Background—Knowledge of the burden and causes of sudden cardiac death (SCD) is sparse in persons aged <50 years; better understanding is needed to lower the risk of SCD. The aim of this study was to report SCD incidence rates and autopsy findings in persons aged 1 to 49 years.

Methods and Results—All deaths in persons aged 1 to 49 years were included in 2007 to 2009. Death certificates were reviewed by 2 physicians. History of previous admissions to hospital was assessed, and discharge summaries were read. Sudden unexpected death cases were identified and autopsy reports were collected. In the 3-year study period, there were 7849 deaths of which we identified 893 (11%) SCD cases. The annual incidence rate per 100,000 persons increased from 2.3 (95% confidence interval, 2.0–2.7) to 21.7 (95% confidence interval, 20.2–23.4) in persons aged 1 to 35 and 36 to 49 years, respectively. Coronary artery disease was the most common cause of death and was found in 158 (36%) autopsied cases, followed by 135 (31%) cases of sudden unexplained death.

Conclusions—In a nationwide cohort of persons aged <50 years, the annual incidence rate of SCD was 10× higher in persons aged 36 to 49 years than in persons aged 1 to 35 years. Notably, coronary artery disease was the most common cause of SCD, followed by unexplained deaths. These findings may help in developing strategies to prevent SCD in the future. (Circ Arrhythm Electrophysiol. 2014;7:205-211.)

Key Words: autopsy ■ death, sudden, cardiac ■ epidemiology ■ pathology ■ registries

Sudden cardiac death in the young (SCDY, 1–35 years) is a devastating event with a significant psychological and social impact in families and communities. It is a major public health issue accounting for millions of deaths each year worldwide.1-3 Several strategies have been suggested to reduce the number of these deaths. This includes targeted screening in children and adolescents, both athletes and nonathletes.4,5 An accurate estimate of the burden and the cause of sudden cardiac death (SCD) below the age of 50 years are essential in developing strategies to improve public health. Previous studies have estimated the incidences and causes of death through different approaches.6-9 We have previously conducted a retrospective nationwide study, describing SCD incidence rates and causes of death, in persons aged 1 to 35 years in Denmark from 2000 to 2006.10 Furthermore, using the Danish Family Relations Database, we have shown that family members of these young SCD victims are in a significant increased risk of several often preventable cardiovascular diseases.11

Clinical Perspective on p 211

Conduct of an autopsy is essential when trying to identify potentially inheritable diseases in SCD victims, and extension of the traditional autopsy with a molecular autopsy allows one to perform genetic testing and cascade screening in SCD-affected families. A substantial inheritable component is present in cases of SCDY.12 Our knowledge on SCD in the age group ≤50 years, however, is sparse. In particular, we do not fully know the incidence rate or the distribution of causes of SCD and to what extent inheritable diseases play a role in this age group. More information is needed to further
improve risk stratification tools and preventive strategies in the future.\textsuperscript{13}

The aim of this first nationwide study of SCD in persons aged 1 to 49 years was to report incidence rates, autopsy rates along with autopsy findings, as well as examine differences between age groups. We hypothesized that several deaths remain unexplained after autopsy although differences between age groups are expected.

Methods

Study Design

The methods used for this study have been described previously in detail.\textsuperscript{10} In brief, this is a nationwide retrospective study using the availability of all death certificates, the registration of all in- and outpatient activity in Danish hospitals and emergency rooms together with access to all medical records and autopsy reports. We included all deaths in a 3-year period (2007–2009) in persons aged 1 to 49 years. 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 (7-505-29-58/6).

Danish Registries

All Danish citizens have a unique and personal civil registration number that can be linked to national registries on an individual level. The Danish National Patient Registry contains information on all in- and outpatient activities in Denmark since 1977. The content, validity, and coverage of the Danish National Patient Registry have been described previously and diagnoses have been validated previously.\textsuperscript{14–17}

In the Danish Cause of Death Registry, all primary and contributing causes of death are available.\textsuperscript{18} These data are extracted from the Danish death certificates using \textit{International Classification of Diseases, Tenth Revision (ICD-10)} diagnosis. The diagnoses will, however, be evaluated and corrected by the Danish Health and Medicines Authorities in case of obvious mistakes. In this study, we used the information from the Cause of Death Registry to extract the place of death and hence the location at which the autopsy was conducted.

