Sudden cardiac death: A nationwide cohort study among the young

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This review has been accepted as a thesis together with 4 previously published papers by University of Copenhagen 27.01.2015 and defended on 09.06.2015

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Dan Med J 2016;63(12):5321

PREFACE

This PhD thesis is the result of the work that I performed between 2012 and 2014 in the Laboratory of Molecular Cardiology, Department of Cardiology, The Heart Center, University Hospital Rigshospitalet, Copenhagen, Denmark. The thesis is based on the 4 following scientific papers.

I. Risgaard B, Winkel BG, Jabbari R, Behr ER, Ingemann-Hansen O, Thomsen JL, Ottesen GL, Gislason GH, Bundgaard H, Haunsø S, Holst AG, Tfelt-Hansen, J. Burden of sudden cardiac death in persons aged 1 to 49 years: nationwide study in Denmark. Circulation Arrhythm Electrophysiol. 2014 Apr; 7(2):205-11.

II. Winkel BG, Risgaard B, Sadjadieh G, Bundgaard H, Haunsø S, Tfelt-Hansen J. Sudden cardiac death in children (1-18 years): Symptoms and causes of death in a nationwide setting. Eur Heart J. 2014 Apr; 35(13):868-75.

III. Risgaard B, Winkel BG, Jabbari R, Behr ER, Glinge C, Ingemann-Hansen O, Thomsen JL, Ottesen GL, Haunsø S, Holst AG, Tfelt-Hansen, J. Sports-related sudden cardiac death in a competitive and a noncompetitive athlete population aged 12 to 49 years: Data from an unselected nationwide study in Denmark. Heart Rhythm. 2014 oct; 7(2):205-11.

IV. Risgaard B, Waagstein K, Winkel BG, Jabbari R, Lynge TH, Glinge C, Albert C, Correll CU, Haunsø S, Fink-Jensen A, Tfelt-Hansen J. Sudden cardiac death in young adults with previous hospital-based psychiatric in- and outpatient treatment – A nationwide cohort study from Denmark. J Clin Psychiatry. 2015 Sep;76(9):e1122-9

ACKNOWLEDGEMENTS

The last three years in the Laboratory of Molecular Cardiology have truly been very exciting. When I someday look back, I am sure I will think of these years as some of the best. I have learned so much and met so many people whom I would like to thank. Without all of your guidance, help, and friendships, I would never have reached my goal of obtaining a PhD.

First, I would like to thank Professor Stig Haunsø for allowing me to work in his lab. Your support and mentorship have been invaluable to me. I would also like to thank Associate Professor Jacob Tfelt-Hansen for being an excellent supervisor. I am so grateful that you included me in your research group. You have always been on call, and over the last three years, we have had talks almost weekly, discussing current and future projects. You are a true inspiration to me, and I look forward to continuing our friendship, as well as working together. I would also like to thank Bo Gregers Winkel for being an excellent supervisor as well. Your guidance and friendship have been very important to me, and I am glad that we will continue our work together. Henning Bundgaard and Gunnar Gislasson supported the investigation of sudden deaths. Your support and advice have been invaluable. My partner in crime, Reza Jabbari, you have become a very good friend over the last three years. We have worked together on several projects, and I have truly enjoyed being around you at work, as well as outside the laboratory.

I would like to thank all of my previous colleagues in the laboratory. I have greatly enjoyed all of the laughter and the many scientific discussions during lunch hours. In particular, I would like to thank Morten Olesen for his daily leadership in the laboratory and Anders Holst for his great work with the reviewing of death certificates. I am also grateful to all of the forensic pathologists working in the three forensic pathology departments in Denmark. Without access to your departments, this project would never have been carried out. I appreciate that I have been able to learn from you, and it has been very inspiring learning from your specialty.

Finally, I wish to thank my family for their unlimited support. In particular, I would like to thank my wife, Hanne, for her support, understanding, and patience whenever needed.

Bjarke Risgaard, Copenhagen 27.04.2015

Abbreviations

CAD Coronary artery disease
ECG Electrocardiogram
SCD Sudden cardiac death
SD Sudden unexpected death
SUD Sudden unexplained death
SrSCD Sports-related sudden cardiac death

1. INTRODUCTION

1.1 SUDDEN CARDIAC DEATH BEFORE THE AGE OF 50 YEARS: INCIDENCE RATES AND CAUSES OF DEATH

Sudden cardiac death (SCD) is a tragic event affecting millions of people each year worldwide (1–3). SCD is often defined as a death that suddenly and unexpectedly occurs within 1 hour of the onset of symptoms. However, other definitions, including a 24-hour limit in unwitnessed cases, are also used (4). SCD has a major impact on the affected families and can also have a major economic impact on society. SCD has recently been estimated to be responsible for 40% to 50% of the years of potential life lost due to heart disease (5).

Over the last decade, several diseases causing SCD have been shown to be inherited. This knowledge has led to an increasing need for follow-up of the family members of SCD victims in clinics for inherited cardiac diseases (6).

Many methodical obstacles must be considered when investigating the epidemiology of SCD. First, deaths that are sudden and unexpected must be identified; then, the correct cardiac cause of death must be established. Most registry studies do not allow the identification of unexpected deaths, and because autopsy rates are low and have declined in most countries (7,8), the identification of the cause of death relies heavily on the physician completing the death certificate (9).

To overcome some of these methodical issues, previous studies have been performed using different selected populations (10–12), and these studies have included surrogate measurements of presumed unexpected death, including only out-of-hospital cardiac arrests, or autopsied SCD (13,14). However, previous studies using these approaches might have been affected by reporting and referral biases; these biases are likely reflected in the incidence rate and/or the distribution of the causes of SCD, which have varied considerably among studies (15–20). To address some of these issues, we previously conducted a nationwide and unselected study of SCD that included all deaths in Denmark between 2000 and 2006 among individuals aged 1-35 years (21).

Although several studies have been conducted, certain aspects of the epidemiology of SCD remain incompletely understood. The gap in knowledge was recently emphasized in the *Journal of the American College of Cardiology*, as well as in a report, published by the National, Heart, Lung, and Blood Institute Working Group (10,22). To date, the incidence rate and causes of SCD, particularly in persons aged 36-49 years in the general population, have been incompletely described. This gap is also the case for SCD in children, which is defined as SCD in persons aged 1-18 years and which is often described as part of deaths in young adolescents up to 40 years of age (15–17,23,24). The focus has recently shifted toward preventing SCD in this very young population (22,25–28).

1.2 PREVENTION OF SUDDEN CARDIAC DEATH

1.2.1 Screening the general population

Over the last decade, whether and how the most optimal and realistic screening strategies to lower the burden of SCD should be implemented have been discussed (29,22,30). Efforts have been made to identify patients or patient groups at high risk. Considering the low cost-effectiveness reported until now, there is a growing awareness that new strategies to identify high-risk patients are needed (27,28). However, most of these programs, including those for athletes, cannot eliminate the risk of SCD and may also introduce unwanted side effects such as false positive results (31).

1.2.2 Pre-participation screening of athletes

It has particularly been heavily debated whether nationally mandated screening programs using electrocardiogram (ECG) should be recommended and implemented for all competitive athletes, to reduce the numbers of sports-related SCD (SrSCD) cases (32). On the one hand, the American Heart Association argues against implementing these new programs, focusing on the many ethical and economic challenges and obstacles (33–35). On the other hand, the European Heart Association currently recommends ECG screening for all competitive athletes (36,37). The data that favor such a strategy mainly come from the Veneto region in Italy. Since the implementation of these mandated screening programs in Italy, the SrSCD incidence rate has decreased to a rate less than that of SCD in the general population (38). In Denmark, no systematic screening of all competitive athletes has been conducted. Hence, Denmark is a suitable population in which to investigate differences in the incidence rates between SCD in the general population and SCD in competitive athletes. We previously showed, that SrSCD in competitive athletes aged <36 years is a rare occurrence in Denmark and that SCD is much more prevalent in the general population (39).

Before discussing the optimal screening strategies for athletes, several issues must be addressed. First, because most studies have been conducted mainly in young competitive athletes aged <35 years, the extent to which competitive athletes aged >35 years are at the same or even greater risk remains unknown. Second, pre-participation screening programs have mainly focused on competitive athletes, whereas the SrSCD incidence rate in non-competitive athletes has gained very little attention.

1.2.3 Symptoms prior to sudden cardiac death

One possible way to identify persons at risk of SCD/SrSCD could be to increase awareness of cardiac symptoms in the young (chest pain, dyspnea, palpitations, etc.). Very few studies, to our knowledge, have investigated how common cardiac symptoms are prior to SCD (18,40,41). Furthermore, some of the data that exist are quite old. For instance, symptoms described prior to SCD in children (1-18 years) derive mainly from a study conducted almost three decades ago (42). To identify individuals at risk and to estimate their risk of SCD, more information about these tragic occurrences is needed.

