Sudden cardiac death in 14- to 35-year olds in Ireland from 2005 to 2007: a retrospective registry

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Introduction

Sudden cardiac death (SCD) in young people is a rare but devastating event for families and communities. Ireland has previously had no measure of the incidence of SCD in young people. We report the incidence and causes of SCD in persons <35 years of age.

Methods and results

We undertook a retrospective study of SCD between 2005 and 2007 in persons aged 15–35 years in the Republic of Ireland. We identified potential cases of out of hospital SCD through the Central Statistics Office (CSO) death certificate records. Autopsy, toxicology, and inquest reports were then obtained and analysed by an expert panel who adjudicated on the cause of death. A total of 342 potential SCD cases were identified through the CSO. Fifty were younger than 15 years of age, and 86 had either incomplete or unavailable post-mortem reports. Of 206 full reports obtained, 116 were adjudicated as cases of SCD. Cases were predominantly male (75%), with a mean age of 25.8 years (standard deviation 6.3). The incidence of SCD in this age range was 2.85 per 100 000 person-years (4.36 for males and 1.30 for females) and the incidence of sudden arrhythmic death syndrome (SADS) was 0.76 per 100 000 person-years. The commonest causes were SADS, 26.7% (31 of 116), followed by coronary artery disease, 20.7% (24 of 116), hypertrophic cardiomyopathy (HCM), 14.7% (17 of 116), and idiopathic left ventricular hypertrophy not fulfilling criteria for HCM, 10.3% (12 of 116).

Conclusions

The incidence of SCD in the young in Ireland was 4.96 (95% CI 3.06, 6.4) for males and 1.3 (95% CI 0.62, 2.56) for females per 100 000 person-years. Sudden arrhythmic death syndrome was the commonest cause of SCD in the young, and the incidence of SADS was more than five times that in official reports of the Irish CSO.

Keywords

Sudden cardiac death • Sudden arrhythmic death syndrome • Hypertrophic cardiomyopathy • Post-mortem • Autopsy
inherited cardiomyopathies or channelopathies.\textsuperscript{13,14} This has implications for identification of these disorders in surviving relatives, who may also be at risk of the same disease, with prior studies suggesting that these disorders can be identified in 25--50\% of surviving relatives.\textsuperscript{15,16} In 4--5\% of all SCD, a cause of death cannot be ascertained, even after comprehensive post-mortem, toxicology screen, and cardiac pathologic examination. These are classified as sudden arrhythmic death syndrome (SADS).\textsuperscript{14--16}

In the Republic of Ireland, a number of high-profile SCD events in young persons have focused attention on this condition. A single retrospective study in 2005 of death certificate-registered SCD in persons aged 15--35 years estimated an SCD incidence of 3.18 per 100 000 person-years.\textsuperscript{17} This unexpectedly high estimate has highlighted the need to monitor the incidence of this condition in Ireland. In this report, we describe the incidence and causes of out of hospital SCD in persons aged 14--35 years in the Republic of Ireland from 2005 to 2007. We also describe the methodological considerations when extrapolating incidence rates from the death registration system.

**Methods**

This is a retrospective death registration study of SCD in persons aged 15--34 years inclusively.

**Sampling frame**

The Irish Sudden Cardiac Death in the Young Registry was set up in 2007 by the Health Services Executive to identify all sudden deaths in the 2008 registration year in persons aged 15--35 years inclusively. The Central Statistics Office of Ireland (CSO) provided a list of all deaths in persons aged 15--35 years from the 2006 national population census (\textit{Dr Mary Sheppard at the Royal Brompton Hospital, London, UK}), at the discretion of the certifying pathologist.

