0.05$ ). Les mesures ECG ont révélé que les hommes avaient des ondes P relativement plus grandes que les femmes ( $96.0\pm 12.0$  vs.  $89.9\pm 11.5$  ms,  $p=0.02$ ). De même, les hommes avaient un complexe QRS significativement plus long que les femmes ( $96.6\pm 11,1$  vs.  $90.3\pm 8.6$  ms,  $p=0.005$ ). Tous les indicateurs étaient dans les limites de la normale. Les manifestations électriques les plus fréquentes chez les triathlètes étaient une repolarisation précoce (46.5%) et un BBD incomplet (39.5%). Il n'y a pas de différence statistique entre les manifestations électriques entre les deux sexes ( $p>0.05$ ).

### **1.4 Conclusion**

Pour des volumes d'entraînement presque similaires (environ 20 heures/semaine), les triathlètes masculins avaient une durée d'onde P relativement plus longue et un voltage QRS plus élevé que les femmes, mais tous les schémas ECG se situaient dans les limites normales. Les manifestations ECG les plus courantes chez les triathlètes étaient une repolarisation précoce et un BBD incomplet, quel que soit le sexe. Les résultats de l'étude suggèrent que les triathlètes masculins sont plus sensibles aux changements physiologiques que les femmes. De grands échantillons sont nécessaires pour confirmer ces résultats et pour mieux comprendre le remodelage cardiaque chez les triathlètes afin de déterminer les raisons du risque cardiaque accru chez les triathlètes masculins.

## **2 Étude 4 : Dépistage cardiaque basé sur l'électrocardiogramme chez les triathlètes et cyclistes Elite**

### ***2.1 Objectifs de l'étude***

Comme nous l'avons vu précédemment, le triathlon semble être à risque de pathologies cardiovasculaires. Bien que normal, les ECG des triathlètes présentent des particularités telles que la forte proportion de repolarisation précoce prononcée et de BBD incomplet. De plus, les triathlètes masculins semblent plus touchés que les femmes. Néanmoins, dans le but de mieux comprendre le remodelage cardiaque des triathlètes et dans une perspective de prévention, il nous a semblé intéressant de comparer le triathlon à l'un des trois sports qui le constituent, le cyclisme, en termes de remodelage cardiaque. L'objectif de notre 4ème étude était donc de comparer les caractéristiques ECG entre des triathlètes et des cyclistes Elite.

### ***2.2 Matériel et méthodes***

Des triathlètes et des cyclistes Elite de sexe masculin ont participé à cette étude. La liste des athlètes et les dossiers des examens physiques de routine, y compris les résultats de l'ECG, ont été obtenus auprès de la Fédération Française de Triathlon, de la Fédération Française de Cyclisme et de MediSharp. L'ECG a été interprété par un cardiologue (TL). Les schémas ECG ont été évalués conformément aux critères cliniques généralement acceptés. Les mesures quantitatives, y compris la FC, l'intervalle RR, l'onde P, l'intervalle PR ou PQ, le complexe QRS, l'axe QRS, l'intervalle QT et le QTc, ont été calculées automatiquement et confirmées par une inspection visuelle.

### **2.3 Résultats**

Tous les 105 athlètes masculins, 42 d'entre eux pratiquant le triathlon courte distance (40%), et 63 le cyclisme sur route (60%). L'âge moyen était de  $22.1 \pm 4.2$  ans (triathlètes  $21.1 \pm 5.1$  ans, cyclistes  $22.8 \pm 3.4$  ans,  $p=0.07$ ). Les évaluations ECG ont révélé que l'amplitude de l'onde P était significativement plus faible chez les triathlètes que chez les cyclistes ( $95.5 \pm 11.6$  vs.  $102.1 \pm 11.4$  ms,  $p=0.005$ ). Aucune différence statistique significative n'a été trouvée dans la FC, l'intervalle RR, l'intervalle PR ou PQ, le complexe QRS, l'axe QRS, l'intervalle QT et le QTc ( $p>0.05$ ). Tous les indicateurs se situaient dans la fourchette normale. Les manifestations électriques les plus fréquentes chez les athlètes étaient la repolarisation précoce (60.95%, 64/105) et le BBD incomplet (43.81%, 46/105). La prévalence de la repolarisation précoce chez les triathlètes était de 52,38% (22/42) et chez les cyclistes de 66,67% (42/63) ; la prévalence du BBD incomplet chez les triathlètes était de 42.86% (18/42) et chez les cyclistes de 44,444% (28/63). Pour tous les indicateurs, aucune différence statistique n'a été trouvée entre les triathlètes et les cyclistes.

### **2.4 Conclusion**

La repolarisation précoce et le BBD incomplet étaient les manifestations ECG les plus courantes chez les triathlètes et les cyclistes, ce qui indique une adaptation physiologique à un exercice d'endurance intensif et prolongé. Cependant, aucune différence significative dans les paramètres ECG n'a été observée entre les deux populations. Ainsi, les adaptations de l'ECG pourraient ne pas expliquer le risque cardiaque plus élevé chez les triathlètes que chez les cyclistes. D'autres études sont nécessaires pour explorer l'effet de la discipline sportive sur le remodelage cardiaque prononcé chez les triathlètes Elite.

