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ORIGINAL ARTICLE

Nationwide Study of Sudden Cardiac Death in People With Congenital Heart Defects Aged 0 to 35 Years

BACKGROUND: Congenital heart defects (CHD) are among the leading causes of sudden cardiac death (SCD) in the young. Nationwide incidence of SCD in people with CHD (SCD-CHD) has not been established in the young general population. The aims of this study were to investigate incidence of SCD-CHD and whether incidence of SCD-CHD in infants declined after implementation of nationwide fetal ultrasound screening in Denmark.

METHODS: All deaths (n=11 451) among people aged 0 to 35 years in Denmark in 2000 to 2009 (24.4 million person-years) were included. Danish death certificates, autopsy reports, records from hospitals and general practitioners, and data from nationwide Danish registries were used to identify SCD-CHD cases.

RESULTS: We identified 90 (11%) cases of SCD-CHD from 809 SCD. The incidence rate of SCD-CHD was 0.4 per 100 000 person-years among people aged 0 to 35 years. In total, 53 (59%) were diagnosed with CHD before death. Incidence of SCD was 9.6× higher among patients with CHD compared with people without CHD (P<0.01). Annual incidence of physical activity–related SCD-CHD among patients aged 2 to 35 years diagnosed with CHD was 0.9 per 100 000. The annual incidence rate of SCD-CHD in infants declined after implementation of nationwide fetal ultrasound screening (incidence rate ratio, 3.8; P<0.01).

CONCLUSIONS: The proportion of SCD-CHD in the young was 11%, which is higher than previously reported. Physical activity–related SCD-CHD was a rare event among patients with CHD. We observed an ≈4-fold lower incidence of SCD-CHD among infants born after implementation of nationwide screening.

VISUAL OVERVIEW: An online visual overview is available for this article.

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WHAT IS KNOWN?

- People with congenital heart defects (CHD) have increased morbidity and mortality, in part because of an increased risk of sudden cardiac death (SCD) among people with CHD (SCD-CHD).
- Because of improved surgical and medical treatments and increased use of fetal ultrasound screening, the epidemiology of SCD-CHD is likely to have undergone changes in recent years.

WHAT THE STUDY ADDS?

- Only 59% of SCD-CHD cases were diagnosed with CHD before death. Many of these cases would have been treatable or curable.
- The incidence rate of SCD during physical activity among people with CHD was low.
- There was a significant decline in incidence of SCD-CHD among infants born after implementation of nationwide fetal ultrasound screening.

Congenital heart defects (CHD) affect ≈0.8% of all live births.[1,2] Despite substantially improved survival over the past decades, morbidity and mortality remain significant, in particular among patients with complex CHD.[2–5] The decreased life expectancy is, in part, explained by an increased risk of sudden cardiac death (SCD) among people with CHD (SCD-CHD).[4,6–8] Because of improved surgical and medical treatments and increased use of fetal ultrasound screening, the epidemiology of SCD-CHD is likely to have undergone changes in recent years.[2,3,9–11] Nationwide fetal ultrasound screening was implemented in Denmark in 2005.[12]

In large population-based studies of CHD, the identification of patients with CHD is often based on information from registries established for other purposes than examination of CHD.[13–16] These studies depend heavily on correct diagnostic coding, which may be inaccurate, particularly regarding subtypes of CHD.[17,18] Furthermore, only few population-based studies have examined SCD-CHD in the young.[6,19–22] These studies have exclusively included patients diagnosed with CHD before death, and the incidence of SCD-CHD is, therefore, unknown in the young general population.[6,19–22]

Consequently, larger studies of SCD-CHD in the general population using validated CHD diagnoses are warranted. Using a nationwide, population-based design with examination of all deaths in a 10-year period, we aimed to determine incidence of SCD-CHD in individuals aged 0 to 35 years and to explore changes in incidence rates (IR) of SCD-CHD in infants born after implementation of nationwide fetal ultrasound screening. Furthermore, we aimed to determine to which extent cases were diagnosed with CHD antemortem and how often death occurred during physical activity.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

This nationwide population-based study conducted in Denmark covers all deaths from January 1, 2000, to December 31, 2009, in people aged 0 to 35 years. We used death certificates, national registries, autopsy reports, and records from hospitals and general practitioners to identify and characterize all people aged 0 to 35 years who experienced SCD-CHD in 2000 to 2009.

Danish Healthcare System and Danish Registries

The Danish National Health service provides public healthcare for all Danish residents free of charge. Free medical care is guaranteed for all visits to general practitioners, outpatient clinics, emergency departments, and public hospitals. Patients with CHD are exclusively treated at public hospitals.

All Danish citizens are assigned a personal Civil Registration Number, which can be linked unambiguously to national registries on an individual level. Information on prior medical history can be retrieved from the National Patient Register. This register contains information on all inpatient activity at Danish hospitals since 1977 (and outpatient contacts since 1995) using *International Classification of Diseases* codes, revisions 8 and 10.[23] Information on cause of death can be obtained from the Danish Register of Causes of Death, in which immediate, contributory, and underlying causes are recorded using *International Classification of Diseases* Tenth Revision codes.

Study Population and Data Collection

We have previously identified all SCD in individuals aged 0 to 35 years in Denmark, 2000–2009.[24,25] In these studies, death certificates were used to identify cases of sudden and unexpected death. Danish death certificates can only be issued by a medical doctor and are valid for identification of sudden unexpected deaths because of a supplemental information field (see Data Supplement; Winkel et al[24]). This field includes a description of the circumstances leading to death, including information on previous medical conditions, and often information from interviews with eyewitnesses, family members, and the patient's general practitioner. To identify cases of sudden and unexpected death, all death certificates issued in 2000 to 2009 for people aged 0 to 35 years were reviewed independently by 2 physicians. In cases of disagreement, the 2 investigators re-evaluated the death certificate together to reach a consensus. Cases of sudden death because of cardiac causes (SCD) were subsequently identified using the National Patient Register, the Danish Register of Causes of Death, and autopsy reports together with access to discharge summaries and in selected cases medical records.[24,25]

In this study, all SCD cases were reviewed, and we initially included all cases with a diagnosis of CHD in the National Patient Register or the Danish Register of Causes of Death and cases with a postmortem diagnosis of CHD determined by autopsy. For all cases, all available medical records from

general practitioners and relevant hospital departments were retrieved. Through careful review of medical records from hospitals and general practitioners, death certificates, and autopsy reports, we validated all CHD diagnoses and divided patients into subgroups of CHD. In cases of uncertainty, all information on the patient in question was reviewed by an expert in CHD.