Review of Death Certificate

Death certificates were retrieved digitally and read independently by 2 physicians to identify deaths that were sudden and unexpected. In case of disagreement a consensus was reached after re-evaluating the circumstances surrounding the death, including a review of previous medical history, which was taken into account in each case. Danish death certificates can only be issued by a medical doctor and are informative and highly suitable to identify sudden unexpected deaths as they have a supplemental information field.\textsuperscript{19} This field is mandatory in all medicolegal external examinations (external examinations), including cases in which it is decided not to conduct an autopsy. In cases where citizens or patients are found dead and the death is sudden and unexpected, external examinations are mandatory by law. The external examination is performed by the police and one of the 34 medical officers of public health (certified medical doctor). The medical officer of public health always has access to (1) first responder (emergency medical service) records, (2) the medical files related to the death (if any), (3) the entire police record including all witness statements, and (4) the body. Information from these examinations, describing circumstances surrounding the death, can be found in the supplemental information field on the Danish death certificate.

Discharge Summaries

Discharge summaries were available through an electronic hospital records system. We had access to information describing the time surrounding the death, including a description of the treatment and management in the emergency room or hospital department. Discharge summaries were also available from the prehospital trauma and emergency doctors who in some cases escort patients to the emergency room. The discharge summaries were read for all patients when available, unless the death certificate clearly indicated that death could not be sudden and unexpected.

Conduct of Autopsies

In Denmark, an autopsy is to be performed when an external examination concludes that the mode of death cannot be established. All forensic autopsies are supervised by another forensic pathologist and follow a protocol in which all organs are thoroughly examined. Toxicology screens are performed in unexplained adolescent and adult cases of sudden unexpected death.

In Denmark there are 3 forensic departments conducting >1500 autopsies per year, but hospital autopsies are also performed in local pathology departments throughout the country. These autopsies can be requested by a physician and the relatives when, after external examination, it is decided not to perform a forensic autopsy.

Definitions

We defined the sudden unexpected death as the 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 dead.

SCD in autopsied cases was defined as the natural unexpected death of unknown or cardiac cause, in witnessed cases as an acute change in cardiovascular status with time to death being <1 and in unwitnessed cases as a person last seen alive and functioning normally <24 hours before being found dead.\textsuperscript{7,10,13}

Autopsied SCD was subdivided in 2 groups: (1) explained SCD, in which a cardiac cause of death was established (including thoracic aortic dissections) and (2) sudden unexpected death (SUD), where causes of death after autopsy remained unknown.

In nonautopsied cases the same criteria were used in cases presumed to be of cardiac origin based on the circumstances relating to the death including all information from death certificates and discharge summaries. As the autopsy ratio was 56\%, the SCD incidence rate was calculated using both autopsied and nonautopsied cases. Because nonautopsied cases may have been misclassified, the incidence rates reported are upper limits and may be regarded as highest possible.

Macroscopic and histological criteria for different explained SCD categories have been published previously.\textsuperscript{19–23} In the Data Supplement, we have described pathological criteria used for this study.

Statistical Analysis

All calculations and data analysis were performed with the use of Stata software package (StataCorp, College Station, TX, version 11.0). Incidence rates were calculated using the mean age group population as a denominator. Confidence intervals (CIs) for incidence rates were calculated using the Poisson distribution. Sensitivity analyses for incidence rates and most common causes of SCD were performed. Categorized nominal data were compared using the \(\chi^2\) test. If any cell values were <5, the Fisher exact test was used. Medians were compared using the Wilcoxon rank-sum test. We considered a 2-sided \(P\) value <0.05 to be statistically significant.

Results

Review of Death Certificates

In the study period, in Denmark, there was a mean population of 5.48 million inhabitants, of whom, 3.47 million were in the age group 1 to 49 years. From 2007 to 2009 there were 8338 deaths among person aged 1 to 49 years. There were 7849 death certificates issued during this period. The 489 death certificates missing represented foreigners or Danes dying outside Danish borders. Twenty-seven (<1\%) cases were excluded because of incomplete data on the death certificate (Figure 1).
SCD Population
From the review of death certificates, registry information on previous medical history, and discharge summaries, we identified 1066 sudden unexpected death cases. In 718 (67%) of these deaths, an external examination was performed. Information from these examinations and information from discharge summaries were available in 687 (93%) of all deaths occurring out of hospital. We excluded additional 27 deaths as they were not considered to be of cardiac cause although they were all sudden and unexpected.

