# Sudden Cardiac Death Among Adolescents in the United Kingdom

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## ABSTRACT

**BACKGROUND** Causes and precipitating factors of sudden cardiac death (SCD) in adolescents are poorly understood.

**OBJECTIVES** The authors sought to investigate the etiologies of SCD and their association with physical activity in a large cohort of adolescents.

**METHODS** Between 1994 and June 2022, 7,675 cases of SCD were consecutively referred to our national cardiac pathology center; 756 (10%) were adolescents. All cases underwent detailed autopsy evaluation by expert cardiac pathologists. Clinical information was obtained from referring coroners.

**RESULTS** A structurally normal heart, indicative of sudden arrhythmic death syndrome was the most common autopsy finding (n = 474; 63%). Myocardial diseases were detected in 163 cases (22%), including arrhythmogenic cardiomyopathy (n = 36; 5%), hypertrophic cardiomyopathy (n = 31; 4%), idiopathic left ventricular hypertrophy (n = 31; 4%), and myocarditis (n = 30; 4%). Coronary artery anomalies were identified in 17 cases (2%). Decedents were competitive athletes in 128 cases (17%), and 159 decedents (21%) died during exercise. Arrhythmogenic cardiomyopathy was diagnosed in 8% of athletes compared with 4% of nonathletes ($P = 0.05$); coronary artery anomalies were significantly more common in athletes (9% vs 1%; $P < 0.001$), as well as commotio cordis (5% compared with 1% in nonathletes; $P = 0.001$). The 3 main comorbidities were asthma (n = 58; 8%), epilepsy (n = 44; 6%), and obesity (n = 40; 5%).

**CONCLUSIONS** Sudden arrhythmic death syndrome and myocardial diseases are the most common conditions diagnosed at autopsy in adolescent victims of SCD. Among causes of SCD, arrhythmogenic cardiomyopathy, coronary artery anomalies, and commotio cordis are more common in young athletes than in similar age sedentary individuals.

Sudden cardiac death (SCD) is a tragic event that occasionally affects young individuals. A spectrum of cardiac conditions may cause SCD with variable prevalence depending on the age and other demographics of the cohort. Inherited cardiac diseases, such as cardiomyopathies and channelopathies, are the predominant cardiac causes in individuals <35 years of age.[1] Autopsy is

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

**ABBREVIATIONS AND ACRONYMS**

**AC** = arrhythmogenic cardiomyopathy

**AED** = automatic external defibrillator

**CAD** = coronary artery disease

**CHD** = congenital heart disease

**CRY** = Cardiac Risk in the Young

**DCM** = dilated cardiomyopathy

**ECG** = electrocardiogram

**HCM** = hypertrophic cardiomyopathy

**LVH** = left ventricular hypertrophy

**PM** = post-mortem examination

**SADS** = sudden arrhythmic death syndrome

**SCD** = sudden cardiac death

**VHD** = valvular heart disease

an essential first diagnostic step that guides clinical evaluation of surviving relatives toward inherited structural diseases or primary arrhythmogenic syndromes.

Adolescence is the period of life between childhood and adulthood, from ages 10 to 19 years. It is an important phase of development with rapid physical and psychological growth. Genetic conditions that cause SCD may express during the peripuberal phase transitioning from a preclinical state to overt phenotype.[2,3] Therefore, knowledge regarding the precise causes and precipitating factors for SCD in this specific subgroup is required to implement prevention through screening methods and widespread availability of automated external defibrillators (AEDs). Screening with electrocardiograms (ECGs) may facilitate the early diagnosis of cardiomyopathies and channelopathies,[4-6] but has limited value in detecting coronary artery disease (CAD).[4] Conversely, the AED appears to be more effective in the termination of arrhythmias in individuals with CAD or coronary artery anomalies than in athletes with cardiomyopathy.[7]

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The objective of this study was to investigate the causes and circumstances of SCD in a large cohort of adolescents whose heart was referred following a SCD to our cardiovascular pathology center and examined by expert cardiac pathologists.

## METHODS

**SETTING.** The Cardiac Risk in the Young (CRY) center for cardiac pathology is based at St George's University of London. The center has 2 expert cardiac pathologists (M.N.S. and J.W.) and receives >400 whole hearts of cases of SCD across the United Kingdom each year (Supplemental Figure 1). Autopsy practitioners are likely to refer when the clinical history is suggestive of inherited cardiac disease, especially when the death affects a young or athletic individual or when the cause of death is uncertain after the initial autopsy.

**STUDY POPULATION.** We reviewed a database of 7,675 cases of SCD that were referred to the CRY center for cardiac pathology between 1994 and May 2022. SCD was defined as death occurring within 12 hours of apparent wellbeing. On examining the database, we retrieved a subgroup of 756 consecutive cases (10%) who were between age 10 and 19 years at the time of death. Circumstances of death were subdivided broadly into death occurring during exercise and death during rest or sleep. Athletes were defined arbitrarily as individuals engaging in regular organized competitive exercise activity (at least 5 hours/week), outside the usual school commitments.

**AUTOPSY EXAMINATION.** All SCD cases underwent a full autopsy evaluation by the local pathologist. Following the exclusion of extracardiac causes and negative toxicology, the heart was referred to our center after written consent of the coroner and the family of the deceased. Comprehensive macroscopic examination of the whole heart and histological analysis were performed in accordance with the "Guidelines on Autopsy Practice for Sudden Death: With Likely Cardiac Pathology"[8] of the Royal College of Pathologists and the Association for European Cardiovascular Pathology.[9] All cardiac structures were systematically examined. The heart weight was recorded in grams, and ventricular wall thickness and internal cavity dimensions were measured at midventricular level excluding the papillary muscles and fat. A minimum of 10 blocks of tissue were taken for histological analysis as reported previously.[1,10] Sections of myocardium were fixed in formalin, embedded in paraffin, and stained with hematoxylin and eosin, as well as Picrosirius red to highlight collagen.