## ● OUVERTURE

À l'heure actuelle, certaines questions doivent encore être résolues: (1) La limite supérieure des bénéfices de l'activité physique pour la santé et la "dose optimale" ne sont pas claires; (2) Les causes et circonstances spécifiques chez les athlètes devraient être clarifiées davantage en fonction du sexe, des disciplines sportives, de l'âge, de l'origine ethnique et des niveaux d'entraînement; (3) L'interprétation de l'ECG d'un athlète est souvent déléguée à l'expérience personnelle et est généralement basée sur les critères ECG traditionnels utilisés dans la population générale. Il existe donc un besoin critique de formation des médecins à l'interprétation moderne de l'ECG qui distingue les adaptations physiologiques normales des modèles distinctement aberrants qui peuvent indiquer une pathologie sous-jacente ; (4) Bien que l'ECG au repos puisse détecter la plupart des causes de SCD chez l'athlète, l'ECG a des limites à la fois en termes de sensibilité et de spécificité. Plus précisément, l'ECG ne permet pas d'identifier les anomalies coronaires, l'athérosclérose coronaire prématurée et les aortopathies, et les résultats faussement positifs de l'ECG sont fréquents dans la détection de la CMH. Par conséquent, l'ECG d'effort, l'évaluation échocardiographique et l'imagerie par résonance magnétique cardiaque doivent être envisagés pour réduire le diagnostic différentiel, en particulier pour les athlètes présentant une hypertrophie de la "zone grise"; (5) Bien que le dépistage cardiaque préalable à la participation des athlètes joue un rôle important dans la prévention des événements tragiques, il est important de noter que la plupart des athlètes, en particulier dans les sports amateurs et de loisirs, ne se soumettent pas à un dépistage régulier. En outre, on estime que 10 % des événements cardiaques ne peuvent être évités par un dépistage avant la participation. Compte tenu de tous ces effets, les mesures de prévention secondaire et de "secours sur le terrain" sont d'une importance capitale. Ainsi, la meilleure stratégie consiste à combiner de manière synergique la prévention primaire en identifiant les athlètes présentant un risque cardiaque avant la pratique du

sport et la prévention secondaire en cas d'arrêt cardiaque arythmique imprévisible; (6)

La survie après un SCA peut être améliorée de manière significative en impliquant des sauveteurs non professionnels dans la réanimation cardio-pulmonaire et l'utilisation d'un DEA par le biais de programmes de défibrillation accessibles au public, spécifiquement conçus pour réduire le délai entre l'arrêt cardiaque et l'administration du choc. Toutefois, les programmes de sécurité cardiovasculaire présentent de nombreuses lacunes. Par exemple, une étude intéressante montre que 28% des clubs consultés ne disposaient pas de ADE dans leur stade et 36% n'avaient pas de plan d'action médical documenté décrivant les procédures de sécurité cardiovasculaire. En outre, 41% des clubs ont indiqué que le temps de transport entre le stade et l'hôpital le plus proche était supérieur à 5 minutes. D'après ce qui précède, il est concevable que les installations pour l'ADE soient également inadéquates sur les sites d'autres sports. Par conséquent, la disponibilité immédiate d'un ADE pourrait potentiellement sauver la vie des athlètes asymptomatiques, en fournissant un filet de sécurité pour l'imprécision de la stratégie proactive chez les athlètes. En outre, environ 81 % des retards de réanimation cardio-pulmonaire sont dus à une mauvaise interprétation ou à une méconnaissance des symptômes. Par conséquent, une formation régulière à la réanimation cardio-pulmonaire des athlètes et du personnel ayant un accès direct à un ADE est également recommandée pour faire du SCA un événement plus courant auquel il est possible de survivre.



# PART 7. APPENDIX

## 1 Search strategies

- ✧ Keywords: athletes; sudden cardiac arrest; sudden cardiac death
- ✧ Searching date: 2022.12.28-2023.06.15, updated until 2023.12.31

### **PubMed** Results: 2049

- #1 "Athletes"[MeSH Terms] OR "Athletes"[Title/Abstract]
- #2 "death, sudden, cardiac"[MeSH Terms] OR "sudden cardiac death" [Title/Abstract] OR "sudden death"[Title/Abstract] OR "cardiac death"[Title/Abstract] OR "sudden cardiac arrest"[Title/Abstract] OR "cardiac arrest"[Title/Abstract]
- #3 #1 AND #2

### **Embase** Results: 3635

- #1 athletes'/exp OR athletes
- #2 'sudden cardiac death'/exp OR 'sudden cardiac death' OR (sudden AND ('cardiac'/exp OR cardiac) AND ('death'/exp OR death)) OR 'cardiac death':ab,ti OR 'sudden death':ab,ti OR 'sudden cardiac arrest':ab,ti OR 'cardiac arrest':ab,ti
- #3 #1 AND #2