1.2.4 Sudden cardiac death in patients with psychiatric disease

Patients with psychiatric diseases constitute a subgroup of patients with increased mortality (43–48). Their reduced life expectancy is likely explained to some extent by several factors, such as unhealthy living habits, including smoking, obesity and several other often preventable comorbidities.

Over the past few years, these deaths have received significant media attention in Denmark, and it is becoming increasingly evident that treatment with antipsychotic medications and/or mood stabilizers might increase the risk of SCD (49–51). Additionally, most drugs associated with SCD have the propensity of prolonging the QTc interval, which is considered the substrate for the potentially life-threatening arrhythmia, Torsades de Pointes ventricular tachycardia (50,52).

To the best of our knowledge, the SCD incidence rate in patients with psychiatric diseases has never been described nationwide in the general population. A thorough description of the causes of

death may further elucidate the extent to which these deaths may be associated with the use of prescribed medications.

2. AIMS

The overall aims of this thesis were as follows:

1) Describe the nationwide incidence rate and causes of SCD in individuals aged 1-49 years (Paper I).
2) Establish the autopsy ratios and autopsy findings and examine the differences between the 1-35 and 36-49-year age groups (Paper I).
3) Establish the incidence rates and causes of SCD in children, including a thorough description of previous medical conditions (Paper II).
4) Describe the nationwide incidence rates of SrSCD in competitive and non-competitive athletes aged 12-35 years and 36-49 years
(Paper III).
5) Describe the nationwide incidence rates and causes of SCD in patients with previous psychiatric diseases (Paper IV).

3. METHODS

3.1 IDENTIFICATION OF SUDDEN UNEXPECTED DEATH

The identification of sudden unexpected death (SD) included in this thesis was undertaken in two steps. The first step included deaths occurring between 2000 and 2006 in persons aged 1-35 years (Papers II and IV). The second step included deaths occurring between 2007 and 2009 in persons aged 1-49 years (Papers I and III).

3.1.1 Review of death certificates

All death certificates were retrieved digitally from *The Danish Cause of Death Registry* (53) and were reviewed by two physicians to identify sudden and unexpected deaths. A consensus was reached in cases of disagreements after all materials were reviewed, including a review of previous medical conditions, which were taken into account in each case.

Danish death certificates are suitable to identify SD cases because they contain a supplemental information field (see appendix page 50). This field is mandatory in all medico-legal external examinations (external examinations) and contains information describing the circumstances surrounding the death. The certified medical doctors who conduct these external examinations have access to the following: 1) medical files related to the death; 2) police records, including witness statements; and 3) first responder records. In all cases of sudden and unexpected deaths, external examinations are mandatory according to Danish law, including cases in which it is decided not to perform an autopsy.

3.1.2 Danish registries and discharge summaries

The unique Danish civil registration numbers were used to link all individuals to the Danish registries. *The Danish National Patient Registry* contains information on all in- and outpatient activities since 1978 (54). The registry was used to access information on previous medical conditions and to identify hospital or emergency medical records to be manually retrieved.

The Danish Central Psychiatric Case Register contains information from all psychiatric hospitalizations since 1969 and was used to identify SCD cases with previous psychiatric in- or outpatient contact with hospitals (55). All involved psychiatric hospital departments and emergency rooms were contacted by letter, and all records were manually retrieved. A detailed analysis of the psychiatric clinical history was assessed using all available materials, including the full hospital records, the death certificates and the autopsy reports. In cases with several psychiatric diagnoses, one primary diagnosis was chosen based on clinical evaluation by two psychiatrists.

From 2007 onwards, we had access to discharge summaries available in an electronic hospital records system. Here, information regarding treatment and patient management in the emergency room or hospital department was available. Discharge summaries were also available from the pre-hospital trauma and medical doctors who, in selected cases, escorted the patients to the hospital.

3.2 IDENTIFICATION OF SUDDEN CARDIAC DEATH

3.2.1 Conduct of autopsies

A forensic autopsy is only mandatory following SD if the mode of death is not well established (accident, natural deaths, etc.) or if a criminal act is suspected. The police ultimately decide whether an external examination and a subsequent forensic autopsy must be performed. There are three forensic departments in Denmark that conduct approximately 1200 autopsies each year.

A forensic autopsy follows a protocol in which all organs are thoroughly examined, and the autopsy is supervised by a second forensic pathologist. Histopathology is routinely performed, and toxicology screening is performed for all unexplained deaths. Importantly, there were no SCD cases for which the forensic pathologist concluded that the toxicology profile could explain the death.

In Denmark, in cases for which it is decided not to perform a forensic autopsy, the family or the treating physician can request a hospital autopsy. All of the autopsy reports were read, and the causes of death were established.

3.3 ESTIMATING THE DENOMINATOR

The size of the general background population was calculated using information from Statistics Denmark. Information was retrieved from *The Civil Registration System Registry*, which allows for the tracking of births and deaths as well as of immigrations in and out of Denmark (56). However, Statistics Denmark does not contain information enabling estimation of the size of the non-competitive and competitive athlete population. Hence, to do this, we used data from *The Danish National Institute of Public Health*. The institute conducted a large study entitled "How are you 2010," in which they investigated, among other things, the extent of physical activity in the Danish population (57). In this large-scale questionnaire of 96,075 individuals in the investigated age group, respondents were asked to choose one of four responses that best described their daily activity. Data were stratified according to several variables and were weighted for non-respondents by Statistics Denmark (56).

We also used data from *The Danish Central Psychiatric Case Register* to estimate the psychiatric population with a previous psychiatric hospital contact in Denmark. Individuals aged 18-35 years in 2000-2006 with a prior hospital-based psychiatric in- or outpatient contact (irrespective of age and diagnosis) were considered to be at risk of SCD (International Classification of Disease (8^{th} version, ICD-8); 290-315 and International Classification of Disease (10^{th} version, ICD-10); F00-F99) (55).

3.4 CARDIAC SYMPTOMS PRIOR TO DEATH

To investigate the frequency of symptoms (see definitions below) prior to SCD, we used the following three distinct approaches: 1) the supplemental information field on all death certificates was carefully reviewed to examine whether cardiac symptoms were mentioned during the interviews with witnesses and/or family members (Papers II, III, and IV); 2) each general practitioner, one of whom is assigned for each individual in Denmark, was contacted by letter and/or phone to retrieve the full medical record (Papers III and IV); and 3) selected medical records from visits to emergency departments and/or hospitalizations were manually or electronically retrieved (Papers III and IV). All materials were evaluated by two physicians, and all cardiac symptoms were recorded.

3.5 STATISTICS

All incidence rates were calculated using the age-specific background population as the denominator. Confidence intervals for incidence rates were calculated using the Poisson distribution. Sensitivity analyses were performed when deemed necessary. Categorized nominal data were compared using the chi-square test. If any expected cell values were <5, Fisher's exact test was used. Medians were compared using the Wilcoxon rank-sum test. We considered a two-sided *p*-value <0.05 to be statistically significant. Data management and analyses were performed using the Stata software package (StataCorp, Collage Station, TX, version 11.0)

3.6 DEFINITIONS

We defined SD as the sudden, natural unexpected death. In witnessed cases, this was defined as an acute change in the cardiovascular status with a time to death <1 h; in unwitnessed cases, this was defined as a person last seen alive and functioning normally <24 h before being found dead.

SCD in *autopsied* cases was defined as the sudden, natural, unexpected death of unknown or cardiac cause. In *witnessed* cases, this was defined as an acute change in the cardiovascular status with a time to death <1 h; in *unwitnessed* cases, this was defined as a person last seen alive and functioning normally <24 h before being found dead. *Autopsied* SCD was subdivided in the following two groups: 1) *explained* SCD, for which a cardiac cause of death was established, and 2) *sudden unexplained death* (SUD), for which the cause of death after autopsy remained unknown.

In *non-autopsied* SCD cases, we used the same criteria as above in cases presumed to be of cardiac origin based on the circumstances leading to death. That is, the prior medical history was taken into account in every case, and cases with obvious non-cardiac causes were excluded (i.e., pulmonary embolisms judged by echocardiography).

An SrSCD was defined as an SCD occurring during or within 1 hour after moderate- to high-intensity exercise. The deceased was considered a *competitive athlete* if he or she did moderate- to high-intensity sports on a regular level and took part in competitions, whereas a *non-competitive athlete* was defined as a person not participating in competitions but who did moderate to high intensity sports on a regular level in the months prior to death.

The following symptoms prior to death were recorded: chest/arm pain (angina pectoris), uncharacteristic chest pain (described as "sharp" or "stabbing" chest pain), stomach pain, dyspnoea, syncope, seizures, palpitations, and fatigue.