The criteria for defining specific cardiac pathologies have been previously described and are summarized in **Table 1**. Sudden arrhythmic death syndrome (SADS) was a diagnosis of exclusion, defined as a structurally normal heart with no evident abnormality on macroscopic and histological evaluation, and a negative toxicology screen.

**CLINICAL INFORMATION.** The referring coroner and pathologist were asked to complete a questionnaire inquiring about the demographics of the deceased, past medical history, family history, cardiac symptoms, the nature and level of physical activity, and exact circumstances of death. The data were derived from a number of sources including interview with the family of the deceased, potential witnesses of the SCD, and reports from the deceased's family physician. Data were collected prospectively and stored on our electronic database. Ethical and research governance approval have been granted for this study (London - Stanmore Research Ethics Committee, 10/H0724/38).

**STATISTICAL ANALYSIS.** Statistical analysis was performed using the PASW 18.0 software (SPSS). Results are expressed as mean ± SD for continuous variables or as number of cases (percentage) for categorical variables. Comparison of groups was

**TABLE 1 Pathological Macroscopic and Microscopic Criteria Defining Main Underlying Diseases**

| | Macroscopic | Microscopic |
|---|---|---|
| Hypertrophic cardiomyopathy | Increased left ventricular wall thickness (globally or focally) and/or increased heart weight | Myocyte hypertrophy, myocyte disarray (>20% of myocardial disarray in at least 2 tissue blocks of 4 $cm^2$) and interstitial fibrosis |
| Idiopathic left ventricular hypertrophy | Increase left ventricular wall thickness and increased heart weight | Myocyte hypertrophy ± fibrosis in the absence of myocyte disarray |
| Idiopathic left ventricular fibrosis | Normal heart weight and wall thickness with/without scarring macroscopically | Fibrosis (>20% in at least 2 tissue blocks of 4 $cm^2$) with no myocyte disarray |
| Arrhythmogenic cardiomyopathy | Right or left ventricular thinning, fatty replacement, fibrosis on the epicardial surface or outer wall | Fat and fibrosis (>20% in at least 2 tissue blocks of 4 $cm^2$) in the wall of the right and/or left ventricle, particularly in outer wall, with degenerative changes in the myocytes |
| Myocarditis | Normal or dilated ventricles | Inflammation (>20% in at least 2 tissue blocks of 4 $cm^2$) with myocyte Necrosis |
| Anomalous coronary artery | Anomalous origin of the coronary artery, coronary artery atresia, stenosis | Fibrosis/acute/chronic infarction in the left ventricle |
| Coronary atherosclerosis | Atherosclerosis with estimated luminal narrowing >75% | Acute or chronic infarction in the left ventricle |
| Dilated cardiomyopathy | Increase in heart weight with dilated left ventricle (>4 cm) and thin wall (<10 mm). Absence of coronary artery disease. | Diffuse interstitial and replacement fibrosis (>20% in at least 2 tissue blocks of 4 $cm^2$) in the left ventricle with degenerative changes in the myocytes |
| Mitral valve prolapse | Prolapse of mitral valve above the atrioventricular junction with ballooning between chordae in 1 or both leaflets | Myxoid degeneration with expansion in spongiosa of leaflets and destruction of fibrosa layer |
| Bicuspid aortic valve | Fusion of 2 aortic cusps, with or without presence of a raphe often with significant valve stenosis | |
| Morphologically normal heart | Normal | Normal |

performed using Student's *t*-test for continuous variables with correction for unequal variance when necessary, and chi-square test or Fisher exact test, as appropriate for categorical variables.