**Definition**

Sudden death was defined as a sudden, unexpected death either within 1 h of symptom onset (event witnessed) or within 24 h of having been observed alive and symptom free (unwitnessed event). Such deaths were deemed to be SCD if there was felt to be a cardiac cause of death, or if the cause of death was unascertainable after post-mortem evaluation (SADS, a subset of SCD in this analysis). Persons with sudden death associated with electrocution, drowning, poisoning, toxicology suggesting drug overdose as the cause of death, toxicology indicating presence of drugs, or substances known to cause cardiac arrhythmias such as sympathomimetics or cocaine were not included as SCD. Persons with alcohol levels \(\geq 100\) mg/dL were not included as SCD. Although it is recognized that these circumstances of death do not preclude the possibility of an underlying heart condition that resulted in a fatal arrhythmia it was considered preferable to exclude such deaths to avoid inclusion of cases that were possibly non-cardiac.

**Case selection**

From the CSO-provided list of all deaths in this age group, persons with the following ICD codes were selected as possible cases of SCD. International Classification of Diseases-9 codes (used in 2005 and 2006) were (i) disease of the circulatory system 390--459.7; (ii) other heart disease 420--423; and (iii) sudden death 798--799. International Classification of Diseases-10 codes (used in 2007) were (i) disease of the circulatory system 100--199 and (ii) ill-defined and unknown causes of mortality (including sudden death) R95--99. Subjects with serious non-cardiac or terminal illnesses were excluded. The Republic of Ireland has a coronial system for the investigation of sudden or unexplained deaths. For all such deaths, post-mortem evaluation is performed as requested by the coroner, unless he or she determines that there is sufficient evidence to determine the cause of death without such an examination. Post-mortem results are not held centrally in the Republic of Ireland, but rather with the investigating coroner or pathologist. For each suspected case of SCD identified through the CSO registration system, the relevant pathologist or coroner was identified, and full post-mortem and toxicology reports were requested. Toxicology screening is a standard component of the post-mortem evaluation. During the study period, a small number of cases (5 of 119) deemed to require an expert or second opinion were referred to a specialist cardiac pathologist, but in the overwhelming majority of cases the routine post-mortem examination was sufficient to classify the death as SCD.

**Confirmation of case status**

Each potential case (post-mortem report, including specialist pathologist reviews and toxicology reports as relevant) was reviewed by a panel to determine whether they fulfilled study criteria for SCD. The panel included a cardiac electrophysiologist, and a cardiologist with an interest in sudden death. Where consensus could not be reached, independent review was sought from two consultant pathologists with special interest in SCD, who gave a final decision. If post-mortem details were not available on a potential case, that case was not included in the SCD count or further analyses.

Once SCD was confirmed on post-mortem review, the underlying cause was determined. Cases with no macroscopic or microscopic evidence of cardiac disease and no potentially causative findings on toxicological screen were classified as SADS. Hypertrophic cardiomyopathy (HCM) cases were classified in the presence of left ventricular hypertrophy (LVH), with either myofibrillar disarray or interstitial fibrosis on histological examination. Cases with LVH (wall thickness \(>15\) mm or a cardiac weight \(>500\) g considered excessive for the subject’s size by the examining pathologist) without myofibrillar disarray or fibrosis were described as idiopathic LVH.

**Incidence rate calculation**

The CSO provided data on the population aged between 15 and 35 years from the 2006 national population census (\textit{Table 1}).\textsuperscript{18}
From this, the overall incidence of SCD and the incidence of specific cardiac diseases per 100 000 person-years were estimated. Confidence intervals were estimated using Poisson distribution modelling. The statistical package used was Intercooled Stata 9 (StataCorp, TX, USA).

**Ethical approval**

Ethical approval was obtained from the Department of Health and Children and the CSO to obtain the dataset of registered deaths and the post-mortem and inquest results from the coroners and pathologists throughout the country.