There were 585 autopsies conducted on the sudden unexpected death cases and in 146 (25%) cases death was ascribed to a noncardiac disease. Hence, we identified 439 (75%) autopsied SCD cases. To report the highest possible incidence rate of SCD, autopsied SCD cases were pooled with the 454 nonautopsied sudden unexpected death cases presumed to be of cardiac origin. Hence, the SCD population consisted of 893 cases (11% of all deaths; Figure 1). SCD characteristics are presented in Table 1.

Autopsied SCD Versus Nonautopsied SCD
Comparing the autopsied SCD cases with the nonautopsied SCD cases, the autopsied group was younger (42; Q1 to Q3: 42–46 versus 45; Q1 to Q3: 41–48 years; \( P < 0.0001 \)) and more often without previous medical history (202/439 [47%] versus 168/454 [37%]; \( P = 0.003 \)). The nonautopsied group more frequently had a known heart disease (111/454 [24%] versus 62/439 [14%]; \( P < 0.001 \)) and there were a higher percentage of deaths occurring during sleep in the autopsied group compared with that in the nonautopsied group (147/439 [34%] versus 55/439 [12%]; \( P < 0.001 \); for comparison, see the Table in the Data Supplement).

Incidence Rates
The highest possible annual SCD incidence rate in persons aged 1 to 49 years was 8.6 (95% CI, 8.0–9.2) per 100 000 persons using both autopsied and nonautopsied cases. In persons aged 36 to 49 years, the annual incidence rate was 21.7 (95% CI, 20.2–23.4) per 100 000 persons compared with 2.3 (95% CI, 2.0–2.7) per 100 000 persons in persons aged 1 to 35 years. The incidence rate was higher in men in both age groups (Table 2). Age-related distribution of incidence rates are presented in Figure 2 (see Figure [A and B] in the Data Supplement for incidence rates in men and woman, respectively).

Cause of Death
The cause of death was a structural heart disease in 304 of 439 (69%) autopsied SCD cases. The most common structural cause of cardiac death was coronary artery disease (CAD; 158/439; 36%) followed by hypertrophic heart (34/439; 8%), arrhythmogenic right ventricular cardiomyopathy (20/439; 5%), and myocarditis (19/439; 4%). In 135 of 439 (31%) cases, death remained unexplained (SUD) after autopsy (Figure 3). There was a shift toward CAD being more dominant (140/322 [44%] versus 18/117 [15%]; \( P < 0.001 \)) and SUD being less dominant (79/322 [25%] versus 56/117 [48%]; \( P < 0.001 \)) in the older age groups (Table 3).

Table 1. SCD Characteristics: Place of Death and Activity at Time of Death in Cases of Sudden Cardiac Death in Persons Aged 1 to 49 Years in Denmark From 2007 to 2009

<table>
<thead>
<tr>
<th>SCD Population, %</th>
<th>Total (n=893)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autopsied SCD</td>
<td>439 (49)</td>
</tr>
<tr>
<td>Nonautopsied sudden unexpected death</td>
<td>454 (51)</td>
</tr>
<tr>
<td>Explained SCD (after autopsy)</td>
<td>304 (69)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>158 (36)</td>
</tr>
<tr>
<td>Sudden unexplained death</td>
<td>135 (31)</td>
</tr>
<tr>
<td>Ratio of explained SCD or SUD after autopsy</td>
<td>439/585 (75)</td>
</tr>
<tr>
<td>Age, y, median (Q1 to Q3)</td>
<td>43 (38–47)</td>
</tr>
<tr>
<td>Witnessed deaths</td>
<td>342/795 (43)</td>
</tr>
</tbody>
</table>

8338 deaths in total

849 deaths in included

6756 non-sudden death

27 (0.3%) incomplete death certificate data

27 sudden unexpected death (causing death)

454 non-autopsied sudden unexpected death

585 autopsied sudden unexpected death

146 sudden non-cardiac death

439 autopsied sudden cardiac death

803 (11%) sudden cardiac death

- 336 explained (after autopsy)
- 135 unexplained (after autopsy)
- 454 no autopsy performed

Figure 1. Flowchart of the identification of all sudden unexpected deaths and all sudden cardiac deaths in persons aged 1 to 49 years in Denmark 2007 to 2009.
Autopsy Rates

The 585 autopsies were conducted on 1066 sudden unexpected death cases. Excluding those 27 cases with competing causes, this corresponds to an autopsy ratio of 56%. Autopsy ratios were lowest in the age group 40 to 49 years in which autopsy was conducted in 331 of 705 (47%) cases. All 10 (100%) sudden unexpected death cases below the age of 10 years had an autopsy conducted. In the age decades 10−19, 20−29, and 30–39 years, autopsy ratios were constant (73%−78%; \( P = 0.816 \)).