## RESULTS

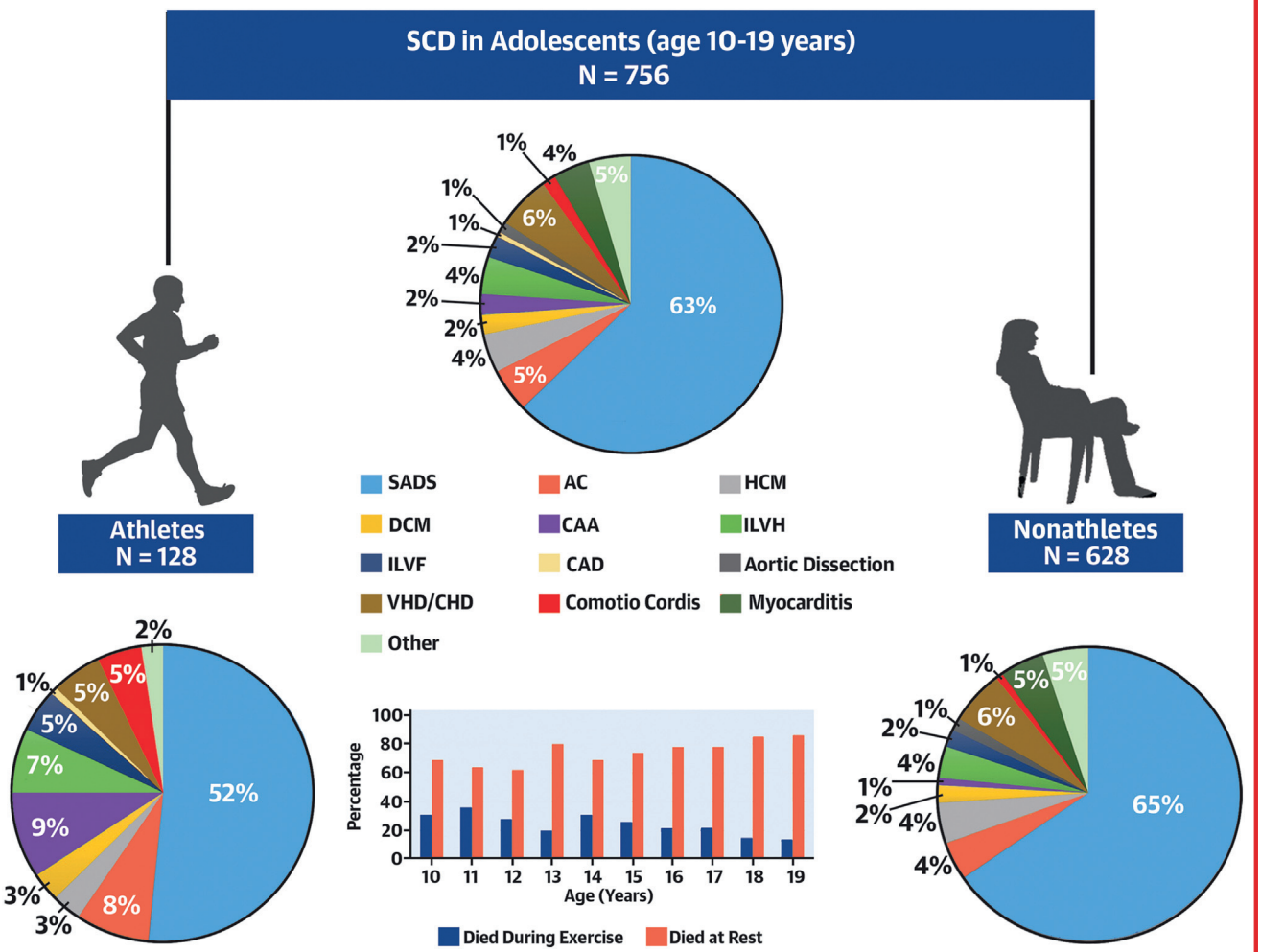
**CLINICAL CHARACTERISTICS.** The mean age at death of the 756 adolescents was 16 ± 2 years, with a male predominance (n = 521; 69%). A total of 128 (17%) were athletes, participating in regular training and competition. Sporting disciplines were soccer (n = 59; 46%), daily frequenters of the gym (n = 12; 9%), swimming (n = 10; 8%), running (n = 10; 8%), cycling (n = 8; 6%), and rugby (n = 8; 6%).

Most decedents were asymptomatic from the cardiac standpoint (n = 571; 75%) and did not have a prior history of cardiac disease (n = 691; 91%). A significant history of cardiac disease was reported in 65 individuals: 30 were diagnosed during life with a congenital heart disease (CHD) and/or valve disease (VHD), 14 had a diagnosis of cardiomyopathy (2 arrhythmogenic cardiomyopathy [AC], 8 hypertrophic cardiomyopathy [HCM], and 4 dilated cardiomyopathy [DCM]). Sixteen individuals experienced a precedent episode of arrhythmia and/or a diagnosis of channelopathy was made: 4 were found to have exercise-induced ventricular arrhythmias (postmortem examination [PM] consistent with SADS in 3 and CHD in 1), 3 had a diagnosis of long QT syndrome (PM consistent with SADS), 2 were found to have nonsustained ventricular tachycardia (PM consistent with SADS in 1 and AC in 1) and 2 had runs of supraventricular tachycardia at ambulatory ECG monitoring (PM consistent with SADS in both), 2 were reported to have had significant bradycardia (PM consistent with HCM in 1 and SADS in 1), 1 individual was diagnosed with atrioventricular block not requiring a pacemaker (PM consistent with CHD), in 1 case, a diagnosis of Wolff-Parkinson-White syndrome was made (PM consistent with SADS), and 1 young woman experienced a cardiac arrest in the context of hypokalemia and anorexia nervosa (PM consistent with SADS). Four individuals underwent a cardiac transplant (3 for DCM and 1 for AC); 1 had a history of hypertension. A family history of premature sudden death (defined as death of a first-degree relative <50 years) was reported in 116 cases (15%).

The main comorbidities were asthma (n = 58; 8%), epilepsy (n = 44; 6%), obesity (n = 40; 5%), autism (n = 23; 3%), and depression (n = 14; 2%); 168 individuals (22%) were reported to be on regular medications, and asthma medications were the most common (n = 47; 6%), followed by antiepileptic agents (n = 34; 4%).

**ETIOLOGY OF DEATH.** The main causes of death are shown in the Central Illustration. A normal autopsy indicating SADS was the most common finding and accounted for 474 deaths (63%). Myocardial diseases were present in 163 cases (22%). Among these cases, 36 (5%) were diagnosed with AC, followed by HCM (n = 32; 4%), idiopathic left ventricular