**Results**

Cases identified to the Sudden Cardiac Death in the Young Registry

*Figure 1* outlines the case selection process of the potential cardiac cases from the cases identified. For the period 2005–2007 inclusive, there were a total of 342 cases selected from the death registration files of the CSO fulfilling the ICD-9 or ICD-10 cardiac or sudden death criteria. Fifty cases (14.6%) were in persons aged <15 years and were omitted from the final rate calculations. Of

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**Table 1** Population census numbers divided by gender and age group adapted from the Central Statistics Office of Ireland national population census 2006

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4</td>
<td>154556</td>
<td>147696</td>
<td>302252</td>
</tr>
<tr>
<td>5–9</td>
<td>147984</td>
<td>140341</td>
<td>288325</td>
</tr>
<tr>
<td>10–14</td>
<td>140504</td>
<td>133368</td>
<td>273872</td>
</tr>
<tr>
<td>15–19</td>
<td>148241</td>
<td>142016</td>
<td>290257</td>
</tr>
<tr>
<td>20–24</td>
<td>172766</td>
<td>169709</td>
<td>342475</td>
</tr>
<tr>
<td>25–29</td>
<td>189252</td>
<td>183826</td>
<td>373078</td>
</tr>
<tr>
<td>30–34</td>
<td>177487</td>
<td>171874</td>
<td>349361</td>
</tr>
<tr>
<td>Total</td>
<td>1130790</td>
<td>1088830</td>
<td>2219620</td>
</tr>
</tbody>
</table>

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*Figure 1* Flow diagram of case selection processes performed by the Sudden Cardiac Death in the Young Registry of potential sudden unexplained or cardiac deaths for 2005–2007 inclusive. *SUDEP*, sudden unexplained death in epilepsy; †’Other’ denotes deaths as a result of trauma/accidents, infections, organ failure, neurologic causes, aortic dissection and deaths not otherwise categorized.
these 50 cases, 39 (66.1%) were deemed to be due to cardiac aetiology on review of their death registration and post-mortem data. Eleven cases were referred for adjudication by the expert panel to the pathology collaborators. Tables 2 and 3 show how cases identified to the registry were classified.

Case status was not ascertainable for 29.5% (86 of 292) of the possible events identified. This was because no post-mortem evaluation was undertaken in 40 of 86 (46.5%), insufficient or unsatisfactory post-mortem details in 7 of 86 (8.1%), an inability to ascertain the correct coroner for that event (inaccurate coroner’s jurisdiction listed by the CSO) in 18 of 86 (20.9%), or because the coroner or pathologist did not forward the post-mortem details to the registry despite multiple requests in 21 of 86 (24.4%). These cases have a mean age of 24.9 ± 6.4 years and are 65%:35% male:female gender distribution, similar to the population included in our study below. Of the 79 CSO registered sudden deaths on which post-mortem reports were either unavailable or not performed, 20 (25.3%) were non-cardiac (as described on death certification) and the rest were felt to be cardiac in aetiology, with 33 (41.8%) being attributed to congenital heart disease (ConHD) and an additional five cases listed as SADS deaths (Table 4).

A total of 116 deaths (39.7% of the total of 292 cases available for examination) were considered by the panel to represent true SCDs. Most deaths occurred in males, with an average age of 25.8 years (range 15–34) (Table 3).

Causes of sudden cardiac death

Causes of SCD in the population examined are shown in Figure 2 and Table 3. Figure 3 demonstrates the causes of SCD by gender over the 3-year period and Figure 4 demonstrates the cause of death by year of registration. The commonest finding at post-mortem examination in this selected population of registered SCDs was SADS, in 31 of 116 cases (26.7%). Other findings were CAD with evidence of acute or prior myocardial infarction in 24 of 116 (20.7%), HCM in 17 of 116 (14.6%), idiopathic LVH in 12 of 116 (10.3%), ConHD in 10 of 116 (8.6%), and myocarditis in 7 of 116 (6.0%).

Table 2 Case selection and categorization by the Sudden Cardiac Death in the Young Registry