Histopathology and Toxicology

In the 439 autopsied SCD cases histopathology and toxicology screens were performed in 390 (89%) and 272 (62%) cases, respectively. In the 135 SUD cases histopathology and toxicology screens were performed in 118 (87%) and 121 (90%) cases, respectively.

Overall, 118 of 272 (43%) toxicology screens were negative. There were 19 (7%) cases with cannabis, 17 (6%) cases with methadone, 7 (3%) cases with amphetamine, and 6 (2%) cases with cocaine. One or >1 prescribed drugs were found in 43 (16%) and 86 (32%) cases, respectively. In 84 (70%) of the SUD cases there was a positive toxicology. However, all illegal drugs were found in trace amounts, and prescribed drugs were found in therapeutic concentrations. None of the cases had a toxicological profile that the forensic pathologists concluded could explain their death.

Sensitivity Analysis

We used different assumptions to report upper and lower boundaries of SCD incidence rates and causes of SCD. Including only out-of-hospital cardiac arrest, in which an external examination had been performed, the annual SCD incidence rate decreased to 5.2 (95% CI, 4.8–5.7) per 100000 persons. Including only cases with autopsy followed by histopathology and toxicology, CAD remained the most common cause of death followed by unexplained deaths, termed SUD (Table 4).

Discussion

Using death certificates, registry entries, discharge summaries, and autopsy reports, we have conducted a study on SCD in Denmark from 2007 to 2009. The aim was to report incidence rates, autopsy rates along with autopsy findings, as well as examine differences between age groups. We found 893 SCD cases including both autopsied and nonautopsied cases. This equals an overall annual incidence rate of 8.6 per 100000 persons. In persons aged 1 to 35 years the incidence rate was 2.3 per 100000 persons, whereas the incidence rate in persons aged 36 to 49 years was 21.7 per 100000 persons.

| Age group, 1–35 y (95% CI interval; n=728) | 2.3 (2.0–2.7) | 3.2 (2.6–3.8) | 1.5 (1.1–1.9) |
| Age group, 36–49 y (95% CI interval; n=165) | 21.7 (20.2–23.4) | 32.1 (29.5–34.9) | 11.1 (9.5–12.8) |

CI indicates confidence interval; and SCD, sudden cardiac death.

Figure 2. Age-related distribution of the annual sudden cardiac death (SCD) incidence rate per 100000 persons in persons aged 1 to 49 years in Denmark 2007 to 2009.
We found a low autopsy rate of 56%, and we report a shift from SUD toward CAD being the most common cause of death in persons aged 36 to 49 versus 1 to 35 years.

**Identification of SCD**

Death certificate–based identification of SCD in the United States has been shown previously to overestimate the incidence of SCD compared with prospective multisource evaluations. We have developed previously a strong method using identification of sudden unexpected deaths through review of death certificates and information from national registries in Denmark. In this regard, it was a concern that the percentage of external examinations in this study were only performed in 67% of all sudden unexpected death cases, which is lower than previously reported for SCDY.

However, this loss of information was counterbalanced by the fact that we had computer-based discharge summaries available for this study, including discharge summaries from the prehospital trauma and emergency doctors first on the scene.

**Table 3. Percentage of Most Common Causes of Death by Age Group**

<table>
<thead>
<tr>
<th></th>
<th>1–49 y (n=439)</th>
<th>≤35 y (n=117)</th>
<th>&gt;35 y (n=322)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD</td>
<td>158 (36.0)</td>
<td>18 (15.4)</td>
<td>140 (43.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SUD</td>
<td>135 (30.8)</td>
<td>56 (47.9)</td>
<td>79 (24.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HH</td>
<td>34 (7.7)</td>
<td>5 (4.3)</td>
<td>29 (9.0)</td>
<td>0.101</td>
</tr>
<tr>
<td>ARVC</td>
<td>20 (4.6)</td>
<td>9 (7.7)</td>
<td>11 (3.4)</td>
<td>0.057</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>19 (4.3)</td>
<td>5 (4.3)</td>
<td>14 (4.4)</td>
<td>0.973</td>
</tr>
</tbody>
</table>

ARVC indicates arrhythmogenic right ventricular cardiomyopathy; CAD, coronary artery disease; HH, hypertrophic heart; SCD, sudden cardiac death; and SUD, sudden unexplained death.

