ABSTRACT

Objective: To examine the incidence of sudden unexplained death in children 1-4yrs (SUDC) in Ireland and to compare the epidemiological profile of SUDC with that of SIDS.

Design: All cases of sudden unexplained death in children <5yrs in Ireland between 1994 and 2008 were reviewed. Epidemiological information was obtained from parental questionnaires and post-mortem reports and data on cases >=52 wks compared with cases <52wks.

Results: SUDC accounted for 5% (n=44) of deaths in children aged 1-4yrs during 1994-2008. During this period the SIDS rate dropped from 0.71 to 0.34 per 1000 live births, while the SUDC rate increased from 0.08 to 0.18 deaths per 10,000 population aged 1-4yrs.

Median age of SUDC cases was 71.5wks and ratio of males to females was 1.3:1. All died during a sleep period, 71% between 10pm and 8am and more than two thirds were found prone. Fewest cases occurred during July-September (11%) and a greater proportion occurred at weekends (55%). Fifty two percent (17/33) had symptoms (any) in the 48hrs before death, and 35% (11/31) visited their GP with symptoms in the week preceding death.

SUDC differed from SIDS in prevalence of maternal smoking (38% vs. 72% P<0.001), bed-sharing (17% vs. 49%, P<0.001), and whether found prone (72% vs. 23% P<0.001).

Conclusion: While SUDC shares some characteristics with SIDS, there are also some important differences. Further data collection will help determine whether SIDS and SUDC represent the same path physiological entity. Standardisation of protocols for investigating sudden deaths is urgently required for accurate diagnosis of cases.

BACKGROUND

In Ireland, all sudden unexpected deaths in infants and young children are reported to the National Paediatric Mortality Register (formerly SIDS Register). In 1994 a population based case control study of associated risk factors was initiated with no age limit imposed on cases notified. During this time, with the help of targeted
intervention campaigns the rate of sudden unexplained death in children less than one year of age (SIDS) dropped continuously with an average rate of 0.34/1000 live births currently (2007-2009). [1] However, the incidence of sudden unexplained death in children >1yr has increased. Every year in Ireland, an average of 6% of deaths certified as ‘unexplained’ occur in children greater than one year of age, accounting for 5% of all deaths in children aged 1-4yrs. [1,2] These deaths, known as Sudden Unexplained Death in Childhood (SUDC), were defined by Krous et al as “the sudden death of a child over one year of age which remains unexplained after a thorough case investigation, including review of the clinical history and circumstances of death, and performance of a complete autopsy with appropriate ancillary testing”. [3] Like that of SIDS, this is a definition of exclusion, employed when all other possible causes of death have been eliminated. [4, 5] The first description of SUDC by Krous et al in 2005 reported a male predominance among cases, a high prevalence of being found prone and a personal/family history of febrile seizures. [3] An earlier description of five cases in the UK described an association with cyanotic episodes and convulsions in 2 out of 5 cases. [6]

The objectives of this study were to examine the incidence of SUDC (1-4yrs) in Ireland, establish an epidemiological profile of cases and compare those characteristics with those of SIDS. Establishing an epidemiological profile of SUDC cases in isolation from classic SIDS may provide valuable information which may aid in future diagnosis of cases and identification of risk factors. In this way we hoped to add to the sparse literature currently available on SUDC and provide baseline information needed to guide future research in this area.

METHODS
In Ireland, all sudden unexpected deaths in infants and young children are reported to the National Paediatric Mortality Register via a 24hr notification system, usually within 48hrs of occurrence. All cases under 5 yrs, where the registered cause of death was coded as ICD-10 R95/R96/R99 or ICD-9 798 were included in the study. All sudden deaths are reported to the local coroner and a postmortem examination is mandatory in all cases. Death certificates and autopsy reports were made available to the SIDS Register by the Central Statistics Office and coroners respectively,. Cross referencing with death certification details confirmed that all cases of all sudden unexplained deaths in children <5yrs in Ireland since 1994 were notified to the register.