3.7 ETHICAL CONSIDERATIONS

The study was approved by the local ethics committee (H-KF-272484), The Danish Data Protection Agency (2011-41-5767), and the Danish National Board of Health (7-505-29-25/6):

4. RESULTS

THE EPIDEMIOLOGY OF SUDDEN CARDIAC DEATH

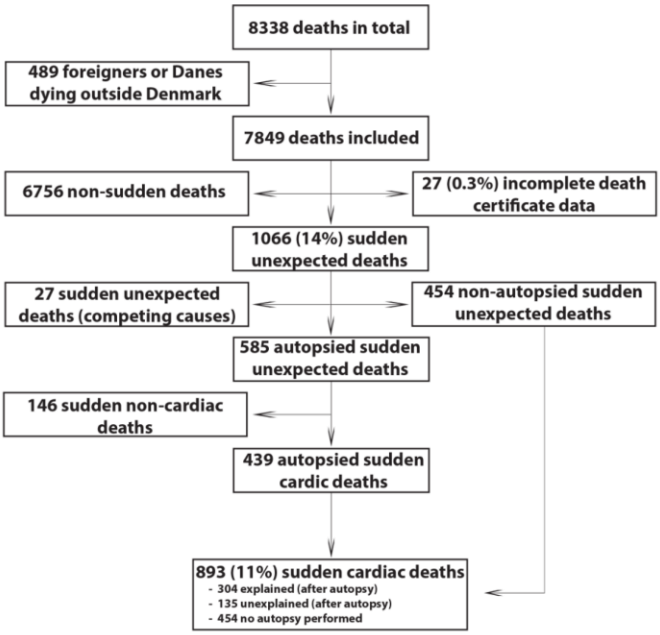
A brief overview of the results is given in the following section. A thorough description of the results is provided in the original manuscripts found in the appendix.

4.1 SUDDEN CARDIAC DEATH BEFORE THE AGE OF 50 YEARS

4.1.1 Paper I

All deaths in individuals aged 1-49 years between 2007 and 2009 were included. A total of 1,066 cases of SD were identified, of which 27 deaths were believed to have non-cardiac causes. There were 585 autopsied cases of SD, yielding an autopsy rate of 56%. In 146 cases, deaths were caused by non-cardiac diseases. Hence, the SCD population comprised 893 individuals; 439 were autopsied SCD cases and 454 were non-autopsied SCD cases (Figure 1).

Figure 1.

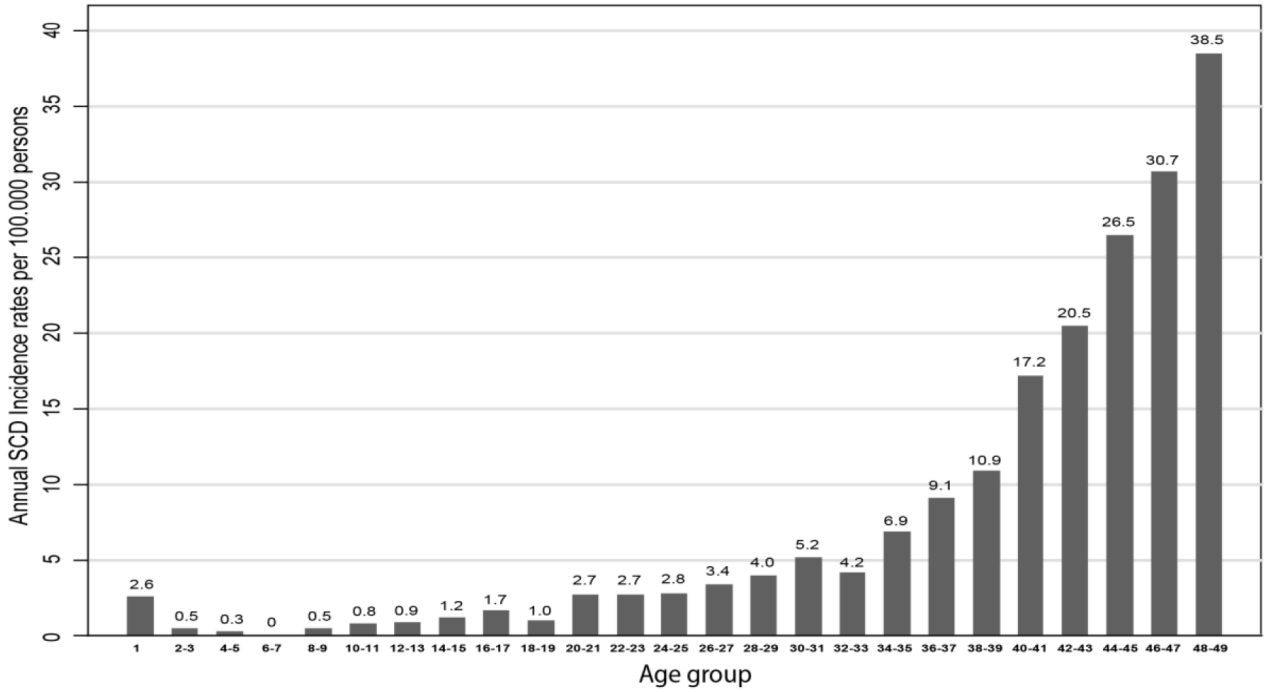


Flowchart of the identification of sudden cardiac death (SCD) in Denmark, 2007-2009

The median age of the SCD population was 43 years (Q1 to Q3; 38-47) and 43% (n=342) died in the presence of witnesses. Most deaths occurred at home (n=570, 67%) while the individuals were awake and relaxed (n=358, 54%). The overall annual SCD incidence rate was 8.6 (95% CI, 8.0-9.2) per 100,000 person-years in persons aged 1-49 years. Table 1 includes incidence rates according to sex and age (Table 1). Figure 2 depicts the age-related incidence rate, which reached 38.5 (95% CI, 32.9-44.7) per 100,000 person-years in the eldest age groups (Figure 2).

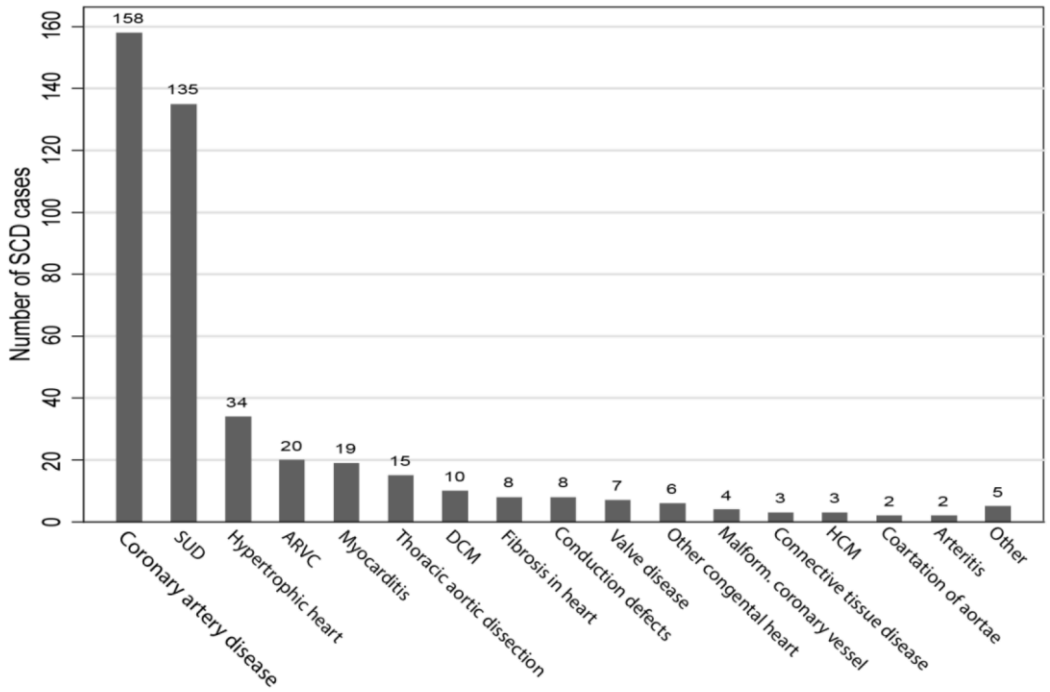
The most common causes of death, depicted in figure 3, were as follows: coronary artery disease (CAD) (n=158), SUD (n=135), cardiac hypertrophy (n=34), arrhythmogenic right ventricular cardiomyopathy (n=20), and myocarditis (n=19) (Figure 3).

Figure 2.



Age-related distribution of the annual sudden cardiac death (SCD) incidence rate per 100,000 person-years among individuals aged 1 to 49 years in Denmark from 2007 to 2009

Figure 3.



Distribution of the causes of death in 439 autopsied cases of sudden cardiac death (SCD) in individuals aged 1-49 years in Denmark from 2007 to 2009. SUD: sudden unexplained death, ARVC: arrhythmic right ventricular cardiomyopathy, DCM: dilated cardiomyopathy, HCM: hypertrophic cardiomyopathy

CAD was significantly more prevalent in the 36-49-year age group than in the 1-35-year age group (n=140, 44% vs. n=18, 15%,

p<0.001). In contrast, SUD was more prevalent in 1-35-year age group than in the 36-49 old age group (n=56, 48% vs. n=79, 25%, p<0.001) (58).