**Table 4. Sensitivity Analysis: Annual Incidence Rates Per 100,000 Persons and Most Common Causes of Sudden Cardiac Death**

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual Incidence Rates of SCD</td>
<td>7.1 (6.6–7.6)</td>
</tr>
<tr>
<td>SCD out of hospital</td>
<td>6.6 (6.1–7.1)</td>
</tr>
<tr>
<td>With EE or discharge summary</td>
<td>5.2 (4.8–5.7)</td>
</tr>
<tr>
<td>Autopsied SCD</td>
<td>4.2 (3.8–4.6)</td>
</tr>
<tr>
<td>With histopathology and toxicology</td>
<td>2.4 (2.1–2.7)</td>
</tr>
<tr>
<td>Most common causes of SCD</td>
<td>(n=390; 89%)</td>
</tr>
<tr>
<td>CAD, %</td>
<td>140 (35.9)</td>
</tr>
<tr>
<td>SUD, %</td>
<td>118 (30.3)</td>
</tr>
<tr>
<td>HH, %</td>
<td>31 (8.0)</td>
</tr>
<tr>
<td>Autopsied SCD</td>
<td>(n=250; 57%)</td>
</tr>
<tr>
<td>With histopathology and toxicology</td>
<td>72 (28.8)</td>
</tr>
<tr>
<td>CAD, %</td>
<td>106 (42.4)</td>
</tr>
<tr>
<td>HH, %</td>
<td>18 (7.2)</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; EE, external examination; HH, hypertrophic heart; SCD, sudden cardiac death; and SUD, sudden unexplained death.
Incidence Rates
Comparisons of SCD incidence rates between studies are generally difficult because of different study designs used and different age groups investigated. Previous studies have been conducted on selected populations, and this is the first study describing nationwide incidence rates in an unslected population aged 1 to 49 years. As expected, the incidence rate was lowest in the youngest, increasing substantially with increasing age and nearly exponential among adults (Figure 2). Excluding nonautopsied cases, in-hospital SCDs, or autopsied cases without histopathology and toxicology, the incidence rate declined (Table 4). Like previous studies, we found that men had a higher incidence rate of SCD (Table 2).

In persons aged 1 to 35 years (SCDY), we found an annual incidence rate of only 2.3 per 100,000 persons, whereas the incidence rate was 21.7 per 100,000 persons in persons aged 36 to 49 years. This is lower than we have reported previously in the young (2.3 versus 2.8 per 100,000 persons). The differences are probably explained by variations in the relatively few numbers of deaths and by the shorter time period investigated (7 versus 3 years). However, the incidence rate of SCDY in this study remains higher than what has been reported by others.

As unselected, nationwide data are lacking, the incidence rate of SCD in the age group 1 to 49 years is of considerable interest. Although previous studies have been conducted on young populations (1–35 years), most other studies have been conducted on populations with mean ages >50 years. In West Ireland the SCD incidence rate was 51.2 per 100,000 person-years, and in a study from Oregon it was 53.0 per 100,000 person-years. This is much higher than we have reported, but not surprising with a mean age of 63 and 69 years, respectively. In a study from United Kingdom with a median age >50 years, they reported the incidence rate of SCD to be 10.5 per 100,000 person-years. The discrepancy might not be too surprising because this study only included autopsied SCDs. We think that the available literature suggests that the epidemiology on those aged <50 years is not fully understood. This has also been underscored by Kong et al. in a recent thorough review on SCD in which it is highlighted that the true incidence rate of SCD in the United States is largely unknown.

Cause of SCD
SUD and CAD are the 2 major causes of SCD in persons aged 1 to 49 years and account for 31% and 36% of all autopsied SCD cases, respectively. Although 70% of the SUD cases had a positive toxicology, it was either prescribed drugs in therapeutic concentrations or illegal drugs in trace amounts. None of the cases had a toxicological profile that the forensic pathologists concluded could explain their death. It could be speculated, however, that some drugs, even in therapeutic concentrations, could have caused a fatal arrhythmia through, that is, prolongation of the QT interval. Interestingly, in persons aged 36 to 49 years, we saw a shift toward CAD being more common than SUD (Table 3). It is well known that CAD plays a major role in older populations; however, it is surprising to us that CAD played such a great role in this unslected population aged <50 years.