Definitions

The abbreviation SCD-CHD refers to SCD in a person with a CHD.

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

SCD in autopsied cases was defined as a sudden death of unknown or cardiac cause and in nonautopsied cases as a sudden death presumed to be of cardiac origin after review of all available information.

We applied Mitchell et al's[26] definition of CHD: Gross structural abnormalities of the heart or intrathoracic great vessels that are of actual or potential functional significance. We specifically excluded cases with isolated cardiomyopathies, cases with isolated rhythm disturbances, cases with isolated nonstenotic bicuspid aortic valves, and cases diagnosed exclusively with persistent ductus arteriosus (PDA) or atrial septal defects (ASD). Furthermore, we excluded cases with cardiac surgery within 30 days of death.

Severe CHD was defined as atrioventricular septal defects, coarctation of aorta, aortic valve stenosis, tetralogy of Fallot, pulmonary atresia with ventricular septal defect or intact septum, Ebstein anomaly, transposition of the great arteries, univentricular heart, coronary artery anomalies, and common arterial trunk.[27]

Physical activity–related SCD was defined as SCD occurring during or within 1 hour of moderate- to high-intensity exercise in people ≥2 years of age. Infants were defined as children <1 year old.

Statistical Methods

All data analyses were performed using SAS software package 9.4. IR of SCD-CHD in the general population were calculated based on the mean resident population of Danes aged 0 to 35 years in 2000 to 2009 as provided by Statistics Denmark.[28] We used the National Patient Register to estimate the prevalence of CHD in the Danish population and to calculate the IR of SCD among patients diagnosed with CHD. Confidence intervals (CIs) were calculated using Poisson distribution. Age-adjusted IR are provided using direct age adjustment. The entire Danish population aged 0 to 35 years was used as reference population when adjusting IR among the general population and when comparing SCD rates among people diagnosed with CHD and the general population. For each subtype of CHD, the population of all Danes diagnosed with the specific CHD was used as reference population. To compensate for overdispersion in our data, IR ratios were also tested using a negative binomial distribution. Medians were compared using Wilcoxon rank-sum test. Categorized nominal data were compared using a χ^2 test or Fisher exact test where appropriate. A 2-sided $P<0.05$ was considered statistically significant.

Approvals

This study was approved by the local ethics committee (H-KF-272484), The Danish Data Protection Agency (2011-41-5767), and the Danish Nation Board of Health (7-505-29-58/6). No informed consent was required for this study.

RESULTS

Study Population

In Denmark in 2000 to 2009, there was an average of 2.4 million people aged 0 to 35 years. During this 10-year study period, there were 11 451 deaths from a total of 24.4 million person-years in the age group (Figure 1). Through thorough review of all death certificates by 2 physicians, 1094 (9.6% of all deaths) cases of sudden and unexpected death were identified, of which 809 (7.1% of all deaths) were SCD. Among these, 121 (1.1% of all deaths) were either registered with CHD in the National Patient Register or the Danish Register of Causes of Death or had autopsy findings of CHD. After reviewing autopsy reports, deaths certificates, and medical records from hospitals and general practitioners, 90 (0.8% of all deaths) cases with structural CHD were found to have died suddenly and unexpectedly while 31 cases were excluded. Of these, 13 were exclusively diagnosed with either PDA or ASD (10 and 3, respectively), 11 were erroneously coded with CHD in the National Patient register or the Danish Register of Causes of Death, 2 had a nonstructural CHD, and 5 received cardiac surgery within 30 days of death (Figure 1).

Of the 90 SCD-CHD cases, 64 (71%) were autopsied, of which 37 (58%) were not diagnosed with CHD before death (Table 1). The 26 (29%) nonautopsied cases were identified through review of all available information, including medical records. All 26 nonautopsied cases had echocardiography findings of CHD.

Clinical Characteristics

In total, 34 (38%) cases died within first year of life (Figure 2). A comparison between SCD-CHD cases aged 0 to 1 year and 1 to 35 years is shown in Tables 1 and 2. In cases who experienced a witnessed cardiac arrest (n=53; 59%), asystole was the most predominant heart rhythm registered by prehospital personnel and emergency departments (n=26; 49%; Table 2). In the majority of unwitnessed deaths, information on initial heart rhythm was unavailable (n=27; 73%). Resuscitation was attempted in 75 (83%) of all cases. Of these, 2 (3%) were successfully resuscitated initially but died shortly thereafter. In only 4 (4%) cases, death occurred during moderate- to high-intensity activity