Table 1. Annual incidence rates of sudden cardiac death per 100,000 person-years by age and sex.

Annual incidence rates of SCD	Total (n=893)	Men (n=659)	Women (n=234)
Age 1-35 years (95% CI)(n=728)	2.3 (2.0-2.7)	3.2 (2.6-3.8)	1.5 (1.1-1.9)
Age 36-49 years (95% CI)(n=165)	21.7 (20.2-23.4)	32.1 (29.5-34.9)	11.1 (9.5-12.8)

CI: confidence interval.

4.1.2 Paper II

In this subgroup analysis of children aged 1-18 years, we identified 114 cases of SD between 2000 and 2006. Autopsy was conducted in 88 individuals, yielding an autopsy rate of 77%. The SCD population comprised 87 individuals, giving an SCD incidence rate of 1.1 (95% CI 0.9-1.3) deaths per 100,000 person-years. Of these 87 deaths, 37 (43%) were *explained* SCD, 25 (29%) were SUD, and 25 (29%) were non-autopsied SCD. The most common causes of death and previously known diseases are presented in Table 2. After review of death certificates and autopsy reports we found that antecedent symptoms, prodromal symptoms, or both were noted in 59% (46/78) of all SCD cases. The most common symptoms were dyspnea, stomach pain, seizure, syncope, and chest/arm pain.

With the exception of 4 individuals, all non-autopsied SCD cases were known to have either a severe congenital heart disease or other forms of diseases prior to death. Thus, we concluded that almost all cases of SCD in children with a potential inherited cardiac disease were autopsied (59).

4.2 SUDDEN CARDIAC DEATH DURING PARTICIPATION IN SPORTS

4.2.1 Paper III

In the 12-49-year age group, we identified 881 SCD deaths between 2007 and 2009, of which 44 were SrSCD. Of the total, 33 deaths occurred in non-competitive athletes, whereas 11 deaths occurred in competitive athletes. In non-competitive athletes aged 12-35 years, the SrSCD incidence rate was 0.43 (95% CI 0.16-0.94) per 100,000 non-competitive athlete person-years, whereas in competitive athletes aged 12-35 years, the rate was 0.47 (95% CI 0.10-1.14) per 100,000 competitive athlete person-years.

In non-competitive and competitive athletes aged 36-49 years, the SrSCD incidence rate increased to 2.95 (95% CI 1.95-4.30) and 6.64 (95% CI 2.86-13.1) per 100,000 athlete person-years, respectively. Importantly, in the general population 12-35 years of age, the SCD incidence rate was 3.15 (95% CI 2.67-3.69) per 100,000 person-years, whereas in those 36-49 years of age, it was 21.7 (95% CI 20.1-23.4) per 100,000 person-years (Table 3).

As shown below, the incidence rates were quite similar between competitive and non-competitive athletes. The SCD incidence rate ratios of competitive versus non-competitive athletes were 1.1 (95% CI 0.2-5.1, p=0.88) in those aged 12-35 years and 2.2 (95% CI 0.9-5.1, p=0.06) in those aged 36-49 years. Tables 4 and 5 describe the clinical characteristics, including a description of cardiac symptoms prior to death, of non-competitive and competitive athletes, respectively (Tables 4 and 5) (60)

Table 2. Causes of death and congenital and cardiovascular diseases known prior to death.

Cause of death, autopsied sudden unexpected death cases (n=88)	n	Potentially inherited disease	Congenital and cardiovascular diseases known prior to death	n
Unexplained death	25	X	Transposition of great arteries	3
Myocarditis	8		Persistent ductus arteriosus	2
ARVC	4	X	Tetralogy of Fallot	2
Connective tissue diseases	3	X	DCM	2
Thoracic aortic dissection	3	X	VSD	1
Valvular disease	3		ASD	1
Pulmonary cardiac disease	3		Bicuspid aortic valve	1
Malformation of coronary artery	3		Atresia of pulmonary valve	1
Coarctation of the aorta	2	X	MV insufficiency and non- specified congenital heart dis.	1
Acute myocardial infarction	2	X	Aortopulmonary window and pulmonary hypertension	1
Endocarditis	1		Coarctation of aortae	1
DCM	1	X	Stenosis of pulmonary artery	1
Conduction defect	1	X	Hypoplasia of right ventricle	1
LVH	1	x	Downs syndrome, ASD, ostium secundum	1
Rejection transplant heart	1		Hurler syndrome	1
LQTS	1	x		

ARVC: arrhythmogenic right ventricular cardiomyopathy, DCM: dilated cardiomyopathy, LVH: left ventricular hypertrophy, LQTS: long QT syndrome, VSD: ventricle septum defect, ASD: atrium septum defect, MV: mitrale valve

4.3 PREVIOUS PSYCHIATRIC DISEASE AND SUDDEN CARDIAC DEATH

4.3.1 Paper IV

Between 2000 and 2006, 395 cases of SCD occurred among individuals aged 18-35 years. Of these cases, the psychiatric SCD population comprised 77 individuals, whereas the non-psychiatric SCD population comprised 318 individuals. Individuals with previous in- or out-patient psychiatric hospital contact had a signifiantly higher SCD incidence rate of 14.8 (95% CI 11.7-18.5) per 100,000 psychiatric person-years, compared with 3.8 (95% CI 3.4-4.3) per 100,000 person-years in individuals without previous psychiatric hospital contact. This corresponds to an incidence rate ratio of 4.3 (95% CI, 3.3-5.5, p<0.01). Particularly in men with previous psychiatric contact the SCD incidence rate was higher than in men without psychiatric disease (incidence rate ratio 5.3 (95% CI 3.9-7.1, p<0.01) (Table 6).

Table 3. Sports-related sudden cardiac death by different age groups in Denmark from 2007 to 2009.

Age group (years)	12-49	12-35	36-49
SrSCD† cases (n)	44	9	35
Of whom were competitive athletes (n)	11	3	8
Incidence rates per 100,000 person-years (denominator)	**(95% CI)**	**(95% CI)**	**(95% CI)**
SCD* (general population)	10.7 (10.0-11.5)	3.15 (2.67-3.69)	21.7 (20.1-23.4)
SrSCD† (general population)	0.54 (0.39-0.72)	0.19 (0.08-0.35)	1.05 (0.73-1.45)
Non-competitive athletes (non-competitive athletes)	1.43 (0.99-2.01)	0.43 (0.16-0.94)	2.95 (1.95-4.30)
Competitive athletes (competitive athletes)	1.51 (0.75-2.71)	0.47 (0.10-1.14)	6.64 (2.86-13.1)
Sensitivity analyses: Incidence rates per 100,000 person-years (denominator)			
Autopsied cases only:			
Non-competitive athletes (non-competitive athletes)	1.08 (0.6-2.5)	0.43 (0.16-0.94)	2.08 (2.3-12.0)
Competitive athletes (competitive athletes)	1.37 (0.7-1.6)	0.47 (0.10-1.14)	5.81 (1.3-3.3)

Table 4. Characterization of sports-related sudden deaths in *non-competitive athletes* by age group in Denmark from 2007 to 2009

	SrSCD in non-competitive athletes						
Age group	**Age at death**	**Gender**	**Sport**	**HLR**	**Prodromal symptoms**	**Antecedent Symptoms**	**Autopsy**
≤35 years	12	Male	Running	Yes	None	Angina	ARVC
	14	Male	Football	Yes	None	None	Con. Heart
	15	Male	Running	Yes	Dizziness, dyspnea	Syncope, presyncope	SUD
	20	Female	Dancing	Yes	None	Syncope	VD
	30	Male	Running	Yes	None	None	CAD
	34	Male	Running	Yes	None	Syncope	ARVC
>35 years	36	Male	Running	Yes	Unspecific	Angina, dyspnea	ARVC
	36	Male	Cycling	No	None	None	CAD
	36	Male	Running	Yes	None	None	Myocarditis
	36	Male	Running	Yes	None	Angina, dyspnea	ARVC
	37	Male	Running	Yes	Unspecific	None	CAD
	38	Male	Running	Yes	None	None	NcHH
	39	Male	Running	No	None	None	N/A
	39	Male	Running	Yes	Dyspnea	Palpitations	N/A
	40	Male	Running	Yes	None	Presyncope, angina, dyspnea	MCD
	42	Male	Running	Yes	Angina	None	HCM
	42	Male	Cycling	Yes	Angina	None	Myocarditis
	42	Female	N/A	Yes	None	None	SUD
	42	Male	Cycling	Yes	Angina	Angina, palpitations, and presyncope (in pain)	CAD
	42	Male	Gymnastics	Yes	Dyspnea, Palpitations	None	HH
	43	Male	Running	Yes	Unspecific	Dyspnea	HH
	43	Male	Cycling	Yes	None	Syncope, angina, dyspnea treated as asthma	CAD
	43	Male	Cycling	Yes	Unspecific	Angina	N/A
	44	Female	Cycling	No	None	Dyspnea, unspecific	N/A
	44	Male	Stepping	No	None	None	CAD
	44	Male	Cycling	Yes	Presyncope	Angina	N/A
	45	Male	Ice skating	Yes	None	Angina	N/A
	46	Male	Cycling	Yes	Fatigue	None	CAD
	47	Male	Swimming	Yes	Dizziness, angina	Dizziness	N/A
	47	Male	Running	Yes	None	Angina	CAD
	49	Male	Cycling	Yes	None	Dyspnea	CAD
	49	Male	Cycling	Yes	Unspecific	None	CAD
	49	Male	Cycling	Yes	None	None	N/A

ARVC; arrhythmogenic right ventricular cardiomyopathy, CAD; coronary artery disease, Con. Heart; congenital heart disease, SUD; sudden unexplained death, VD; valve disease, MCD; malformation of coronary vessel, HCM; hypertrophic cardiomyopathy, HH; hypertrophic heart, N/A; not available, NcHH; Non-concentric hypertrophic heart.