All families were invited by letter to participate in a standardized home interview, conducted by register staff within six weeks of the death. Information was collected on socio-demographics, pregnancy, the infant/child’s medical history, the home environment, parenting practices and details of the last 48 hours, and last sleep period. [7] A social disadvantage index, scoring 0-5 (5-most deprived), was employed as described previously. [7] Additional information was extracted from autopsy reports, from maternity hospitals and general practitioners records.

The distribution of variables between cases i.e. SUDC (cases >=52wks) vs. SIDS (<52wks), was examined by chi square analysis or exact tests. In 2004, new restrictions preventing early contact with bereaved families led to a reduction in response rates and for this reason, SIDS data are restricted to the years 1994-2003. In the case of SUDC families, response rates remained at an acceptable level. Data may be accepted as missing at random. All statistical analysis was conducted in STATA version 11. This study was approved by the Dept of Health and informed consent obtained from parents.
RESULTS

Incidence of SUDC in Ireland

Between 1994 and 2008, a total of 735 sudden unexpected deaths in children <5yrs were reported to the register. Of these, 587 (79.8%) remained unexplained following post mortem investigation, a cause of death was established for 139 (19%) and 9 (1.2%) had insufficient information for follow up. Of the 587 cases that remained unexplained, 44 (7.5%) were >1yr.

A comparison of trends in SUDC and SIDS rates for the period 1994-2008 are shown in table 1. A list of the categories and frequency of other causes of death in toddlers reported to the register during this period are listed in table 2. While the SIDS rate declined during this time, the SUDC rate, increased gradually from an average of 0.08 per 10,000 (1.7 deaths/year) to an average of 0.18 per 10,000 (4.3 deaths/year). During 2006-2008, SUDC accounted for 8.8% of all deaths in the 1-4yr age group in comparison with only 3.1% in 1994-1996.

Table 1. Annual trend in prevalence of SUDC in Ireland 1994-2008.
Table 2. Categorisation of sudden deaths reported to the register 1994-2008 for which a cause of death was established following autopsy.

<table>
<thead>
<tr>
<th>Cause of Death Category</th>
<th>Total number of cases</th>
<th>Age &lt;52 wks</th>
<th>Age &gt;=52 wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accidental asphyxia (mechanical/aspiration of food, foreign body, other)</td>
<td>13</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>External causes (RTAs, Drownings, other vehicle accidents)</td>
<td>6</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Epileptic seizure</td>
<td>6</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Head trauma</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac causes (arrthymias, viral myocarditis, cardiomyopathy, congenital structural abnormalities)</td>
<td>26</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>Respiratory tract infection (bacterial/viral)</td>
<td>40</td>
<td>26</td>
<td>14</td>
</tr>
<tr>
<td>Meningitis/encephalitis (bacterial/viral)</td>
<td>6</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Sepsis- various pathogens</td>
<td>17</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>Metabolic disorders including mitochondrial disease</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Disorders of the gastrointestinal tract</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Other disorders of the CNS</td>
<td>6</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Conditions relating to prematurity</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Conditions originating in the perinatal period</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>139</td>
<td>92</td>
<td>47</td>
</tr>
</tbody>
</table>
NB. The above represents only deaths reported to the National Sudden Infant Death Register during 1994-2008 and do not represent the actual number of deaths that occurred in each category during this period.

Description of epidemiological characteristics of SUDC cases in Ireland, 1994-2008.

Questionnaires were completed for 66% (n =29/44) of SUDC cases. Additional information was retrieved from medical records or autopsy reports where possible. Median age of cases was 71.5 wks and almost two thirds were aged 12 -18 months (table 3). More males than females died, at a ratio of 1.3:1 and fewer deaths occurred during the third quarter of the year. All SUDC deaths occurred during a sleeping period, the majority (71%) between 10pm and 8am. A greater proportion of cases occurred at weekends than other days of the week.