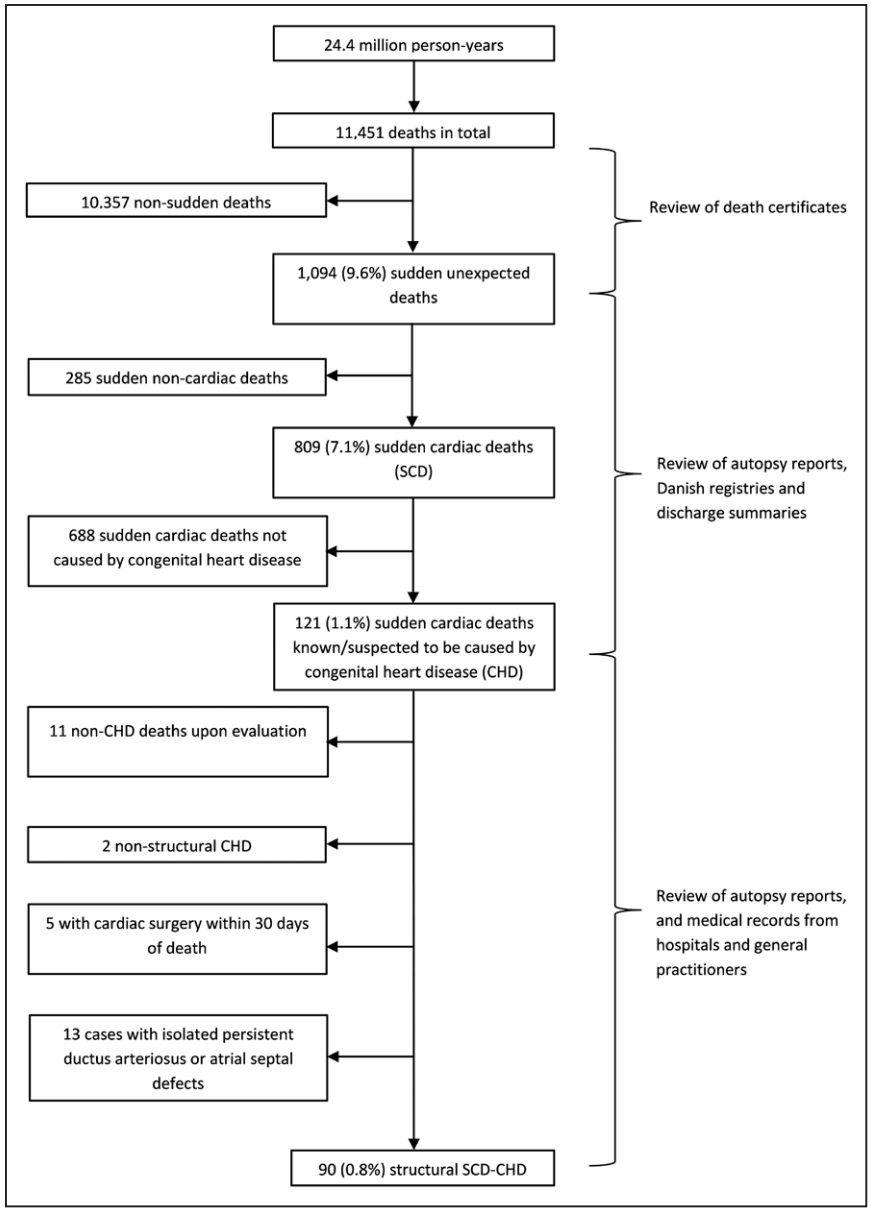

Figure 1. Flowchart of the process used to identify all sudden cardiac deaths in people with congenital heart defects aged 0 to 35 y in Denmark, 2000 to 2009.

(Table 2). An overview of these 4 cases is shown in Table I in the Data Supplement.

In total, 68 (76%) cases had a known comorbidity, and 19 (28%) of these had a noncongenital heart disease (Table 1). Of the 53 cases diagnosed with CHD before death, 34 (64%) had previously undergone surgery in relation to their CHD; 15 (28%) cases underwent 1 heart surgery while 19 (36%) underwent ≥2 heart surgeries. More than half of the surgeries were performed on people <2 years of age (n=18; 53%). In cases diagnosed with CHD before death, 13 (25%) received device therapy; 12 (23%) were implanted with a pacemaker and one (2%) with an implantable cardioverter defibrillator (Table 1). Of these, 3 (23%) patients had recordings of supraventricular tachycardia before death, and the patient with an implantable cardioverter defibrillator received an appropriate shock 12 months before death. A total of 66 (73%) cases presented cardiac symptoms before death (Table 3). On basis of cardiac symptoms, 36 (40%) cases sought medical attention.

Incidence Rates

The IR of SCD-CHD in people aged 0 to 35 years was 0.4 (95% CI, 0.3–0.5) per 100 000 person-years in the general population.

The IR of SCD was 3.3 (95% CI, 3.1–3.6) per 100 000 person-years in the general population. Age-adjusted IR of SCD-CHD among patients diagnosed with CHD was 28.5 (95% CI, 20.0–37.0) per 100 000 person-years while age-adjusted IR of SCD in the CHD-free background population was 3.0 (95% CI, 2.8–3.2) per 100 000 person-years (IR ratio, 9.6; $P<0.01$). In infants,

Table 1. Clinical Characteristics and Medical History in Cases of Sudden Cardiac Death in People With Congenital Heart Defects Aged 0 to 35 Years in Denmark, 2000 to 2009

Clinical Characteristics and Medical History	SCD-CHD age 0–35 y (n=90)	SCD-CHD age 0–1 y (n=34)	SCD-CHD age 1–35 y (n=56)	*P* Value*
Males, n (%)	53 (59)	20 (59)	33 (59)	0.992
Whites, n (%)	77 (86)	29 (85)	48 (86)	0.956
Diagnosed with CHD before death	53 (59)	8 (24)	45 (80)	<0.001
Comorbidity, n (%)				
Any	68 (76)	17 (50)	51 (91)	<0.001
Cardiac disease, non-CHD	20 (22)	2 (6)	18 (32)	0.004
Supraventricular tachycardia	9 (10)	0 (0)	9 (16)	0.014
Atrioventricular block	8 (9)	2 (6)	6 (11)	0.705
Endocarditis	3 (3)	0 (0)	3 (5)	0.287
Other	3 (3)	0 (0)	3 (5)	0.287
Neurological disease	14 (16)	1 (3)	13 (23)	0.010
Infectious disease	10 (11)	3 (9)	7 (13)	0.737
Asthma	6 (7)	2 (6)	4 (7)	1.000
Other	4 (4)	1 (2)	3 (5)	1.000
Cardiac intervention, n (%)				
Cardiac surgery	34 (38)	3 (9)	31 (55)	<0.001
Device therapy (PM or ICD)	13 (14)	1 (1)	12 (21)	0.006
Autopsied SCD-CHD cases, n (%)	64 (71)	31 (91)	33 (59)	0.001

CHD indicates congenital heart defect; ICD, implantable cardioverter defibrillator; PM, pacemaker; and SCD, sudden cardiac death.