**CENTRAL ILLUSTRATION** Causes of Sudden Cardiac Death in Adolescents (Athletes and Nonathletes)

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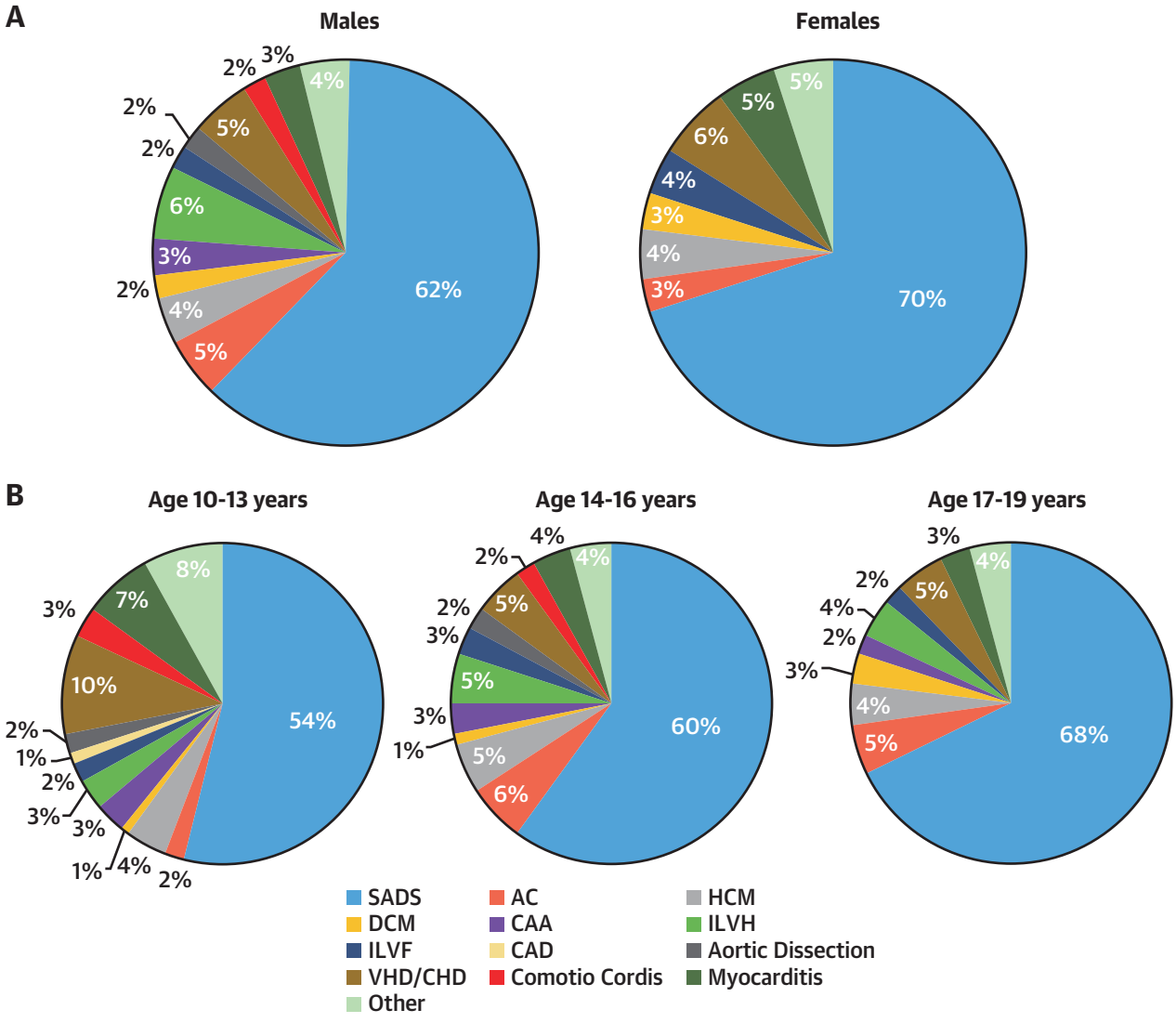
In the overall population the subgroup classified as "Other" (n = 34) comprising: n = 16 myocardial infarction with normal coronaries; n = 4 obesity-related cardiomyopathy; n = 3 transplant vasculopathy; n = 2 left ventricular noncompaction; n = 2 cardiac tumor; n = 2 endocarditis; n = 1 pericarditis; n = 1 thrombosis of mechanical valve; n = 1 sudden death related to diabetes; n = 1 hypertensive heart disease; n = 1 aortitis. AC = arrhythmogenic right ventricular cardiomyopathy; CAA = coronary artery anomaly; CAD = coronary artery disease; CHD = congenital heart disease; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; ILVF = idiopathic left ventricular fibrosis; ILVH = idiopathic left ventricular hypertrophy; SADS = sudden arrhythmic death syndrome; SCD = sudden cardiac death; VHD = valvular heart disease. Etiologies accounting for < 1% are not shown in the pie charts.

hypertrophy (LVH) (n = 31; 4%), and myocarditis (n = 30; 4%). Idiopathic fibrosis and DCM were less common (n = 18; 2%, and n = 16; 2%, respectively). In 21 cases (3%), a coronary artery pathology was the attributed cause of death, with coronary artery anomalies accounting for most of the cases (n = 17; 2%). In 44 decedents, SCD was attributed to a CHD and/or VHD. Among VHD, the most common conditions were mitral valve prolapse (n = 9; 1%) and aortic stenosis due to bicuspid aortic valve (n = 8; 1%).

Commotio cordis was the attributed cause of death in 11 cases (1%) (all decedents showed a morphologically normal heart). Among these, 10 individuals were hit in the chest by a ball practicing sport (6 were playing soccer, 3 cricket, and 1 rugby). One individual died after been hit in the chest by a swing in a playground.

Left ventricular fibrosis was found in 115 cases (15%); the 3 main underlying conditions with myocardial fibrosis were AC (n = 22), idiopathic fibrosis (n = 18), and HCM (n = 16).