<table>
<thead>
<tr>
<th>Variable</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSO identified cases</td>
<td>122</td>
<td>92</td>
<td>128</td>
<td>342</td>
</tr>
<tr>
<td>Omitted due to age &lt;15 years</td>
<td>27</td>
<td>7</td>
<td>16</td>
<td>50 (14.6%)</td>
</tr>
<tr>
<td>Potential cardiac cases adjudicated</td>
<td>95</td>
<td>85</td>
<td>112</td>
<td>292</td>
</tr>
<tr>
<td>Cardiac cases as adjudicated by SCDYR</td>
<td>42</td>
<td>35</td>
<td>42</td>
<td>119/292 (40.7%)</td>
</tr>
<tr>
<td>Non-cardiac cases as adjudicated by SCDYR</td>
<td>14</td>
<td>27</td>
<td>49</td>
<td>90/292 (30.8%)</td>
</tr>
<tr>
<td>Incomplete PM/missing cases</td>
<td>39</td>
<td>24</td>
<td>23</td>
<td>86/292 (29.7%)</td>
</tr>
</tbody>
</table>

Incidence of sudden cardiac death and incidence of the various identified causes

Over the period 2005–2007, the incidence of SCD in the 15–35-year-old age group was 2.85 per 100 000 person-years (95% CI 2.05, 3.93). This equated to an incidence of SCD in males of 4.36 per 100 000 person-years (95% CI 3.06, 6.4) and an incidence of SCD in females of 1.3 per 100 000 person-years (95% CI 0.62, 2.56). The incidence of SADS in the 15–35-year-old age group was 0.76 per 100 000 person-years (95% CI 0.35, 1.40) with an incidence in males of 0.96 per 100 000 person-years (95% CI 0.41, 2.10) and an incidence in females of 0.54 per 100 000 person-years (95% CI 0.16, 1.5). The incidence of sudden death due to coronary disease...
was 0.59 (95% CI 0.26, 1.20) per 100 000 person-years [1.01 (95% CI 0.60, 2.50) per 100 000 person-years in males and 0.14 (95% CI 0.04, 0.84) per 100 000 person-years in females]. The incidence of sudden death due to HCM was 0.41 (95% CI 0.16, 0.96) per 100 000 person-years [0.67 (95% CI 0.24, 1.70) per 100 000 person-years in males and 0.14 (95% CI 0.04, 0.84) per 100 000 person-years in females].

Non-cardiac sudden death cases

Figure 1 outlines the selection of potential cardiac cases from the overall number of deaths registered. From the cohort of potential cardiac cases, on expert panel consensus, a total of 87 cases were attributed to non-cardiac causes. The commonest cause of death in these cases was sudden unexpected death from epilepsy, accounting for 22 of 87 (25.2%). Drug- or alcohol- related deaths accounted for 19 of 81 cases (23.5%). Other non-cardiac causes included pulmonary embolism, 12 of 87 (13%), acute respiratory distress, bacterial endocarditis, and intracerebral haemorrhage. There were three cases of aortic dissection, which, although included in other reports of sudden death, we excluded from our analysis.

Circumstances and activity surrounding sudden death

In 43% of cases (50 of 116), no details of the circumstances of death were known. In 7.7% of cases (9 of 116), death was specified as occurring during exertion. Five out of 17 deaths (29%) due to
HCM occurred during exertion, with one death each occurring while playing football, rugby, cycling, skipping, and herding cattle. Two deaths due to SADS occurred during soccer. One death due to an anomalous coronary artery occurred during football and one death due to CAD occurred during basketball. The remaining 45% (50 of 109) occurred during non-exertion or sleep.

**Discussion**

The incidence of SCD of 2.85 per 100 000 persons per year for persons aged 15–35 years and the incidence of SADS of 0.76 per 100 000 persons per year for this age group were derived using structured data collection methodology and strict case definition. National post-mortem-based studies have previously examined the incidence and causes of SCD in the young in Sweden, Iceland, and Denmark and the incidence of SADS in the UK. In Sweden, Wisten et al. found the incidence of SCD to be 0.93 cases per 100 000 persons per year among 15–35 years old between 1992 and 1999 and the commonest finding was a structurally normal heart. In Iceland, Einarsson et al. documented an incidence of SCD of 1.38 per 100 000 persons per year in the age range 12–35 years old and the commonest cause of death was premature CAD. Winkel et al. noted an incidence of SCD of 1.9 per 100 000 cases per year in Denmark with SADS accounting for almost half of the deaths. A prospective study from the Veneto region in Italy, 1979–1996, showed an incidence of sudden death of 0.8 per 100 000 per year in persons under 35 years of age, of which nearly 75% could be attributed to cardiovascular deaths, a large proportion due to arrhythmogenic right ventricular cardiomyopathy. In the USA, a population-based study in Olmstead County reported an incidence of 6.2 sudden deaths per 100 000 in persons aged between 20 and 40 years, with the commonest cause of death being premature CAD, although unlike our study, it included drug-, alcohol-, and cocaine-related deaths.