**P* value for differences between SCD-CHD cases aged 0–1 and 1–35 years, respectively.

the SCD-CHD IR was 5.2 (95% CI, 3.7–7.3) per 100 000 person-years compared with 0.2 (95% CI, 0.2–0.3) in people aged 1 to 35 years. There were no differences in IR between people aged 1 to 18 and 19 to 35 years (*P*=0.18). The physical activity–related SCD-CHD incidence among patients aged 2 to 35 years diagnosed with CHD was 0.9 (95% CI, 0.2–3.5) per 100 000 person-years. The IR of SCD-CDH according to subtypes of CHD is shown in Table 4. Age- and sex-specific IR of SCD-CHD and age-adjusted sex-specific IR of SCD according to CHD subtype are provided in Tables II and III in the Data Supplement, respectively.

Subtypes of CHD

The most frequent CHD subtypes among the SCD victims were coarctation of aorta (n=16; 16%), transposition of the great arteries (n=13; 13%), and univentricular heart (n=10; 10%; Table 4). Of these, 30 (77%) were autopsied, and the mechanism of death was rupture of an aortic aneurysm in 4 (13%) cases while death was presumed arrhythmic in the remaining 26 (87%) cases. Of 7 SCD among infants with undiagnosed coarctation of aorta, 3 were assessed to be secondary to ductal closure.

Comparison Between Patients Diagnosed With CHD Before Death and Undiagnosed Patients

Compared with the 53 (59%) cases diagnosed with CHD before death, the 37 (41%) undiagnosed cases were younger (median age, 0.1 year versus 19.2 years; *P*<0.01), less often had a previous medical history (*P*<0.01), and more often died during sleep (*P*<0.01). The proportion of physical activity–related death in people aged 2 to 35 years was 4% among SCD cases diagnosed with CHD before death and 18% among undiagnosed cases (*P*=0.17). Among undiagnosed patients, SCD occurred more frequently in people with coarctation of the aorta and coronary artery anomaly (*P*=0.02 and *P*=0.01, respectively) while the proportion of deaths in people with tetralogy of Fallot was higher among diagnosed cases (*P*=0.04). Antecedent cardiac symptoms and contact with emergency departments were more common among diagnosed cases compared with undiagnosed cases (60% versus 24%, *P*<0.01 and 34% versus 5%, *P*<0.01, respectively) while prodromal cardiac symptoms were more prevalent among undiagnosed cases (57% versus 30%; *P*=0.01; Table 3).

Comparison Between Infants Born Before and After Implementation of Nationwide Fetal Ultrasound Screening

The IR of SCD-CHD among infants born before implementation of national fetal ultrasound screening was 7.4 per 100 000 person-years compared with 1.9 in infants born after implementation of screening, which corresponds to an IR ratio of 3.8 (95% CI, 1.5–9.9; *P*<0.01; Figure 3). We observed a significant decline in SCD in people with severe CHD after implementation of fetal ultrasound screening (*P*=0.02) while the difference in incidence of SCD in people with nonsevere CHD did not reach statistical significance (*P*=0.15). Among infants, the proportion of SCD in people with undiagnosed severe CHD decreased significantly after implementation of screening (17% versus 6%; *P*=0.03). The proportion of SCDs among infants diagnosed with CHD before death did not change significantly after implementation of screening (4% versus 2%; *P*=0.29).

After implementation of screening, there were no cases of SCD in people with univentricular heart and tetralogy of Fallot.

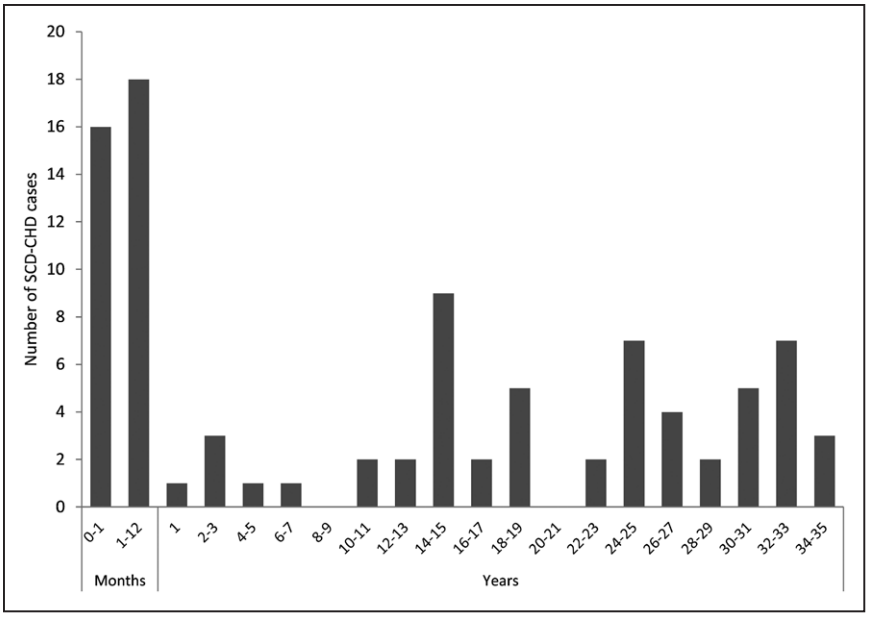

Figure 2. Age-related distribution of sudden cardiac deaths (SCD) in people with congenital heart defects (CHD) aged 0 to 35 y in Denmark, 2000 to 2009.

DISCUSSION

We have conducted the first nationwide study on SCD-CHD in the young general population. All deaths in people aged 0 to 35 years in 2000 to 2009 were included. Our findings provide new insight into the epidemiology of SCD-CHD. First, we found an IR of SCD-CHD in the general population of 0.4 per 100 000 person-years. Second, only 59% of the deceased were diagnosed with CHD before death. Third, the IR of physical activity–related SCD-CHD among patients with CHD was low. Finally, we observed a marked decline in incidence of SCD-CHD after implementation of nationwide fetal ultrasound screening.