Table 5. Characterization of sports-related sudden deaths in competitive athletes by age in Denmark from 2007 to 2009.

SrSCD in competitive athletes							
Age group	Age at death	Gender	Sport	HLR	Prodromal symptoms	Antecedent Symptoms	Autopsy
≤35 years	13	Male	Running	Yes	None	None	ARVC
	20	Male	Football	Yes	None	None	SUD
	31	Male	Squash	Yes	Presyncope, palpitations	Syncope	SUD
>35 years	37	Male	Handball	Yes	Unspecific	None	CAD
	38	Male	Cycling	Yes	None	None	CAD
	40	Male	Football	Yes	Angina	Unspecific	CAD
	41	Male	Handball	Yes	Angina	None	CAD
	44	Male	Cycling	Yes	None	None	HH
	45	Male	Football	Yes	Unspecific	None	N/A
	47	Male	Running	Yes	None	None	CAD
	48	Male	Football	Yes	None	Angina	HH

ARVC: arrhythmogenic right ventricular cardiomyopathy, CAD: coronary artery disease, SUD: sudden unexplained death, HH: hypertrophic heart, N/A: not available.

Cardiac symptoms within one year prior to death can be found in Table 7. Overall, 35 individuals (46%) experienced at least one cardiac symptom in the year prior to SCD (Table 7). An autopsy was conducted in 46 of 77 (60%) psychiatric SCD cases; this autopsy rate did not differ from the non-psychiatric SCD population in which 216 (68%) autopsies were conducted (p=0.17). However, cause of death significantly differed between the groups. Death was more often unexplained in the psychiatric SCD population than in the non-psychiatric SCD population (30/46 (65%) vs. 86/216 (40%), p=0.02), respectively (61)

Table 7. Cardiac symptoms prior to sudden cardiac death in patients with psychiatric disease.

Reported possible cardiac symptoms (%)	n = 77
Any cardiac symptom	35 (46)
Angina	13 (17)
Palpitations	9 (12)
Dyspnea	8 (10)
Seizure	8 (10)
Syncope	6 (8)
Dizziness	4 (5)
Unspecific	7 (9)

Table 6. Sudden cardiac death incidence rates per 100,000 person-years by sex.

Annual incidence rates (denominator)	**All (95% CI)**	**Men (95% CI)**	**Women (95% CI)**	**p-value**
Sudden cardiac death (general population)	4.5 (4.0-5.0)	5.9 (5.2-6.7)	3.0 (2.5-3.5)	<0.01
Sudden cardiac death (no PPHC)	3.8 (3.4-4.3)	4.8 (4.2-5.5)	2.8 (2.3-3.3)	<0.01
Sudden cardiac death (PPHC)	14.8 (11.7-18.5)	25.7 (19.6-33.0)	5.9 (3.4-9.5)	<0.01

PPHC: previous psychiatric hospital contact

5. DISCUSSION

5.1 METHODOLOGICAL CONSIDERATIONS

5.1.1 Identification of sudden unexpected deaths

In a "perfect world," detailed information regarding the circumstances leading to every death would be available in a prospectively collected registry. This, of course, is wishful thinking and will likely never be possible or feasible. How do we then identify all SD cases and, in turn, SCD cases to establish the "true" incidence rate as well as the causes of death?

There are several ways to identify a possible SD, depending on the local health care system. The most common way is to review material from the following sources: 1) emergency medical services; 2) medical examiners; 3) hospital records; 4) death certificates; 5) autopsy reports; and 6) health care registries. The review of autopsy series is the best way to establish a correct cause of death (62). However, because autopsy rates are low in most countries (63), the true SD/SCD incidence rate will naturally be underestimated using this approach alone.

The use of nationwide registries, such as *The Danish Cause of-Death Registry*, has the advantage that all deaths within a country (Denmark) are included (53). Hence, the study population included will represent the general population and will prevent the selection of specific populations (selection bias). In *The Cause of Death Registry*, the cause of death is classified according to the International Classification of Disease (10th version, ICD-10). ICD-

10 codes are extracted from the death certificates, which are completed by the medical staff (general practitioner or physician in hospital) in cases where an external examination is not performed. Obvious mistakes on the death certificate will be corrected by non-medical staff in the cause of death registry. However, *The Danish Cause of Death Registry* has the major disadvantage of not allowing identification of sudden and unexpected deaths. Hence, the registry alone may be suitable for identifying cardiac deaths but not for identifying sudden and unexpected deaths and, therefore, SCD (21).

In countries, such as the US, without these nationwide registries, the review of death certificates is one way to collect all deaths within a certain area/region to estimate the SD and/or SCD burden (1). However, in the US, the review of death certificates has previously been shown to overestimate the SCD burden compared with prospective multisource evaluations using emergency and hospital medical records (12). Overall, identifying SCD by reviewing death certificates was shown to have a sensitivity of 59% and a specificity of 86%. In other words, the use of death certificates in the US will correctly classify 59% of all SCDs, whereas 41% percent will be misclassified. Naturally, this has led to concern regarding whether our method of reviewing death certificates would also overestimate the SD burden in Denmark. However, Danish death certificates (see appendix page 50) significantly differ from US death certificates in that they contain a supplemental information field. In this large text field, we were able to collect valuable information regarding the circumstances surrounding the death. Notably, this information field is mandatory whenever an external examination has been performed.

Our previous findings (1-35 years, 2000-2006) showed that external examinations are performed in 84% of all SD cases and that a subsequent autopsy is carried out in 75% of the cases (21). Naturally, we were concerned that that the percentage of external examinations performed would decrease with increasing age. In the 1-49 year age group (paper I), external examinations were performed in 76% of the cases occurring outside the hospital. This lower percentage of external examinations was, however, counterbalanced by the availability of electronic discharge summaries from 2007-2009. These electronic records, which also included records from pre-hospital medical doctors, are a unique tool from which we could extract important information regarding the circumstances leading to death. Overall, we found that information from external examinations and/or from discharge summaries was available in 93% of all SD cases occurring out-of-hospital.

5.1.2 Identification of sudden cardiac deaths

Whenever a sudden and unexpected death occurs, it must be established whether it was an SCD. SCD generally refers to an unexpected death from a cardiovascular cause in a person with or without a pre-existing disease (4). The definition has varied depending on whether the event was witnessed, as suggested by *The National Heart, Lung and Blood Institute,* which previously suggested distinguishing between *established* and *probable* SCD (29). However, several studies have used the definition of the World Health Organizations (WHO), which suggests distinguishing between two time intervals depending on the witnessed status (witnessed cases: symptoms <1 h; unwitnessed cases: symptoms <24 h) (11–13,25). Regardless of the definition used, an SD case for which no autopsy has been performed could easily be mistakenly classified as an SCD.

Conducting an autopsy is, without a doubt, the gold standard for establishing the correct cause of death (62,64). Autopsy rates are continuously decreasing in most countries, forcing cause of death statistics to rely heavily on the physician completing the death certificate (7,8,63). Importantly, several studies have shown that, after autopsy of a SD, the causes of death could be divided into the following two categories: 1) SCD; and 2) deaths caused by non-cardiac diseases (sudden non-cardiac deaths) (11,17,24,65,66). Overall, we found that 26% of all autopsied cases of SD were caused by non-cardiac diseases, emphasizing that studies with much lower autopsy rates might have overestimated the true SCD burden (Papers I and II).

Standardization of autopsy, with a thorough examination of all organs, is necessary. For instance, both histopathology and a toxicology screen should be performed. A review of the *state of the art* forensic autopsy was recently published (67); one key conclusion was that using dissection protocols, as well as tissue sample collection together with histopathology, toxicology and molecular biology, was closely linked to the quality of the autopsy. In Denmark, all forensic autopsies follow a thorough protocol in which every organ is examined, and toxicology screening is performed in all SUD cases in the young.