Our SCD population consisted of both autopsied and nonautopsied cases, which is problematic as we do not know the exact cause of death in the nonautopsied group. However, as autopsy ratios are low, especially in the older populations, it was necessary to report the true magnitude of SCD. Although not directly comparable, we found that the nonautopsied SCD and the autopsied SCD were similar with regard to previously known noncardiac medical diseases, sex, and whether death was witnessed. However, nonautopsied cases more often had a known heart disease (24% versus 14%; P < 0.001), they were older (45 versus 42 years; P < 0.001), and less often died during sleep (12% versus 34%; P < 0.001). We find it likely, however, that the majority of the nonautopsied sudden unexpected death cases would have been attributed to SCD or SUD if they had been autopsied. In support of this, we found that 75% of the autopsied sudden unexpected deaths were categorized as SCD after reviewing the autopsy report. These data are consistent with previous studies. Although an autopsy ratio of 56% seems low in Denmark, autopsy ratios are without doubt even lower in many other parts of the world. Our findings support that autopsy always should be conducted in case of a sudden unexpected death in a person <50 years. This has also just been recommended by the Danish Society of Cardiology.

Study Limitations
It is a limitation that the study was retrospective in design. In witnessed cases it was easy to extract information on whether the person was seen alive <24 hours before death, but it was difficult to assess more precise time limits in unwitnessed cases. As shown in the sensitivity analysis, incomplete data such as lack of autopsies, histopathology, toxicology, and external examinations bring some uncertainty into the estimates of the SCD incidence rates. Furthermore, we do not know the cause of death for decedents dying outside of the country. The lower percentage of external examinations may be counterbalanced by the availability of discharge summaries, which is a unique tool in which we were able to extract important information. Electrocardiograms were not available before death. Hence, we could not evaluate for long QT syndrome or other primary arrhythmogenic disorders in the SUD population and no genetic analysis or information on family history was available.

Conclusions
This is the first nationwide study reporting incidence rates, autopsy rates along with autopsy findings in SCD victims aged 1 to 49 years. We report a high overall annual SCD incidence rate of 8.6 per 100,000 persons. We see a substantially increase in the incidence rate from 2.3 to 21.7 per 100,000 persons in persons aged 1 to 35 versus 36 to 49 years. Autopsy rates in sudden unexpected death cases are low with autopsies only being conducted in 56% of all cases. The most common cause of SCD was CAD, followed by deaths that were unexplained. We see a shift toward CAD being more dominant and SUD being less dominant in persons >35 years. Because CAD and SUD are potentially preventable, these findings could help generate future strategies to prevent SCD.

Sources of Funding
This work was supported by Danish National Research Foundation Centre for Cardiac Arrhythmia (DARC), University of Copenhagen, Copenhagen, Denmark; Laboratory of Molecular Cardiology, The Heart Centre, Department of Cardiology, University Hospital Rigshospitalet, Copenhagen, Denmark; The John and Birthe Meyer Foundation; The Danish Heart Foundation (12-04-R01-A3790-22689); and The Research Fund of Rigshospitalet, Copenhagen University Hospital. All funding sources contributed to the salary of the principal investigator.
Disclosures
Dr Holst is an employee of Novo Nordisk AS, Søborg, Denmark. The other authors report no conflicts.

References

CLINICAL PERSPECTIVE
Sudden cardiac death in a young individual is a devastating event. Several strategies have been suggested to reduce these deaths, including targeted screening in children and adolescents, but an accurate estimate of the burden of these deaths is needed. Previous studies on selected populations using different approaches have reported various incidence rates. Using Danish death certificates and registries, we have identified all sudden cardiac deaths in persons aged 1 to 49 years in Denmark from 2007 to 2009. We find that the incidence rate increases with increasing age, with an almost exponential increase in young adults. The most common cause of sudden cardiac death is coronary artery disease followed by deaths that remain unexplained after autopsy. As many of the causes of SCD in the young are potentially inherited and preventable cardiac diseases, an autopsy is essential to identify cause of death. However, we find that autopsy ratios remain low, a problem that should be addressed in the future. The findings from the current study could help generate future strategies to prevent sudden cardiac death in the young.
Burden of Sudden Cardiac Death in Persons Aged 1 to 49 Years: Nationwide Study in Denmark