IR in the General Population and Among Patients Diagnosed With CHD Before Death

In recent years, several population-based studies on SCD in the young has been conducted.[24,25,29–38] In these studies, the reported proportion of SCD caused by CHD has varied considerably, ranging from 0% to 9% in the young and up to 12% among infants and children.[30–38] In the present study, 11% of all SCD cases in the young occurred in people with CHD. The discrepancy between the reported results is, in part, explained by different study designs and definitions of CHD. Results from previous studies are often based on findings in 1 forensic department or a region of a country with data almost exclusively being obtained from autopsied decedents.[30–37] Because autopsy is not consistently conducted in most countries, the frequency of SCD-CHD is likely under-reported. In the 10-year period in Denmark, the autopsy ratio among people experiencing sudden death was 76%.[24,25,39] In total, 26 of the SCD-CHD cases in this study were nonautopsied. Excluding those would lead to a 29% decline in the annual IR of SCD-CHD (0.4 versus 0.3 per 100 000 person-years; P=0.03), highlighting the need for studies examining both autopsied and nonautopsied SCD-CHD cases.

Only few studies have focused on SCD-CHD in the young.[6,19–22,40] These studies exclusively include patients diagnosed with CHD before death.[6,19–22,40] However, 41% of the SCD-CHD cases in our study were not diagnosed with CHD before death, and exclusion of these would have led to a false low annual IR of SCD in the general population. This underlines the importance of not only including patients known with CHD before death when studying the epidemiology of SCD-CHD.

Physical Activity–Related SCD-CHD

Fear of SCD has led to restrictions of physical activity in patients with CHD, and these patients have lower levels of physical activity compared with healthy peers.[41] However, as a growing number of patients with CHD reach older age, the cardioprotective effects of physical activity become increasingly important.[41] Appropriate counseling of these patients requires estimates on risk of SCD in relation to physical activity. We found a low annual incidence (0.9 per 100 000 person-years) of physical activity–related SCD-CHD among patients aged 2 to 35 years diagnosed with CHD. In support of this, it has previously been shown that SCD in children aged 2 to 18 years diagnosed with CHD rarely occurs during physical activity.[20] However, as the authors of the study state it is unknown to what degree children diagnosed with CHD are restricted from physical activities on basis of their CHD diagnosis. As our study included SCD-CHD cases undiagnosed before death, we were able to estimate the burden of SCD-CHD during physical activity

Table 2. Circumstances of Cardiac Arrest in Cases of Sudden Cardiac Death in People With Congenital Heart Defects Aged 0 to 35 Years in Denmark, 2000 to 2009

Circumstances of Cardiac Arrest	SCD-CHD age 0–35 y (n=90)	SCD-CHD age 0–1 y (n=34)	SCD-CHD age 1–35 y (n=56)	*P* Value*
Witnessed cardiac arrest, n (%)	53 (59)	19 (56)	34 (61)	0.652
Attempted resuscitation, n (%)	75 (83)	31 (91)	44 (79)	0.120
Activity before cardiac arrest, n (%)				0.004
Awake and relaxed	48 (53)	15 (44)	33 (59)	
Sleep	29 (32)	18 (53)	11 (20)	
Physical activity	4 (4)	0 (0)	4 (7)	
Unknown	9 (10)	1 (3)	8 (14)	
Place of cardiac arrest, n (%)				0.178
Home	54 (60)	24 (71)	30 (54)	
Hospital/ambulance	21 (23)	8 (24)	13 (23)	
Public place	14 (16)	2 (6)	12 (21)	
Unknown	1 (1)	0 (0)	1 (2)	
Heart rhythm at cardiac arrest in witnessed cases (n=64), n (%)				0.080
Asystole	26 (49)	13 (68)	13 (38)	
VF	13 (25)	1 (5)	12 (35)	
PEA	3 (6)	1 (5)	2 (6)	
Unknown	11 (21)	4 (21)	7 (21)	

CHD indicates congenital heart defect; PEA, pulseless electrical activity; SCD, sudden cardiac death; and VF, ventricular fibrillation.

**P* value for differences between SCD-CHD cases aged 0–1 and 1–35 years, respectively.

among undiagnosed people. In the 10-year study period, we found only 2 cases of physical activity–related SCD-CHD in undiagnosed people. Both of these deaths occurred in people with coronary anomalies. Coronary anomalies are among the most common causes of SCD during physical activity, and restriction of physical activity may be warranted in these patients.[42] However, taken together, our findings indicate a low risk of SCD during physical activity among people with CHD.

Cause of Death

Consistent with previous studies, we found that patients with severe defects, such as transposition of the great arteries, univentricular heart, and Ebstein anomaly, were at greatest risk of SCD.[6,20,21,43]

It is difficult to ascertain whether a CHD is causatively responsible for SCD. In nonautopsied cases, although information from all possible sources, including all medical information and circumstances surrounding death, pointed strongly toward death being caused by CHD, these deaths could potentially have non-CHD causes. In all autopsied cases, a forensic pathologist concluded that the CHD was the cause of death. However, especially among nonsevere cases of CHD, there is some risk that the forensic pathologist in search of an explanation of cause of death has overestimated the significance of a finding of CHD. Consequently, this study describes the association between SCD and CHD as causality between SCD and a given CHD cannot be established in all cases.

Initially, we identified 13 cases of SCD in people with either PDA or ASD. In all 13 cases, either a forensic pathologist concluded that PDA or ASD was the most likely cause of death (n=10) or the deceased had corrective surgery for PDA/ASD and no other diagnosed clinical condition that could cause the death of the patient (n=3). However, both PDA and ASD are not commonly associated with SCD. Consequently, some of these cases could in fact have experienced sudden arrhythmic death syndrome, where SCD remains unexplained after postmortem evaluation. The 13 cases were, therefore, excluded from the study.