**FIGURE 1** Causes of Sudden Cardiac Death According to Sex and Age




Causes of sudden cardiac death according to sex **(A)** and age **(B)** are shown. Sudden arrhythmic death syndrome (SADS) appears to be predominant in both genders but even more so in females. SADS was most common in individuals aged 17 to 19 years. Myocardial disease instead had a different trend according to the underlying pathology. Myocarditis was more frequently diagnosed in the 10- to 13-year-old (YO) group, and arrhythmogenic right ventricular cardiomyopathy (AC) appeared to be more common in the 14- to 16-year-old bracket. CAD = coronary artery disease; CHD = congenital heart disease; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; ILVF = idiopathic left ventricular fibrosis; ILVH = idiopathic left ventricular hypertrophy; VHD = valvular heart disease. Etiologies accounting for < 1% are not shown in the pie charts.

In most of individuals with a diagnosis of asthma and with a diagnosis of epilepsy, SADS was the attributed cause of death (64% and 86%, respectively).

**SCD IN ATHLETES.** The contribution of specific cardiac pathologies differed in athletes and nonathletes (**Central Illustration**). SADS was less common in athletes (52% compared with 65% in nonathletes; $P < 0.001$). Conversely, myocardial diseases were more common in athletes (27% compared with 21% in nonathletes; $P = 0.136$). More specifically, AC was diagnosed in 8% of athletes compared with 4% of nonathletes ($P = 0.05$), whereas myocarditis was exclusively found in nonathletes (n = 30; 5%; $P < 0.001$).

Coronary artery anomalies accounted for 9% of deaths in athletes compared with 1% in nonathletes ($P < 0.001$), and commotio cordis was more common in athletes (5% compared with 1% in nonathletes; $P = 0.001$). Twenty-two athletes had at least 1

comorbidity, among which the most common were asthma (n = 12; 9%), epilepsy (n = 2; 2%), autism (n = 2; 2%), and diabetes (n = 2; 2%).

**CAUSE OF DEATH BY AGE AND SEX.** The contribution of specific cardiac pathologies varied with age and sex (Figure 1).

There were 235 females (31%) in our cohort. The majority (70%) showed a normal heart at the autopsy (compared with 62% in males; $P = 0.034$) (Figure 1A). Myocardial disease accounted for SCD in 20% of females compared with 22% in males ($P = 0.68$). Idiopathic LVH was observed only in 1 case among females (compared with 6% of males; $P < 0.001$) and AC was less common in females (3% compared with 5% in males; $P = 0.214$). In the small subgroup of female athletes (14 decedents), myocardial diseases were frequently found (42%), followed by SADS (36%), and AC was the most common cardiomyopathy (21% of the cases).

SADS was most common in individuals aged 17 to 19 years (67% compared with 60% in age 14 to 16 years and 54% in age 10 to 13 years) (Figure 1B). Myocardial disease instead had a different trend according to the underlying pathology. Myocarditis was more frequently diagnosed in the 10- to 13-year-old group (7%, compared with 4% in the 14- to 16-year-old group and 3% in the 17- to 19-year-old group). Conversely, AC appeared to be more common in the 14- to 16-year-old bracket (6% compared with 2% in the 10- to 13-year-old group and 5% in the 17- to 19-year age group). CHD and VHD accounted for 10% of deaths in the younger individuals, compared with 5% in each of the other groups.

**CIRCUMSTANCES OF DEATH.** Most decedents died at rest (n = 597, 79%), including 114 who died during sleep (15%) (Figure 2A). The differences between decedents who died at rest and during exercise are summarized in Table 2. Individuals who died at rest were more likely to demonstrate a normal heart at PM examination (65% compared with 51% in individuals who died during exercise; $P = 0.001$). Conversely, individuals who died during exertion were more likely to exhibit features of AC (9% vs 3%; $P < 0.001$), HCM (9% vs 3%; $P < 0.001$), left ventricular fibrosis (22% vs 13%; $P = 0.005$), and coronary artery anomalies (7% vs 1%; $P < 0.001$).

Athletes died more commonly during exercise (n = 86, 67%). The distribution of athletes and circumstances of death according to age are shown in Figure 2B. Although only 14% of deaths occurred during exercise in decedents aged 19 years, individuals aged ≤13 years died relatively frequently during exercise (in more than 25% of cases). Clinical and pathological differences between athletes who died at rest and during exercise are summarized in Supplemental Table 1.