Bjarke Risgaard, Bo Gregers Winkel, Reza Jabbari, Elijah R. Behr, Ole Ingemann-Hansen, Jørgen Lange Thomsen, Gyda Lolk Ottesen, Gunnar H. Gislason, Henning Bundgaard, Stig Haunso, Anders Gaarsdal Holst and Jacob Tfelt-Hansen

_Circ Arrhythm Electrophysiol_. 2014;7:205-211; originally published online March 6, 2014;
doi: 10.1161/CIRCEP.113.001421

_Circulation: Arrhythmia and Electrophysiology_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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SUPPLEMENTAL MATERIAL

Macroscopic and histological criteria’s;

**Coronary artery disease (CAD)**, 1) Moderate to severe atherosclerosis in ≥1 major coronary artery, 2) thrombosis in one or more major coronary arteries, or 3) acute or healed/chronic myocardial infarction (as described by the pathologist); **Sudden unexplained death, SUD**, no cause of death established after autopsy; **Hypertrophic Cardiomyopathy (HCM)**, significant myocyte disarray in the left ventricle with/without interstitial fibrosis and/or microvasculature pathology; **Hypertrophic heart (HH)**, presence of macroscopic concentric hypertrophy of left ventricle, with a wall thickness (>13mm) and/or a cardiac weight considered excessive for the subject’s body size, in the absence of CAD, valvular or congenital heart disease, and without microscopic evidence of myocardial disarray; **Arrhythmogenic right ventricular cardiomyopathy (ARVC)**, extensive replacement of the right ventricle myocardium with fibrofatty tissue with or without chronic inflammatory infiltrate; **Myocarditis**, multiple foci of interstitial inflammatory infiltrate with/without myocyte necrosis in the myocardium; **Fibrosis in heart (FH)**, significant fibrosis in the left ventricle with no evidence of ventricular wall thinning or thickening; **Dilated cardiomyopathy (DCM)**, thin walled left ventricle with fibrosis throughout the left ventricle with no CAD; **Thoracic aortic dissection**, rupture of the aortic artery above mediastinum

The finding of **conduction defects, malformed coronary vessels** and **congenital heart diseases** were considered causative when autopsy revealed no other cause of death.
**Supplemental Table.** Comparison of cases of young autopsied sudden cardiac death and non-autopsied sudden unexpected death cases in Denmark in 2007-2009

<table>
<thead>
<tr>
<th>SCD (n = 893)</th>
<th>Autopsied (n = 439) (%)</th>
<th>Non-autopsied (n = 454) (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No previous medical history</td>
<td>205 (47)</td>
<td>168 (37)</td>
<td>0.003</td>
</tr>
<tr>
<td>Male</td>
<td>317 (72)</td>
<td>342 (75)</td>
<td>0.289</td>
</tr>
<tr>
<td>Female</td>
<td>122 (28)</td>
<td>112 (25)</td>
<td>-</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>42 (IQR:34–46)</td>
<td>45 (IQR:41–48)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Witnessed deaths</td>
<td>181 (42)</td>
<td>161 (45)</td>
<td>0.429</td>
</tr>
<tr>
<td>Death during sleep</td>
<td>147 (34)</td>
<td>55 (12)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Previous medical history**

<table>
<thead>
<tr>
<th></th>
<th>Autopsied (n = 439) (%)</th>
<th>Non-autopsied (n = 454) (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-cardiac disease</td>
<td>183 (42)</td>
<td>217 (48)</td>
<td>0.066</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>10 (2)</td>
<td>7 (2)</td>
<td>0.421</td>
</tr>
<tr>
<td>Known heart disease</td>
<td>62 (14)</td>
<td>111 (24)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Supplemental Figure A: Title: Annual sudden cardiac death incidence rates in men – Age-related distribution of the sudden cardiac death incidence rate per 100,000 persons in persons aged 1-49 years in Denmark 2007-2009
**Supplemental Figure B**: Title: Annual sudden cardiac death incidence rates in women – Age-related distribution of the sudden cardiac death incidence rate per 100,000 persons in persons aged 1-49 years in Denmark 2007-2009