We found coronary artery anomalies among 6% of all SCD-CHD cases. The proportion of SCDs caused by coronary anomalies has been variably reported ranging from 0% to 4% in the young general population and up to ≈20% among athletes.[31,36–38,44,45] These differences are probably a consequence of the different populations examined and different classification/definition of coronary artery anomalies postmortem.[46]

Implementation of Nationwide Fetal Ultrasound Screening

We observed an ≈4-fold decrease in SCD-CHD among infants after implementation of nationwide fetal ultrasound screening in 2005. Prenatal screening for CHD can lead to a decreased incidence of SCD-CHD in several ways: First, detection of severe CHD may in some countries lead to termination of pregnancy; second, prenatal detection allows for delivery in a specialized tertiary center; third, postnatal and neonatal management can be initiated early (eg, immediate administration of prostaglandins in duct-dependent CHD).[2,10,11] Our data does not allow us to determine whether the relationship between the observed decreased incidence of SCD-CHD and screening is causal. Other explanations for our findings include a decreased live birth prevalence of CHD unrelated to screening and improved medical and surgical treatment of CHD in general.[2,3,9,27,47] A decrease in prevalence of CHD has been observed across several countries.[27,47] In a large cross-European study, prevalence of CHD declined between 2004 and 2007, and the authors proposed that explanatory factors could be increased intake of folic acid, improved treatment of maternal health conditions, such as diabetes mellitus, and reduction of risk factors of CHD (eg, maternal smoking).[47] However, for the most severe CHD, the

Table 3. Cardiac Symptoms and Contact With the Healthcare System Before Sudden Cardiac Death in People With Congenital Hearts Defect Aged 0 to 35 Years in Denmark, 2000 to 2009

Cardiac Symptoms and Contact With the Healthcare System, n (%)	SCD-CHD (n=90)	CHD Known Before Death (n=53)	CHD Unknown Before Death (n=37)	*P* Value*
Antecedent symptoms†	41 (46)	32 (60)	9 (24)	<0.001
Prodromal symptoms‡	37 (41)	16 (30)	21 (57)	0.012
Symptoms overall	66 (73)	41 (77)	25 (68)	0.301
Dyspnea	39 (43)	22 (42)	17 (46)	0.676
Syncope	11 (12)	10 (19)	1 (3)	0.024
Angina	11 (12)	9 (17)	2 (5)	0.116
Seizures	6 (7)	6 (11)	0 (0)	0.041
Presyncope	6 (7)	5 (9)	1 (3)	0.394
Nonspecific chest pain	5 (6)	4 (8)	1 (3)	0.645
Palpitations	3 (3)	3 (6)	0 (0)	0.266
Other (dizziness, fatigue, and discomfort)	27 (30)	14 (26)	13 (35)	0.374
Contact with the healthcare system because of cardiac symptoms before death				
Total	36 (40)	24 (45)	12 (32)	0.221
Emergency departments	20 (22)	18 (34)	2 (5)	0.001
General practitioner	16 (18)	6 (11)	10 (27)	0.055

CHD indicates congenital heart defect; and SCD, sudden cardiac death.
**P* value for differences between cases diagnosed with congenital heart defect before death and undiagnosed cases.
†Symptoms between 1 hour and 1 year before death.
‡Symptoms within 1 hour of death.

total prevalence of CHD (including fetal deaths after 20 weeks of gestation and terminations of pregnancy) was stable between 2004 and 2007 while live birth prevalence decreased. The authors, therefore, concluded that the decreasing trend in live birth prevalence of severe CHD was most likely explained by an increase in prenatal diagnosis and termination of pregnancy.[47] Furthermore, a Norwegian study found improved 1-year survival for live-born children with severe CHD in 1994 to 2009, but an unchanged 1-year mortality throughout the study if stillbirths and late-term terminations in fetuses with severe CHD were included.[48] In our study,

Table 4. Incidence Rates of Sudden Cardiac Death in People Aged 0 to 35 Years With Congenital Heart Defects per 100 000 Person-Years in Denmark, 2000 to 2009

CHD Subtype	SCD-CHD (n=90), n (%)	SCD-CHD in Patients Diagnosed With CHD Before Death, n (% of all SCD-CHD)	SCD-CHD in Infants, n (%)	Incidence Rate of SCD-CHD in the General Population per 100 000 Person-Years (95% CI)	Incidence Rate of SCD-CHD in Patients Diagnosed With CHD per 100 000 Person-Years (95% CI)
CHD in total	90 (100)	53 (59)	34 (100)	0.37 (0.30–0.45)	22.6 (17.3–29.6)
Coarctation of aorta	16 (18)	5 (31)	7 (21)	0.07 (0.04–0.11)	50.6 (21.1–121.6)
Transposition of the great arteries	13 (14)	9 (69)	5 (15)	0.05 (0.03–0.09)	171.1 (89.0–329.8)
Univentricular heart	10 (11)	6 (60)	6 (18)	0.04 (0.02–0.07)	192.1 (86.3–427.5)
Aortic valve stenosis	9 (10)	6 (67)	2 (6)	0.04 (0.02–0.07)	99.5 (44.7–221.4)
Common arterial trunk	7 (8)	2 (29)	5 (15)	0.03 (0.01–0.06)	143.2 (35.8–572.4)
Tetralogy of Fallot	6 (7)	6 (100)	1 (3)	0.02 (0.01–0.05)	88.2 (39.6–196.3)
Coronary artery anomaly	5 (6)	0 (0)	1 (3)	0.02 (0.01–0.05)	…
Ebstein anomaly	4 (4)	3 (75)	1 (3)	0.02 (0.01–0.04)	496.7 (160.2–1540.0)
Ventricular septal defect	4 (4)	4 (100)	1 (3)	0.02 (0.01–0.04)	6.0 (2.2–15.9)
Pulmonary valve stenosis	3 (3)	3 (100)	1 (3)	0.01 (0.004–0.04)	26.6 (8.6–82.5)
Pulmonary atresia	2 (2)	1 (50)	2 (6)	0.01 (0.002–0.03)	72.9 (10.3–517.8)
Other CHD	11 (12)	8 (73)	2 (6)	0.05 (0.02–0.08)	5.1 (2.5–10.2)

CHD indicates congenital heart defect; CI, confidence interval; and SCD, sudden cardiac death.