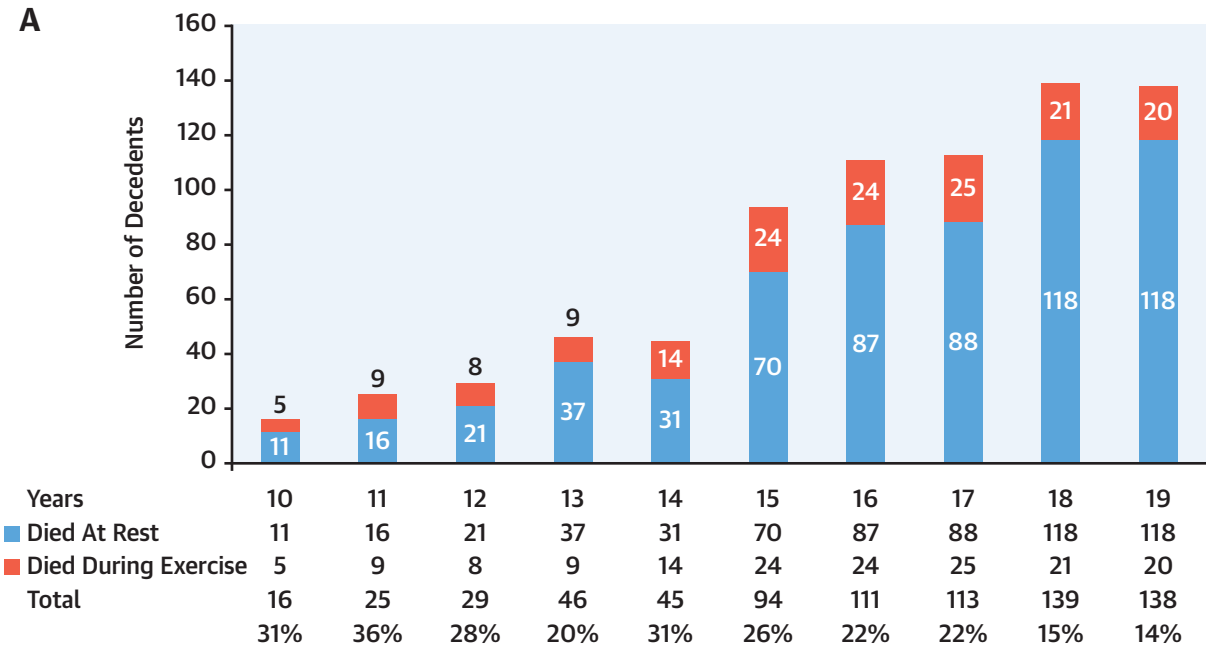
## DISCUSSION

This study reports on a large cohort of adolescents dying suddenly in the United Kingdom where all cardiac autopsies were conducted by cardiac pathologists with expertise in conditions predisposing to SCD. A morphologically normal heart was the predominant autopsy finding in this population, followed by myocardial diseases. Certain conditions, such as AC, coronary anomalies, and commotio cordis, prevailed in young athletes who die suddenly.

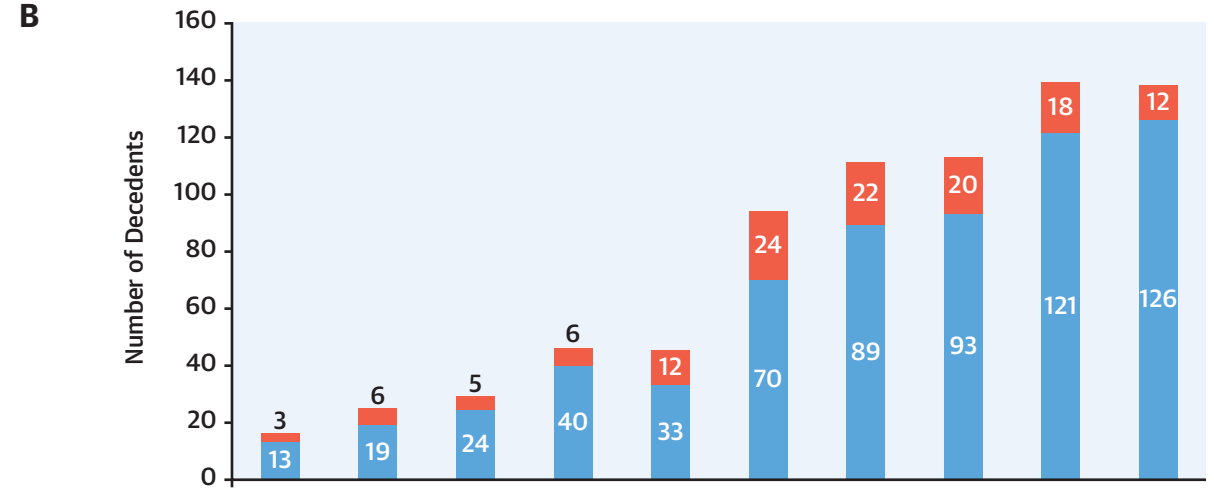
**CAUSES OF SCD IN ADOLESCENTS.** This study shows that a morphologically normal heart was present in 63% of the overall cohort (Central Illustration); these data are in agreement with other reports from our group[1,11,12] and others,[12-16] suggesting a predominance of SADS in young individuals and athletes. While prior studies focused either on individuals younger than a certain age (for example <35 years old[17,18]) or within a specific age bracket (17 to 24 years of age in the case of college athletes[19]), we aimed to investigate the causes of SCD in adolescence. Although the proportion of SADS cases in our cohort may be partly explained by a referral bias, a morphologically normal heart appears to be even more common than prior reports (the prevalence was 42% in individuals <35 years old,[17] 25% in collegiate athletes,[19] and 41% in young military personnel[13]), underscoring the importance of inherited primary arrhythmia syndromes as a major cause of SCD in this specific age group. The discrepancy with prior studies as far as proportion of SADS is concerned may be explained by the stringent age selection (adolescence is different than "youth" on many levels) and by the rigorous standardized protocol used by expert cardiac pathologists in all cases. A prior study from our group showed a disparity of 41% in autopsy diagnosis, between referring pathologists and cardiac pathologists, and the former were more inclined to attribute death to a cardiomyopathy rather than to SADS.[20]

Myocardial disease accounted for 22% of cases. Arrhythmogenic cardiomyopathy, HCM, idiopathic LVH, and myocarditis were the predominant diagnoses. Congenital heart disease and/or VHD accounted for 6% of deaths; in most cases with CHD, a premortem diagnosis was made, something that is in contrast with other etiologies where SCD was the first manifestation of an underlying cardiac disease. It is possible that subtle or incomplete expressions of