Possible explanations for differences in rates and causes of SCD between studies include differences in case definition, methods of case ascertainment, post-mortem utilization rates, methodology reporting and report availability, cardiac arrest response systems, regional and ethnic variations in the frequency or pathogenicity of individual gene mutations responsible for cardiac ion channelopathies or cardiomyopathies as well as environmental factors such as diet or pollution. However, international comparisons of SCD rates are only meaningful if they compare studies with similar methodologies and autopsy rates. In China where autopsies are rarely performed, Hua et al. documented a significantly lower incidence of SCD in the general population through extensive questioning of family members and collection of medical information through the local household administrative system. Variations in relative rates of the underlying causes of SCD are also seen between international studies. The post-mortem diagnosis of HCM and its distinction from LVH for other reasons (such as competitive sports, aortic stenosis, or hypertension) is a challenge in retrospective studies. It is possible that cases of secondary LVH were classified as HCM, if the LVH was associated with myocardial fibrosis or myofibrillary disarray, and this distinction may bias the true prevalence of HCM in our study. Population variations in the allele frequencies of genes associated with cardiomyopathy and ion channelopathy may also account for some of the differences in the rates and causes of SCD between countries. Prior work from Finland and South Africa has identified the concept of ‘founder gene mutation’ effect as a potential explanation for the higher proportion of individuals in those geographic areas who test positive for known long QT syndrome gene mutations. The Irish population is genetically homogenous and is
well known to have high frequencies of gene carriage for inherited conditions such as haemochromatosis and cystic fibrosis. One putative explanation for this apparent international variation in disease incidences may be a similar ‘founder gene mutation’ effect. Comparison of SADS rates and specific gene mutation rates between different countries would be a major undertaking but would be helpful in giving a more complete picture of the contribution of genetic disease not just to SCD in young people but also potentially to determining vulnerability to lethal ventricular arrhythmias in later life in the setting of ischaemic heart disease. This study highlights the many challenges in estimating SCD and SADS events from routine national data collection. Similar to the Behr study, the incidence of SADS is higher than that available from the official national statistics service. Behr et al. estimated the incidence of SADS mortality at 0.16 per 100,000 persons per annum compared with 0.10 per 100,000 persons per annum from the National Office for Statistics. Using our study methodology, we estimated a SADS incidence rate for 2006 which was five times higher than that estimated using national CSO coding alone (0.14 deaths per 100,000 persons per year). Indeed, SADS cases were variably coded as ‘unascertained’, conduction disorder (426), cardiac dysrhythmia (427), heart failure (428), ill-defined descriptions and complications of heart disease (429), Wolff-Parkinson-White, and ‘special symptoms of syndromes not classified elsewhere’. Again in 2007, 11 out of 13 SADS cases (84%) were assigned incorrectly, with at least four different codes listed. Currently, the physician, coroner or pathologist certifying the cause of death issues an official certificate which is then electronically transcribed to an online database by a non-medical administrative staff member. From the electronic free text version of the written cause of death, a dedicated team of ICD-coding staff apply an appropriate ICD code. However, due to the natural variation in the terms used to describe the cause of death, differing codes can be applied to same diagnosis. This suggests the need for the implementation of immediate coding of the cause of death by the physician/coronor/pathologist attesting to the cause of death rather than remote coding by non-medical personnel. We propose that prospective data collection for cases of presumed SCD in young people, with timely acquisition of demographic, clinical, and pathologic information, represents the best possibility of increased precision in estimates of SCD and SADS. Furthermore, this would also facilitate appropriate cardiac screening of first-degree family relatives without undue delay. The use of clear case definitions, a standard SCD post-mortem procedure, with molecular and genetic tissue analysis, and accurate ICD coding at source when death occurs will result in prompt detection of first-degree family members with a 14–20%, as well as providing more accurate epidemiological data. In other jurisdictions such as Denmark, national medical registries allow relatively easy access to a patient’s pre-mortem medical records and post-mortem reports, compared with Irish access, which depends on the co-operation of some 70 coroners and pathologists, some with very limited support staff and resources. Most countries have their own local difficulties in terms of data collection in cases of SCD requiring investigators to create innovative local solutions. In possible SADS cases where doubt or difficulty exists, then expert cardiac pathological and electrophysiological opinion should be sought. Previously, Irish pathologists would consult with an international expert on cardiac pathology, and this occurred in 5 of 204 of the post-mortems reviewed. Through experts in the Faculty of Pathology, and the national SCD in the Young Taskforce, specialized guidelines for post-mortem evaluations in cases of SCD are now available for Irish pathologists.