However, an autopsy can also, in some cases, be more or less focused on certain organs. This is the case, for instance, when a hospital autopsy is performed. In such cases, the pathologist has the option to focus on the organs that he or she believes were the cause of death, based on a clinical evaluation. This approach creates the possibility that findings in the heart may be regarded as the cause of death, thereby missing the real cause of death if death was caused by something such as major cerebrovascular bleeding. Importantly, the toxicology screen is also rarely performed following a hospital autopsy, likely to the very high costs and thereby possibly leading to misclassification of the cause of death. Although we had access to full autopsy reports as well as all medical records, the cause of death category was not always easy to interpret. In these cases, all material was reviewed again with a forensic pathologist to determine the cause of death. In selected cases, experts in cardiac pathology were asked to re-evaluate the findings.

5.1.3 Estimating the incidence rate of sudden cardiac death

Several approaches have previously been used to estimate the "true" public health burden of SCD. Some studies have reported incidence rates for the general population in selected geographic areas (3,12,13,25), whereas others have been additionally restricted to a subset of patients, such as athletes or military recruits (65,68). To ensure that the deaths were truly SCDs, several studies have also further included only coroner cases (14,16,18,24,69). Finally, a few studies have included only out-of-hospital cardiac arrest cases (3,70) or have relied solely on ICD-10 codes from public health registries (71). Most recently, Stecker et al. sought to provide national estimates of SCD in the US, based on data from the Oregon Sudden Unexpected Death Study (5).

As illustrated above, incidence rates vary greatly across studies due not only to the different populations and age groups investigated but also to the different study designs used. Variations in geography, socioeconomic status, healthcare systems, and other factors also likely explain some of the variance in the reported incidence rates, further complicating comparisons between studies.

We included all deaths occurring within Danish borders. SCD cases are therefore not selected from "specific" geographic areas

or from selected populations; thus, these cases more likely represent the general population. We chose to include both autopsied and non-autopsied cases. The incidence rates reported may therefore be regarded as the highest possible, as at least some non-autopsied SCD cases were likely caused by non-cardiac diseases (66).

The population at risk was established using information from Statistics Denmark (denominator); this database retrieves information from the Danish *Civil Registration System Registry*, which allows for the tracking of births and deaths as well as of immigrations in and out of Denmark. Overall, we believe that the current approach is a very solid way to identify both SCD cases (numerator) and the number of individuals at risk (denominator), thereby allowing us to establish the "true" SCD incidence rate in the general population.

5.2 DISCUSSION OF RESULTS

5.2.1 Sudden cardiac death before the age of 50 years

5.2.1a Paper I

As noted above, comparing SCD incidence rates between studies is difficult due to the use of different study designs and study populations. We found that the highest possible annual incidence rate was 8.6 per 100,000 person-years in individuals aged 1-49 years. The rates were 2.3 per 100,000 person-years in persons aged 1-35 years and 21.7 per 100,000 person-years in persons aged 36-49 years. As expected, the incidence rate increased with increasing age, reaching 38.5 per 100,000 person-years in persons aged 48-49 years.

We previously reported an SCD incidence rate of 2.8 per 100,000 person-years in persons aged 1-35 years (2000-2006) (21). The lower incidence rate from 2007-2009 (2.3 vs. 2.8) could be a coincidence, or it could be explained by the fewer deaths included in the shorter time period (3 years vs. 7 years). However, the possibility also exists that the lower incidence rate represented a general decline in SCD mortality from 2000 to 2009, possibly due to general healthcare improvements (72). Notably, the SCD incidence rate of 2.3 in the 1-35-year age group remains higher than those previously reported by others (15,71,73).

Whereas the incidence rate has been described in several studies for the 1-35-year age group, most other studies have had mean ages much higher than 50 years (12–14). That is, few studies have reported the incidence rates and causes of death in the 36-49-years age group (69).

In a sensitivity analysis, we showed that the incidence rate decreased significantly when only out-of-hospital SCDs were included. This finding suggests that studies including only out-of-hospital deaths, underestimate the true SCD incidence rate. Furthermore, applying additional and more stringent criteria to the SCD definition (autopsy, histopathology, and toxicology) will lower the incidence rate. When only autopsied SCD cases in which both histopathology and toxicology examinations were performed were included, the SCD incidence rate decreased from 8.6 to 2.4 per 100,000 person-years. This finding again highlights the many obstacles that exist in comparing incidence rates across different study designs.

To report the highest possible incidence rate, we chose to also include non-autopsied SD cases in the SCD population. We cannot exclude the possibility that some non-autopsied SCD cases were in fact caused by non-cardiac diseases. In support of this, we showed that 26% of all autopsied SD cases were in fact caused by non-cardiac diseases (Papers I and II). However, non-autopsied SCD cases were more often known to have heart disease, suggesting that the deaths were in fact SCD (see supplemental material, Paper I). We have also recently shown an increasing risk of a sudden non-cardiac death in patients with absence of cardiac diseases again suggesting that non-autopsied SCD cases were in fact SCDs (66).

In the 1-35-year age group, the most common cause of SCD was SUD, whereas the most common cause of death in the 36-49-year age group was CAD. A recent suggestion was made to refer to SUD as *Sudden Arrhythmic Death Syndrome* (SADS) (6). These deaths are expected to be caused by primary arrhythmic syndromes, such as *Long QT Syndrome*, *Brugada Syndrome*, or *Catecholiminergic Polymorph Ventricular Tachycardia*.

As previously reported by our group (21), we confirmed that hypertrophic cardiomyopathy (HCM) was very rarely the cause of SCD in Denmark (n=3, <1%). Other studies have reported that 6-13% of SCD cases were caused by HCM (18,24,65,73). However, these differences might have been due to different cause of death categories; upon including idiopathic fibrosis (n=8) and cardiac hypertrophy (n=34), we found an incidence of 10.3% (45/439), in agreement with previous findings (18,24,65,73).

5.2.1b Paper II

SCD in children aged 1-18 years, has been incompletely described in the literature. Often, these deaths are included as part of the young population (1-35 years), and incidence rates have been affected by referral and reporting biases (15–17,23,24). Knowledge of the incidence rates, causes of death and symptoms prior to death, is sparse in this very young age group. Using our previously identified SCD cases between 2000 and 2006 in Danes aged 1-35 years, we conducted a subgroup analysis of the 1-18-year age group (21).

We reported an SD incidence rate of 1.5 per 100,000 person-years and an SCD incidence rate of 1.1 per 100,000 person-years. Other studies have reported incidence rates between 1.3 and 4.6 per 100,000 person-years (42,74). Our results were, however, in agreement with the data from Oregon County, despite the use of a different age distribution (0-18 years) (25).

Overall, an autopsy was not performed in 26 (23%) SD cases. This percentage may seem high, but most of these non-autopsied SD cases were known to have a severe cardiac disorder such as congenital heart diseases. Based on a presumed cause of death, we conclude that in Denmark, almost all SD cases in children that are potentially caused by an inherited cardiac disease are autopsied.

Whereas CAD is the most common cardiac cause of death in the 1-49-year age-group (Paper I), CAD is very rarely the cause of death in children. In children, only 2 deaths were caused by CAD, and we have previously shown that these deaths are caused by familial hypercholesterolemia in some cases (75). In agreement with others, we found that myocarditis was the most common cardiac cause of SCD in children (42). Myocarditis was three times more prevalent in children compared with the 19-35-year age group. Although this observation is purely speculative, myocarditis seems to more often be clinically undiagnosed in the 1-18-year age group compared with the 19-35-year age group. However, myocarditis in children may also be more lethal.

Similarly to the 1-35-year age group, SUD accounted for the vast majority of SCD in children (29% and 28%, respectively). As in young adults, these deaths are presumed to be caused by a primary cardiac arrhythmic event, which may result from a potentially inherited cardiac disease. We combined the inherited diseases to assess the potentially magnitude of inherited cardiac

diseases among SCD cases in children. In total, we found that 49% of all SCD cases in this age group could potentially be caused by an inherited cardiac disease. This result is in agreement with data from the Netherlands, showing that 50-60% of all SCD cases in children are caused by an inherited cardiac disease (76). These results highlight the importance of assessing cardiovascular disease in first-degree relatives of SCD victims (cascade screening) (6,77).

To reduce the SCD burden in children, the extent to which screening high-risk patients with ECG is feasible has been investigated (27,28). As expected, the costs are extremely high, compared with the benefits. The gaps in evidence identified in a recent report from the National Institutes of Health should be filled prior to embarking on such a strategy (22).

Of the 87 total SCD cases in children, 59% experienced symptoms prior to death: 45% experienced antecedent symptoms, and 26% experienced prodromal symptoms. Based on our results and those of prior studies, increased awareness of cardiac symptoms in children might be an alternative and beneficial approach to identify at-risk individuals. Notably, we did not look for these symptoms in a control population; however, we previously showed that cardiac symptoms were seemingly rare among young patients who died in traffic accidents (40).