**FIGURE 2** Death During Exercise and Athletes in Adolescent Victims of Sudden Cardiac Death




| Years | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
|---|---|---|---|---|---|---|---|---|---|---|
| Died At Rest | 11 | 16 | 21 | 37 | 31 | 70 | 87 | 88 | 118 | 118 |
| Died During Exercise | 5 | 9 | 8 | 9 | 14 | 24 | 24 | 25 | 21 | 20 |
| Total | 16 | 25 | 29 | 46 | 45 | 94 | 111 | 113 | 139 | 138 |
| | 31% | 36% | 28% | 20% | 31% | 26% | 22% | 22% | 15% | 14% |




| Years | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
|---|---|---|---|---|---|---|---|---|---|---|
| Nonathletes | 13 | 19 | 24 | 40 | 33 | 70 | 89 | 93 | 121 | 126 |
| Athletes | 3 | 6 | 5 | 6 | 12 | 24 | 22 | 20 | 18 | 12 |
| Total | 16 | 25 | 29 | 46 | 45 | 94 | 111 | 113 | 139 | 138 |
| | 19% | 24% | 17% | 13% | 27% | 26% | 20% | 18% | 13% | 9% |

The histogram describes sudden cardiac death during exercise **(A)** and the number and proportion of athletes **(B)** according to age in our cohort of adolescents. While only 14% of deaths occurred during exercise in decedents aged 19 years, individuals aged ≤13 years died relatively frequently during exercise (in more than 25% of cases).

**TABLE 2 Characteristics of the Population According to Circumstances of Death**

| | Total (N = 756) | Died During Exercise (n = 159) | Died at Rest (n = 597) | *P* Value |
|---|---|---|---|---|
| Age, y | 16 ± 2 | 16 ± 2 | 16 ± 2 | 1.00 |
| Male | 521 (69) | 136 (85) | 385 (64) | <0.001 |
| FH of SD | 116 (15) | 26 (16) | 90 (15) | 0.755 |
| Athletes | 128 (17) | 86 (67) | 42 (33) | <0.001 |
| Heart weight, g | 330 ± 106 | 350 ± 107 | 325 ± 106 | 0.597 |
| LV fibrosis | 115 (15) | 35 (22) | 80 (13) | 0.005 |
| SADS | 474 (63) | 81 (51) | 393 (66) | 0.001 |
| HCM | 32 (4) | 14 (9) | 18 (3) | <0.001 |
| AC | 36 (5) | 14 (9) | 22 (4) | <0.001 |
| ILVH | 31 (4) | 9 (6) | 22 (4) | 0.276 |
| ILVF | 18 (2) | 3 (2) | 15 (3) | 0.496 |
| Coronary anomalies | 17 (2) | 12 (7) | 5 (1) | <0.001 |
| CHD and/or VHD | 44 (6) | 7 (4) | 37 (6) | 0.329 |
| Myocarditis | 30 (4) | 1 (1) | 29 (5) | 0.02 |
| Comorbidities | 225 (30) | 36 (4) | 189 (32) | <0.001 |
| Asthma | 58 (8) | 16 (10) | 42 (7) | 0.205 |
| Epilepsy | 44 (6) | 5 (3) | 39 (7) | 0.06 |
| Obesity | 40 (5) | 6 (4) | 34 (6) | 0.329 |
| Autism | 23 (3) | 4 (3) | 19 (3) | 1.00 |
| Depression | 17 (2) | 0 (0) | 17 (3) | 0.027 |
| Medications | 168 (22) | 27 (17) | 141 (24) | 0.06 |
| Antiasthmatic agents | 45 (6) | 12 (8) | 33 (6) | 0.36 |
| Antiepileptic agents | 34 (5) | 4 (3) | 30 (5) | 0.284 |
| Antidepressants | 13 (2) | 0 (0) | 13 (2) | 0.07 |
| Antiarrhythmics | 13 (2) | 2 (1) | 11 (2) | 0.398 |
| Antidiabetics | 8 (1) | 1 (1) | 7 (1) | 1.00 |

Values are mean ± SD or n (%),

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

cardiomyopathy may have been labeled as SADS, simply because we focused on a very young cohort, where perhaps a genetic abnormality did not manifest through an overt structural phenotype yet. Recent studies have shown that in cases where the autopsy is normal or inconclusive, pathogenic variants may be found in cardiomyopathy genes, and especially in genes linked to AC.[21] Particularly in this condition, the severity of arrhythmias may precede the structural changes.

The significance of idiopathic LVH and idiopathic fibrosis remains uncertain. Idiopathic LVH may be an innocent bystander but may also be a trigger for arrhythmias in individuals with underlying primary arrhythmia syndromes. A recent study based on family screening of decedents with idiopathic LVH at autopsy suggests that this entity is not a variant of HCM.[22] Idiopathic fibrosis may be the result of a healed myocarditis or incomplete expression of a cardiomyopathy.[23,24]

Importantly, male sex was prevalent in our cohort of decedents (69%). This is in line with prior reports on athletes and nonathletes.[25,26] Although there were some differences in causes of SCD according to age subgroups, these were mainly not statistically significant.

Comorbidities including asthma and epilepsy were common in our study. Interestingly, most of individuals with asthma and epilepsy had a normal heart at autopsy. The relatively high proportion of epilepsy among SADS cases raises the possibility of sudden unexpected death in epilepsy, but it is also possible that in some of these decedents, features of epileptic seizures were secondary to hypoxia and ventricular arrhythmias in the context of an underlying primary arrhythmia syndrome.