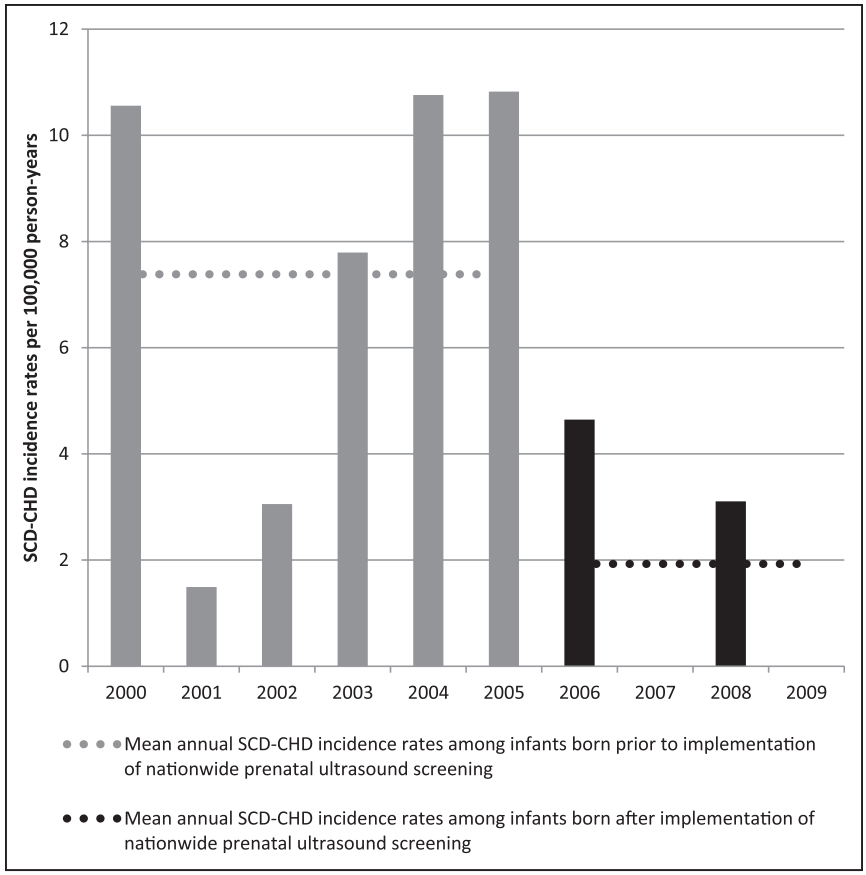

Figure 3. **Incidence rate of sudden cardiac deaths (SCD) in infants with congenital heart defects (CHD) per 100 000 person-years according to implementation of nationwide fetal ultrasound screening.**

we found a significant decrease in incidence of SCD among infants with undiagnosed severe CHD born after implementation of nationwide fetal ultrasound screening, supporting that screening could be causally associated with a decreased incidence of SCD-CHD.

Strength and Limitations

The main strength of our study is the nationwide and unselected approach with inclusion of all deaths in people aged 0 to 35 years in a 10-year period and the subsequent comprehensive follow-up. Instead of solely relying on data from national registries, we reviewed all available autopsy reports, death certificates, and medical records from general practitioners and hospitals.

The study has limitations inherent to any retrospective study. However, the performance of a prospective study is complicated by the low incidence of SCD-CHD in the general population.

SCD-CHD cases can only be identified if an autopsy is performed or if the person is diagnosed with CHD before death. Because the autopsy ratio among victims of sudden death aged 0 to 35 years in the 10-year period was 76%, we might have underestimated the incidence of SCD-CHD. However, if it is decided not to conduct an autopsy of SCD victims in this young age group, cause of death is most likely established from other sources, including medical history.

There is a risk of misclassification because 30% of SCD-CHD cases were not autopsied. Death in these cases could potentially have non-CHD causes although information from all possible sources, including all medical information and the circumstances surrounding death, pointed strongly toward death being caused by CHD. Although a forensic pathologist concluded that CHD was most likely cause of death in all autopsied SCD-CHD cases, there is some risk that the nonsevere CHD were erroneously deemed as cause of death. However, all forensic autopsies follow a standardized protocol, in which all organs are examined and are all supervised by another forensic pathologist, ensuring a high-quality uniform evaluation of all deaths. Furthermore, in cases of uncertainty on cause of death, the entire case in all its contents was reviewed by and discussed with a forensic pathologist and an expert in CHD.[24]

When calculating incidence of SCD among patients diagnosed with CHD before death, we used The National Patient Register to estimate the CHD background population in Denmark. As such registries tend to overestimate the CHD population, our reported incidence of SCD is probably conservative.[16] Furthermore, The National Patient Register has previously been shown to have low validity on certain subtypes of CHD.[17,18] Therefore, our estimates on IR of SCD among patients diagnosed with selected subtypes of CHD carry large uncertainties. Our findings do

not necessarily apply to other populations with different demographics because 86% of cases were whites.

Conclusions

In this nationwide study on SCD-CHD in the young, we found an IR of SCD-CHD of 0.4 per 100 000 person-years in the general population. This corresponds to 11% of all SCD in the young, which is higher than previously reported. We observed an ≈10-fold higher risk of SCD among patients with CHD compared with the general population. Only 59% of SCD-CHD cases were diagnosed with CHD before death. As many types of CHD are curable or treatable, detection of undiagnosed CHD cases could potentially lead to a marked decreased morbidity and mortality in this patient group. Furthermore, we found SCD-CHD during physical activity to be a rare event among patients with CHD. Finally, there was a significant decline in incidence of SCD-CHD among infants born after implementation of nationwide fetal ultrasound screening.

ARTICLE INFORMATION

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Disclosures

None.