### **Scopus** Results: 3628

- #1 TITLE-ABS-KEY ( athletes )
- #2 ( TITLE-ABS-KEY ( sudden AND cardiac AND death ) OR TITLE-ABS-KEY ( sudden AND death ) OR TITLE-ABS-KEY ( cardiac AND death ) OR TITLE-ABS-KEY ( sudden AND cardiac AND arrest ) OR TITLE-ABS-KEY ( cardiac AND

arrest ) )

#3 #1 AND #2

**SPORT Discus** Results: 726

#1 TI athletes OR AB athletes

#2 TI sudden cardiac death OR AB sudden cardiac death OR TI sudden death OR AB sudden death OR TI cardiac death OR AB cardiac death OR TI sudden cardiac arrest OR AB sudden cardiac arrest OR TI cardiac arrest OR AB cardiac arrest

#3 #1 AND #2

**Cochrane** Results: 47

#1 MeSH descriptor: [Athletes] explode all trees

#2 (athletes):ti,ab,kw

#3 #1 OR #2

#4 MeSH descriptor: [Death, Sudden, Cardiac] explode all trees

#5 (sudden cardiac death):ti,ab,kw OR (cardiac death):ti,ab,kw OR (sudden death):ti,ab,kw OR (sudden cardiac arrest):ti,ab,kw OR (cardiac arrest):ti,ab,kw

#6 #4 OR #5

#7 #3 AND #6

## 2 Ethics community



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Avis n° 21.64

Rennes, le 01/06/21

Cher Confrère,

Après étude du projet de recherche

**«Cardiac events in world-class athletes: an internet-based study »**

Le comité d'éthique du CHU de Rennes estime que ce projet de recherche ne contrevient pas à l'éthique médicale.

Cet avis du comité d'éthique a été émis à l'unanimité de ses membres présents.

En vous souhaitant bonne réception.

Veillez agréer, Cher Confrère, l'expression de ma considération la meilleure.

Pour le comité d'éthique  
Vincent MOREL

CHU Rennes La Tauvrais -2 rue de La Tauvrais - 35033 Rennes Cedex 9 - ☎ 02.99.87.35.53





**Title :** The occurrence of cardiovascular disease and electrocardiogram-based cardiac screening in elite athletes

**Keywords:** Cardiovascular disease; Elite athletes; Triathlon; Cycling; Electrocardiogram

**Abstract:** Sudden cardiac death in athletes is a tragic event that has attracted widespread attention. However, the incidence and specific causes remain unclear. To evaluate sex differences of the risk in competitive athletes, study 1 found that the incidence was lower in females than in males; the most common cause in females was congenital coronary anomaly, whereas in males it was hypertrophic cardiomyopathy. To assess the prevalence in elite triathletes, study 2 found that cardiac events were more common in short distance triathlon than in long and ultra-long-distance triathlon, with severe outcomes observed only in males. Due to the morbidity of death in the absence of antecedent symptoms, study 3 assessed the sex differences in electrocardiographic (ECG) characteristics in triathletes; the studies found that ECG changes in athletes represent physiological adaptations to exercise; the most common changes were incomplete right bundle branch block (RBBB) and early repolarization; males were more susceptible to physiological changes than females. Study 4 compared ECG characteristics between triathletes and cyclists. The study found that the ECG manifestations in athletes without sport specificity.

**Titre :** L'apparition de maladies cardiovasculaires et le dépistage cardiaque par électrocardiogramme chez les sportifs de haut niveau

**Mots-clés :** Maladie cardiovasculaire; Athlètes d'élite; Triathlon; Cyclisme; Électrocardiogramme

**Résumé :** La mort cardiaque subite chez les athlètes est un événement tragique qui a suscité une grande attention. Cependant, l'incidence et les causes spécifiques restent floues. Pour évaluer les différences de risque entre les sexes chez les athlètes de compétition, l'étude 1 a révélé que l'incidence était plus faible chez les femmes que chez les hommes ; la cause la plus fréquente chez les femmes était une anomalie coronarienne congénitale, tandis que chez les hommes, il s'agissait d'une cardiomyopathie hypertrophique. Pour évaluer la prévalence chez les triathlètes d'élite, l'étude 2 a révélé que les événements cardiaques étaient plus fréquents dans le triathlon de courte distance que dans le triathlon de longue et d'ultra-longue distance, et que les conséquences graves n'étaient observées que chez les hommes. En raison de la morbidité du décès en l'absence de symptômes antérieurs, l'étude 3 a évalué les différences entre les sexes dans les caractéristiques électrocardiographiques (ECG) chez les triathlètes ; les études ont montré que les changements ECG chez les athlètes représentent des adaptations physiologiques à l'exercice ; les changements les plus courants sont un bloc de branche droit incomplet et une repolarisation précoce ; les hommes sont plus susceptibles de subir des changements physiologiques que les femmes. L'étude 4 a comparé les caractéristiques ECG des triathlètes et des cyclistes. L'étude a montré que les manifestations ECG chez les athlètes ne sont pas spécifiques à un sport.