**YOUNG ATHLETES.** Almost 1 in 5 decedents were athletes engaging in various sporting disciplines (soccer was the most common). Data on SCD in very young athletes are lacking. A study from Minnesota showed a very low incidence of SCD (0.24 per 100,000 athlete-years) in young (12 to 19 years of age) athletes who underwent uniform state-wide preparticipation health screening examination every 3 years.[27] Our study shows that although SADS was predominant, etiologies of death differ in comparison with nonathletes. Arrhythmogenic cardiomyopathy, commotio cordis, and coronary artery anomalies were significantly more common in athletes.

**RELATION OF SCD TO EXERCISE.** As expected, we showed that SCD in athletes occurs more frequently during exercise in comparison with nonathletes. In line with a prior study from our group on SCD in athletes,[1] AC and coronary artery anomalies were associated with death during exercise. Interestingly, this association was observed also in HCM. This is in contrast with our prior study (which included only adult athletes) where deaths from HCM did not show any predilection for exercise.[1] Recent evidence suggest that participation in competitive sport is safe in adult patients with HCM who are deemed at low risk of SCD,[28,29] and this is reflected in international guidelines, which are more liberal on this matter than before.[30] Our findings, however, suggest that adolescent patients with HCM may be particularly vulnerable to exercise-induced arrhythmias, and this evolving paradigm for sports eligibility decisions in athletes may not be applicable to this age group.[31]

**CLINICAL IMPLICATIONS.** Our study provides further understanding on the etiologies of SCD in a large cohort of adolescents. Death occurred mostly at rest (79%) including 15% who died during sleep, suggesting that the provision of AEDs in public venues, although

of great impact for successful resuscitation in the context of cardiac arrest during exercise, would have unlikely prevented these events. Cardiac screening of adolescents, including nonathletes may be a useful way to early diagnose potentially fatal cardiac conditions. A structurally normal heart at autopsy, suggesting a possible primary arrhythmia syndrome as possible cause,[11] and cardiomyopathies were the most common findings. As these conditions are often detectable with an ECG in asymptomatic individuals,[32-34] these deaths are potentially preventable. Our study informs also on the etiologies of SCD in adolescent athletes and on the relation of death to exercise. Cardiomyopathies such as AC and HCM are associated with death during exercise; recommendations for sport activity should be cautious, especially in very young individuals who are diagnosed with these conditions. Adolescents with HCM may be at risk of SCD particularly during exercise with potential implications for sport recommendations.

Interestingly, several organizations that provide cardiac screening in the young, including CRY, recommend testing from the age of 14 years. This is mainly motivated by the higher prevalence of ECG repolarization changes that may be part of a physiological juvenile pattern, with possible misinterpretation of the test as abnormal. The results of our study raise questions on this approach, suggesting that SCD occurs and may be prevented in asymptomatic individuals younger than 14 years.

The relatively high proportion of cases with coronary artery anomalies suggests that the ECG may not be sufficient as a screening tool and perhaps echocardiograms focused on the site of origin of the coronaries should be part of the cardiac assessment in the adolescent athlete.

**STUDY LIMITATIONS.** The CRY center for cardiac pathology at St George's University of London is more likely to receive hearts from subjects where the clinical history is suggestive of an inherited cardiac disease, and local pathologists are more likely to refer challenging cases. These facts introduce a potential referral bias: it is probable that pathologies such as coronary artery atherosclerosis, aortic dissection, and HCM may be under-represented in this cohort. The contribution of less well-defined entities such as idiopathic LVH and a morphologically normal heart may be overestimated. Nevertheless, we receive a high volume of unexpected SCD referrals (>400/year) mainly in individuals <35 years at death, and as SCD in young individuals is a relatively rare event, the large number of examinations performed in our unit in this cohort suggests that the results are a genuine representation of the type and frequency of cardiac diseases implicated in SCD in young athletes.

Clinical data, although thoroughly collected, relied on information sourced from the family physician and the family. Therefore, knowledge of risk factors or subclinical medical conditions that may have not come to the attention of the family doctor (because the patient did not have any symptom) is inherently limited.

Although especially in recent years, spleen samples were collected with the aim of performing molecular autopsy, this was not routinely completed, and as our cohort is historical, we cannot rely on meaningful data from this perspective. Therefore, genetic testing either of the proband or of family members was not part of this analysis.

Our study is a pure autopsy series; therefore, we do not have any data relating to survivors of sudden cardiac arrest. As such, it is possible that the results are biased towards lethal causes of sudden cardiac arrest such as cardiomyopathies and primary arrhythmia syndromes, while diseases more amenable to survival following cardiac arrest are under-represented.[7]

## CONCLUSIONS

Sudden cardiac death is a tragic event that may occur during adolescence, even in apparently healthy individuals and athletes. A structurally normal heart at autopsy and myocardial diseases are the prevalent findings in this population. Coronary anomalies, arrhythmogenic cardiomyopathy, and commotio cordis are common causes of death in young athletes. The strong association of cardiomyopathies and coronary anomalies with exercise-induced SCD reinforces the need for early diagnosis and possible competitive sport restriction in individuals with these conditions. Almost 80% of adolescents die at rest, suggesting the need for complementary preventative strategies, in addition to AED provision.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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** Sudden arrhythmic death syndrome and myocardial diseases are the most common causes of sudden death in adolescents. Arrhythmogenic cardiomyopathy, coronary anomalies and commotio cordis prevail in young athletes who die suddenly. Arrhythmogenic cardiomyopathy, hypertrophic cardiomyopathy, and coronary anomalies are associated with sudden death during exercise.

**TRANSLATIONAL OUTLOOK:** Better understanding of the epidemiology and underlying causes of sudden cardiac death in adolescence could be useful to guide preventive strategies.

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