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Nationwide Study of Sudden Cardiac Death in People With Congenital Heart Defects Aged 0 to 35 Years

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SUPLEMENTAL MATERIAL

Supplementary Table 1. Sudden cardiac death in persons aged 2-35 years with congenital heart defects during or within 1 hour of physical activity in Denmark, 2000-2009

Age at death	Sex	Activity	Witnessed	CHD diagnosed prior to death	Antecedent symptoms	Prodromal symptoms	Congenital heart defect
11	Male	Running	Yes	No	None	Discomfort	Coronary anomaly: LCA with origin from RCA and anomalous course
14	Male	Soccer	Yes	Yes	None	None	Transposition of great arteries
15	Male	Running	Yes	No	Angina a week prior to death	None	Coronary anomaly: LCA with origin from posterior facing sinus and anomalous course
15	Female	School athletic activities	No	Yes	None	None	Pulmonary valve stenosis

LCA, left coronary artery; RCA, Right coronary artery.

Supplementary Table 2. Incidence rates of sudden cardiac death in persons with congenital heart defects per 100,000 person years according to age and sex.

Age group (years)	Overall IR of SCD-CHD (95% CI)	IR of SCD-CHD, Boys/men (95% CI)	IR of SCD-CHD, Girls/women (95% CI)
0-35	0.37 (0.30-0.45)	0.43 (0.33-0.56)	0.31 (0.22-0.43)
0	5.21 (3.73-7.41)	6.01 (3.93-9.31)	4.41 (2.61-7.43)
1-5	0.15 (0.06-0.36)	0.18 (0.06-0.55)	0.12 (0.03-0.49)
6-10	0.03 (0.01-0.21)	0*	0.06 (0.01-0.43)
11-15	0.39 (0.23-0.68)	0.53 (0.28-1.01	0.25 (0.09-0.65)
16-20	0.23 (0.11-0.49)	0.26 (0.10-0.69)	0.20 (0.07-0.63)
21-25	0.28 (0.15-0.55)	0.38 (0.17-0.84)	0.19 (0.06-0.60)
26-30	0.25 (0.13-0.48)	0.39 (0.19-0.81)	0.11 (0.03-0.44)
31-35	0.31 (0.17-0.54)	0.20 (0.08-0.54)	0.41 (0.21-0.83)

IR, incidence rate. *No deaths within age range

Supplementary Table 3A. Incidence rates of sudden cardiac death in male persons with congenital heart defects per 100,000 person-years

CHD subtype	SCD-CHD (n=53), n (%)	SCD-CHD in patients diagnosed with CHD prior to death, n (% of all SCD-CHD)	Incidence rate of SCD-CHD in the general population per 100,000 person years (95% CI)*	Incidence rate of SCD-CHD in patients diagnosed with CHD per 100,000 person years (95% CI)*
CHD in total	53 (100)	33 (62)	0.43 (0.32-0.56)	26.69 (18.37-37.53)
Coarctation of aorta	10 (19)	4 (40)	0.08 (0.04-0.15)	65.42 (17.81-172.24)
Transposition of the great arteries	9 (17)	7 (78)	0.07 (0.03-0.14)	203.06 (81.48-426.52)
Univentricular heart	5 (9)	3 (60)	0.04 (0.01-0.09)	172.1 (34.79-663.12)
Aortic valve stenosis	5 (9)	3 (60)	0.04 (0.01-0.09)	71.63 (14.77-217.49)
Common arterial trunk	4 (8)	1 (25)	0.03 (0.01-0.08)	130.05 (3.29-919.77)
Tetralogy of Fallot	4 (8)	4 (100)	0.03 (0.01-0.08)	102.82 (27.99-266.95)
Coronary artery anomaly	3 (6)	0 (0)	0.02 (0-0.07)	-
Ebsteins anomaly	2 (4)	2 100)	0.02 (0-0.06)	847.52 (100.81-3180.95)
Ventricular septal defect	4 (8)	4 (100)	0.03 (0.01-0.08)	12.08 (3.29-31.05)
Pulmonary valve stenosis	1 (2)	1 (100)	0.01 (0-0.04)	19.63 (0.5-118.66)
Pulmonary atresia	1 (2)	0 (0)	0.01 (0-0.04)	-
Other CHD	5 (9)	4 (80)	0.04 (0.01-0.09)	4.64 (1.26-11.99)

CHD, congenital heart defect; SCD, sudden cardiac death * Age-adjusted

Supplementary Table 3B. Incidence rates of sudden cardiac death in female persons with congenital heart defects per 100,000 person-years

CHD subtype	SCD-CHD (n=37), n (%)	SCD-CHD in patients diagnosed with CHD prior to death, n (% of all SCD-CHD)	Incidence rate of SCD-CHD in the general population per 100,000 person years (95% CI)*	Incidence rate of SCD-CHD in patients diagnosed with CHD per 100,000 person years (95% CI)*
CHD in total	37 (100)	20 (54)	0.31 (0.22-0.43)	17.95 (10.96-27.78)
Coarctation of aorta	6 (16)	1 (17)	0.05 (0.02-0.11)	27.29 (0.69-154.63)
Transposition of the great arteries	4 (11)	2 (50)	0.03 (0.01-0.09)	113.89 (13.75-418.06)
Univentricular heart	5 (14)	3 (60)	0.04 (0.01-0.1)	225.76 (46.49-693.47)
Aortic valve stenosis	4 (11)	3 (75)	0.03 (0.01-0.09)	129.75 (26.74-407.95)
Common arterial trunk	3 (8)	1 (33)	0.03 (0.01-0.07)	160.28 (4.06-929.97)
Tetralogy of Fallot	2 (5)	2 (100)	0.02 (0-0.06)	66.96 (8.11-250.31)
Coronary artery anomaly	2 (5)	0 (0)	0.02 (0-0.06)	-
Ebsteins anomaly	2 (5)	1 (50)	0.02 (0-0.06)	255.87 (6.48-2131.02)
Ventricular septal defect	0 (0)	0 (0)	-	-
Pulmonary valve stenosis	2 (5)	2 (100)	0.02 (0-0.06)	33.1 (4.01-124.23)
Pulmonary atresia	1 (3)	1 (100)	0.01 (0-0.05)	179.92 (4.56-1083.97)
Other CHD	6 (16)	4 (67)	0.05 (0.02-0.11)	5.67 (1.54-14.56)

CHD, congenital heart defect; SCD, sudden cardiac death * Age-adjusted