Study limitations

The authors acknowledge that a major limitation of this study is the lack of adequate or available autopsy reports in 86 of 292 cases of death among the target population. Indeed, 40 of 292 of these missing cases did not actually undergo autopsy examination. Despite multiple requests for the other 39 reports, these missing cases were ultimately not available for inclusion in the analysis. The likely bias resulting from the missing data is an underestimation of the true incidence of SCD in our population. This has been addressed for future surveys by planned prospective collection of data and by raising awareness among coroners and pathologists through the national Faculty of Pathology. We used the CSO classification of causes of death for the initial identification of potential cases. This caused inclusion of inappropriate (non-cardiac) cases, and therefore possible exclusion of some relevant cases because of mis-coding. We have minimized the former by detailed analysis of all cases identified and the latter by using as broad a ‘net’ of ICD codes as possible to capture cases. Post-mortem performance guidelines are available through the Faculty of Pathology, Royal College of Physicians in Ireland. However, there is no audit system in place to ensure that such guidelines are followed. Post-mortem reports in our registry were issued by over 30 different pathologists, and report quality was variable. We therefore retained only those post-mortem reports which had both gross macroscopic and microscopic descriptions of the heart. Again this would likely lead to an underestimation of disease burden of SCD and SADS in the young. We excluded all cases of sudden death that occurred in the setting of alcohol excess, the presence of positive blood levels of drugs of abuse, a history of epilepsy, drowning, or road traffic accidents. Detailed analysis of such cases to identify underlying heart disease which may have led to a fatal arrhythmia was beyond the scope or resources of this registry; however, we acknowledge that some of these cases may have had an underlying arrhythmic aetiology. Due to concerns over the right to privacy, both the CSO and the Data Protection Commissioner precluded the collection of information on pre-mortem electrocardiograms or hospital charts or access to family history unless the pathologist made reference to it in his report. Furthermore, in providing the ICD code data, the CSO expressly stipulated that the data could not be used to make contact with the families of victims. Therefore, we did not have access to any subsequent family screening outcomes. Our registry is restricted to cases of SCD in 15–35-year olds, making comparative analyses with younger age groups impossible. Data on survivors of out of hospital cardiac arrest in the age group were not included. At present, there is no central registry or linked database to allow reliable collection of such data nationwide. Molecular autopsy was not used in any of the cases of SADS in this
registry, and we did not have ethical permission to contact families for further clinical information on either the victim or other family members. As a result, no further clarification of underlying channelopathy diagnoses can be included in the SADS cases.

**Conclusion**

The incidence of SCD in Ireland was 4.36 per 100 000 person-years (95% CI 3.06, 6.4) for males and 1.3 per 100 000 person-years (95% CI 0.62, 2.56) for females. The commonest finding at post-mortem was a structurally normal heart followed by CAD and HCM.

The incidence of SADS after careful examination of postmortem and toxicology reports was more than five times the incidence reported by the Irish CSO.

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**Conflict of interest:** None of the authors report any conflicts of interest.

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