Based on our results, we recommend that a thorough examination be performed when children present with cardiac disease symptoms, including syncope, presyncope, unexplained seizures, chest/arm pain, palpitations, or dizziness. However, SCD in children is a rare event and should be recognized. Nonetheless, clinical examinations should, at minimum, include a physical examination, a resting 12-lead electrocardiogram (ECG), and a detailed questionnaire regarding the family history of cardiac disease/SCD in young (<50 years) family members. Based on the initial evaluation, further diagnostic investigations may then be performed.

5.2.2 Sudden cardiac death during sports

5.2.2a Paper III

The extent to which we should implement mandatory screening programs using ECGs for all young competitive athletes to avoid SrSCD is one of the hottest topics within sports cardiology. Data favoring such a strategy mainly came from a prospective, though initially retrospective, Italian study reporting that pre-participation screening lowered the SrSCD incidence rate in young competitive athletes (38). This study showed that, following the implementation of these programs, the incidence rate of SrSCD decreased to a rate lower than that of SCD in the general population. However, other studies have questioned these findings (31,32,34,39,78). The American Heart Association, in particular, has emphasized the huge economic burden that such a program would create. There are also several ethical dilemmas associated with such programs (33). Nevertheless, screening of all competitive athletes is currently recommended by the European Society of Cardiology (37), and programs have been implemented at different levels but most extensively in Italy and Israel (31,38). Recently, the European Association of Cardiovascular Prevention and Rehabilitation also published a practical method for evaluating the middle-aged, non-competitive athletes (79).

Based in part on our previous findings (39,60), the Danish Society of Cardiology has decided to continue not to follow the European Society of Cardiology recommendations, and mandatory pre-participation screening programs have not been implemented in Denmark (80). That is, no formalized screening programs for athletes occurred during the study period, making the country suitable for investigating SrSCD in a pre-screening era.

Previous studies of SrSCD have been limited to media searches or to smaller autopsy series in limited geographic areas or subpopulations (34,38,68,78,81,82). Using Danish death certificates, we believe that we minimized the risk of missing SrSCD cases. To apply a method used by others, we also conducted a media search, in which we only identified 1 SrSCD case that was not identified by review of the death certificates. The death certificate in this particular case was never completed (page 2 was missing); thus, the death was missed in the initial review process. To ensure that none of the other 26 deaths with incomplete death certificates were SrSCD cases, all discharge summaries were investigated. Overall, we believe that very few, if any, SrSCD cases were missed. Notably, a media search in Denmark identified few SrSCD cases, compared with the review of death certificates.

To establish the correct SrSCD/SCD incidence rates, the number of at-risk individuals (denominator) must be established. Establishing the number of individuals participating in sports on a competitive and/or non-competitive level has proved difficult. We used data collected through questionnaires administered by the Danish National Institute of Public Health (57). Although approaches such as this have previously been criticized (83), we believe that the current large-scale questionnaire and the nationwide identification of SrSCD outweigh any disadvantages that smaller studies might have had in using selected populations from smaller geographic areas.

Previous studies of SrSCD have mainly focused on young competitive athletes aged 12-35 years (31,38,39,73,84), and the SrSCD incidence rate among non-competitive athletes is largely unknown (85). Furthermore, SrSCD in competitive athletes aged 36-49 years is also largely unknown. Hence, we believe that several important issues should be addressed prior to deciding whether these programs should be implemented.

We report that the SrSCD incidence rate does not significantly differ between competitive and non-competitive athletes aged 12-35 years (incidence rate ratio 1.1: 95% CI 0.2-5.1, p=0.88) and 36-49 years (incidence rate ratio 2.2: 95% CI 0.9-5.1, p=0.06). The incidence rate increases with increasing age, but the risk of SrSCD in competitive athletes does not exceed that of non-competitive athletes. However, most importantly, we reported that SCD is much more common in the general population. This is in contrast to the Italian group, which claimed that the lower incidence rate among athletes in Italy is caused by the extensive use of screening (38).

We only included SrSCD cases that occurred during or within one hour from sports activity; thus, deaths in athletes occurring during sleep were missed. However, previous studies have suggested that 90% of SrSCD cases occur during activity, which minimizes this concern (73). Furthermore, potential SrSCD cases that were avoided by using automated external defibrillators were not included. The numbers of such cases among competitive and non-competitive athletes are currently not available in Denmark.

Overall, our results highlight that mandatory pre-participation screening programs of young competitive athletes are of limited value, at least in Denmark, and that these programs are ethically questionable if only available to selected individuals such as competitive athletes. As the general population is at an even higher risk, one might argue that these programs should be available to all. However, because screening has unwanted side effects, notably false positive and false negative results, future debate should

account for the tremendous consequences of these programs. For example, programs could unnecessarily disqualify an athlete from sports. We report that several athletes experienced cardiac symptoms prior to death, and an increased awareness by coaches and athletes themselves may be an alternative approach to identify athletes at increased risk of SrSCD.

5.2.3 Previous psychiatric disease and sudden cardiac death

5.2.3a Paper IV

SCD among patients with psychiatric disorders has gained considerable attention over the last decade (49,86,87). Psychiatric patients are known to have a cardiovascular risk profile that places them at increased risk, compared with the general population (88,89). Even after controlling for these risk factors using Nordic registries, psychiatric patients have still shown an increased cardiovascular risk (43,44,47,48,90). However, Nordic registries have not reported the SCD incidence rates, as described above.

We believe that this study was the first to chart nationwide SCD incidence rates in patients with and without previous psychiatric disorders. We reported an SCD incidence rate ratio of 4.3 (95% CI interval 3.3-5.5, $p<0.01$) in patients with previous psychiatric diseases compared with patients without psychiatric diseases. The higher incidence rate was largely driven by schizophrenia-spectrum and substance-related disorders. Most interestingly, SCD in patients with psychiatric disease was more likely to be caused by SUD, suggesting that these deaths were caused by a primary arrhythmic event. Because patients with psychiatric diseases often have substance-abuse disorders, this finding naturally leads to concern that they were intoxicated. However, toxicology screening is performed for all SUD cases among young individuals in Denmark. Importantly, all illegal drugs were found only in trace amounts, whereas prescribed drugs were found at therapeutic concentrations. That is, none of the SCD cases had toxicology profiles that led the forensic pathologist to conclude that these drugs were the cause of death.

Several studies have shown that psychotropic drugs, including methadone, have the propensity to prolong the QTc interval, thereby increasing risk of Torsade de pointes ventricular tachycardia (91). Many of these drugs have also been associated with an increased SCD risk, which has naturally led to increasing concern regarding the safety of these drugs (49,50,86,91). Of course, some of these drugs, even in therapeutic concentrations or in combination with other drugs, might have triggered a malignant arrhythmia that then caused SUD.

Although some of the drugs in question might seem to increase the SCD risk, withdrawal is impossible because the untreated psychiatric diseases themselves are associated with an increased suicide risk (92). Therefore, to reduce medically induced arrhythmias, the focus has recently shifted toward how to follow patients treated with these drugs (51). The Danish Society of Cardiology has suggested ways in which to follow patients, including those starting treatment with drugs known to prolong the QTc interval, in clinical practice (80). These suggestions were recently published in the European Heart Journal (87). Whether the increased focus on both polypharmacy and ECG deviations following changes in treatment will lead to decreased mortality within the psychiatric population remains unknown.

5.3 HERITABILITY AND SUDDEN CARDIAC DEATH

SCD before 50 years of age is generally expected to be caused by inherited cardiac diseases to some extent (77). In this thesis, we have shown that in both children and young adults, several SCD cases may have been caused by an inherited disease (Papers I and II). Naturally, conducting an autopsy after SD is essential to establish the correct cause of death post-mortem (66). Although we showed that autopsy rates are high in Denmark following SD in children (Paper II), we also showed that the rate significantly declines with increasing age (Paper I). This decline has been recognized by *The Danish Society of Cardiology* together with *The Danish Pathology Society*, *The Society of Forensic Pathologist,* and *The Society of Medical Genetics*, and the recommendation was that all SDs in Denmark before the age of 50 years are recommend to be autopsied (80).

Families of SD victims younger than 50 years whose deaths were attributed to a possibly inherited disease should be examined in an outpatient clinic for inherited cardiac diseases to determine whether they are also at risk (6,77). Without an autopsy, however, these clinical examinations and assessments are much more complicated as the death in question may have been caused by a non-cardiac, non-inherited disease. In fact, we showed that 26% of all SD cases in the young should not be followed in a clinic for inherited cardiac diseases as a means of searching for cardiac disease (Papers I and II). In other words, non-autopsied SD cases may lead to unnecessary examinations in specialized clinics and even worse, unnecessary concern in family members that they too may have an inherited cardiac disease.

The proportion of SCD cases that remains unexplained following autopsy (SUD) are, as noted above, believed to be caused by inherited (primary) arrhythmic syndromes; these deaths are of particular interest. With access to dried blood spot samples from infants in Denmark, we are able to conduct retrospective genetic testing in selected cases (93). However, retaining material (5–10 mL of whole blood in an EDTA tube, dried blood samples, or a frozen sample of heart, liver, or spleen) for genetic analysis is currently recommended, and the possibility of conducting molecular autopsies has never been better. Usually, molecular autopsy would be targeted to examine the genes involved in the diseases in question (77). However, a comprehensive or targeted mutational analysis of the ion channel genes most often involved in primary arrhythmogenic diseases (RYR2, KCNQ1, KCNH2, and SCN5A) could also be conducted (94).

Approximately 20% of all cases of SUD are estimated to harbor mutations in one of the three major genes involved in the long QT syndrome (KCNQ1, KCNH2, and SCN5A) (94,95). However, more recent studies have suggested that, in non-referred populations, this rate might only be 9-11% (96,97).

The heritability of primary arrhythmic syndromes, as well as of cardiomyopathies encountered in many of the SCD cases in this thesis, has been well established. However, SCD from any cause has also been associated with increased risk for several cardiovascular diseases (98).

CAD, the most important cardiovascular disease entity, also has a large genetic component, particularly in the young. Recently, the *European Society of Cardiology* has recommended that the familial prevalence of atherosclerotic disease should be systematically identified in first-degree relatives of any patient affected before 55 and 65 years of age in men and women, respectively (30). The current knowledge regarding SCD highlights the need for cascade screening of first-degree relatives for inherited cardiac diseases in out-patient clinics.

6. CONCLUSION

In this thesis, we examined the SCD burden in Danes aged 1-49 years in Denmark. In particular, we reported updated and valid incidence rates as well as causes of death. SCD occurs with an incidence rate of 8.6 per 100,000 person-years in persons aged 1-49 years. The incidence rate increases with increasing age, and we reported incidence rates of 2.3 and 21.7 per 100,000 person-years in persons aged 1-35 years and 36-49 years, respectively. SUD is significantly more predominant in the 1-35-year age group, whereas CAD is the most predominant cause of death in the 36-49-year age group (Paper I). In a subgroup analysis of SCD in children (1-18 years), we found an SCD incidence rate of 1.1 per 100,000 person years. Of all SD cases in children, 49% were caused by a potentially inherited cardiac disease. Almost all SD cases caused by a potentially inherited disease undergo autopsy. Interestingly, antecedent symptoms, prodromal symptoms, or both were noted in 59% of all SCD cases in children (Paper II).

SrSCD is a rare occurrence in Denmark. The SrSCD incidence rate did not differ between competitive and non-competitive athletes, but the incidence rate did increase with increasing age, as expected. We showed that SCD remains significantly more common in the general population than among athletes. Hence, the results indeed call into question whether recommending mandatory screening programs that are only available to young competitive athletes is ethically acceptable. As several athletes experienced symptoms prior to death, increasing awareness may be an alternative approach (Paper III).

SCD remains significantly more common among individuals with previous psychiatric disease than among individuals without psychiatric disease. The increased risk is largely driven by patients with schizophrenia-spectrum and substance-related disorders (Paper IV).

Overall, the findings presented in this thesis suggest that SCD remains a significant public health issue. Several deaths may be due to inherited causes, highlighting the need for cascade screening of first-degree relatives. Although SCD occurs with a very high incidence rates in subgroups of patients, SrSCD seems to be a minor problem in Denmark.

7. FUTURE PERSPECTIVES

Although this thesis adds important knowledge to the existing literature, several issues remain to be addressed. The importance of an autopsy following SD cannot be overstated, and we should continue to address this problem in future public health debates.

The two most predominant causes of SCD were SUD (1-35 years) and CAD (36-49 years). These causes of death should be investigated further in future projects. SUD may either be due to an inherited condition or be caused by medications that prolong the QT interval. Therefore, a thorough description of the medication taken prior to death using the Danish Prescription Registry may further elucidate the magnitude of this problem. In patients with previous psychiatric disease, the magnitude of this problem is of considerable interest.

Patients with CAD before 50 years should be screened for familial hypercholesterolemia, and the presence of premature CAD should also be assessed among family members. This investigation would elucidate the burden of familial hypercholesterolemia on SCD in Denmark. Nearly one-third of all SD cases are caused by non-cardiac diseases, and future studies should investigate these deaths further. Thorough descriptions of the diseases that cause these deaths are of particular interest. As long as autopsy rates are low, the identification of risk factors associated with SCD among SD cases remains of interest. This would help guide clinicians to decide whether family members of SD victims should be followed in a clinic for inherited cardiac diseases.

The future screening strategies of athletes will likely continue to be debated as this issue is more or less a matter of opinion. To definitively define the role that screening should have, a prospective case-control study should be performed. This study should randomly assign every athlete to be screened or not. However, due to the very low SrSCD incidence rate, the number of individuals that would need to be included to see an effect would be tremendous. Hence, whether such a study will ever be conducted is questionable.

Finally, with the availability of dried blood spot samples from infants in Denmark, we have a very unique opportunity to perform genetic testing of SCD cases in Denmark.

8. English summary

Sudden cardiac death (SCD) is a tragic event affecting millions of individuals worldwide. Although several studies have investigated the epidemiology of SCD, these studies may have been affected by reporting and referral biases, which are reflected in the very different incidence rates and causes of deaths that have previously been reported. Among SCD victims aged <36 years, inherited cardiac diseases are well known to play an important role. However, the extent to which inherited cardiac diseases also play a role in SCD victims aged <50 years has not been completely described. Additionally, SCD in children is of particular interest. These deaths are often described as a part of the deaths of young adolescents up to 40 years of age, and the focus has recently shifted towards the prevention of these deaths. The SCD incidence rate among patients with psychiatric disease has also gained significant attention. Finally, the incidence rate of sports-related sudden cardiac death (SrSCD) has been thoroughly investigated in young competitive athletes. However, whether competitive athletes are at increased risk for SrSCD compared with non-competitive athletes remains unknown. These data should be available prior to discussing optimal screening strategies for (competitive) athletes.

In this thesis, we investigated the SCD burden in Danes aged 1-49 years between 2007 and 2009. By using the unique Danish death certificates, autopsy reports, discharge summaries, and registries, we included all deaths in a nationwide setting. We described the incidence rates and causes of death, and we performed a subgroup analysis of SCD in children (1-18 years, 2000-2006). Furthermore, we described the SCD burden in competitive and non-competitive athletes and investigated how often SCD occurred in patients with previous psychiatric disease.

SCD has an incidence rate of 8.6 (95% Confidence Interval (CI) 8.0-9.2) per 100,000 person-years in persons aged 1-49 years. We found a steep increase in the incidence rate with increasing age, reaching 38.5 (95% CI 32.9-44.7) per 100,000 person-years in persons aged 48-49 years. The most common causes of death were coronary artery disease (CAD) (n=158) and sudden unexplained death (SUD) (n=136). In the 1-35-year age group, SUD was significantly more common than CAD. In contrast, CAD was significantly more common than SUD in the 36-49-year age group.

In children 1-18 years of age, SCD is a seemingly rare occurrence with an incidence rate of only 1.1 (95% CI 0.9-1.3) deaths per 100,000 person-years. Similarly to the 1-35-year age group, SUD is

often the cause of death in children. Overall, 49% of all SCDs in children are caused by a potentially inherited cardiac disease, emphasizing the need for autopsy as well as for follow-up and genetic testing of the affected family members.

In Denmark, SrSCD is a very rare occurrence. The SrSCD incidence rate increases with increasing age but remains much lower than the SCD incidence rate in the general population. Importantly, we found no differences in the incidence rate between competitive and non-competitive athletes aged 12-35 years (incidence rate ratio 1.1; 95% CI 0.2-5.1, p=0.88) and 36-49 years (incidence rate ratio 2.2; 95% CI 0.9-5.1, p=0.06). These results add important knowledge to the ongoing debate regarding whether mandatory screening programs with electrocardiograms should be recommended for young competitive athletes, as suggested by the European Society of Cardiology. The current results suggest that screening only competitive athletes would be ethically questionable because non-competitive athletes are at the same risk for SrSCD.

Patients with psychiatric disease are known to have an increased cardiovascular risk. For the first time, we describe the nationwide SCD incidence rates of SCD as well as the causes of death in patients with previous psychiatric disease. We reported an SCD incidence rate ratio of 4.3 (95% CI 3.3-5.5, p<0.01) in patients with previous psychiatric disease compared with patients without psychiatric disease. The higher incidence rate is largely driven by schizophrenia-spectrum and substance-related disorders. Interestingly, SUD is more common among patients with psychiatric diseases, suggesting that many of these deaths may are triggered by medications that caused a primary arrhythmic event.

Future research should investigate the extent to which CAD among individuals younger than 50 years of age is caused by inherited cardiac conditions such as familial hypercholesterolemia. The extent to which medication use prior to death may contribute to SCD and SUD should also be evaluated. Finally, with the availability of dried blood spot samples from all infants in Denmark, future research should also investigate the genetic substrate of SCD and SUD.

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