Most SUDC mothers were married (65%, n=17) or cohabiting (11.5%, n=3)) with the child’s father. The average maternal age was 30.4yrs (+6.8) with 27% aged < 25yrs. Information on gestational age was available for 27/44 cases of which 22% (n=6) were born prematurely while data on infant birth weight was available for only 18 cases (41%), of which 6 (33%) were <2500g. Of the 31 cases with data on sleep position, 21 (68%) were prone when discovered and the remainder found either on their side (16%) or back (16%). The vast majority (81.5%) died in their own cot/bed and only 6 of 38 cases occurred while co-sleeping; 5 bed-sharing and 1 co-sleeping with an adult on a couch.

83% of SUDC had a history of illness during their lifetime, the most frequently reported problems (50%) being respiratory in nature (table 4). The next most frequently reported illness was a history of febrile seizures, apparent in 31% of cases.
Examination of all available information on SIDS provided evidence of a history of febrile seizures in less than 1% of cases.

Sections from the hippocampus were available to the authors for microscopic examination in only 4 SUDC cases. This low number does not reflect the rate of neuropathological examination but rather the authors’ access to histological material. A detailed macroscopic description of the hippocampus was not available in any case. H&E examination showed focal subpial gliosis in 1/4 cases. However there was no evidence of microdysgenesis on H&E in any case. It must be stressed, however, that as there was no standardisation of the sampling of the hippocampus, these results may not be entirely reliable as many of the features of microdysgenesis depend on the level of the section and the plane of section. Of the 4 cases where the hippocampus could be examined, 1 report indicated a history of febrile seizures.

52% (n=17) of cases had symptoms in the 48hrs prior to death, covering a wide range of problems with no predominant single complaint and 35% (11/31) had visited their GP because of illness in the week preceding death.
Table 3. Epidemiological description of SUDC cases in Ireland 1994-2008.

Table 4. Description of history of illness and/or wellbeing of SUDC cases (1-4yrs) in Ireland 1994-2008.

Distribution of risk factors among cases: SIDS vs. SUDC

Differences in the distribution of variables relating to maternal factors, child health/wellbeing and last sleep environment were compared for SUDC and SIDS. For the purpose of this comparison only data on SUDC cases with completed questionnaires are included in table 5, and as such numbers and proportions of
variables for SUDC in table 5 may vary from those in table 3 where additional data retrieved from post mortem reports is included.

All variables listed in table 5 are known from other studies to be associated with SIDS, being significantly more prevalent among SIDS cases than age matched controls, with the exception of ‘breastfeeding’ and ‘soother use during the last sleep’, both of which have previously been shown to be less prevalent among cases. [7-14] Both groups differed significantly in terms of socio-demographic variables, whether bed-sharing or not, and sleep position found. Although fewer SUDC than SIDS were socially disadvantaged; 33% vs. 54%, this seemingly large difference is not statistically significant (p=0.07), likely due to the small sample size for SUDC. Fewer SUDC than SIDS mothers smoked during pregnancy. The proportion of SUDC found bed-sharing was significantly less than for SIDS; 17% vs. 49% (P<0.001) while a significantly greater proportion were found prone; 72% of SUDC vs. 23% of SIDS (p<0.001). Distribution of variables relating to birth factors did not differ significantly between SIDS and SUDC. The potential bias introduced by the variation in time period of both groups, was examined by rerunning the analysis restricting data to SUDC cases from 1994-2003 only; for all variables, proportions varied only slightly from estimates presented in table 5 and did not alter the overall results.
Table 5. Distribution of risk factors among cases: SIDS vs SUDC

Note: Exact test used where cell count <5%, ns= non significant p value, all p values corrected for multiple testing.

DISCUSSION

This study provides a description of the incidence and epidemiological characteristics of a complete population based dataset of SUDC. Although SUDC is rare with an average annual rate in Ireland of 0.18 per 10,000 population aged 1-4yrs (4 cases per year), annual trends show that SUDC is a growing entity, increasing in proportion and in number, while in contrast the SIDS rate continues to decline. [1] Examination of
the epidemiological profile of these cases showed that while SUDC shares some characteristics with SIDS there are also some important differences. The majority of SUDC occurred during the nighttime sleep in the child’s own home whilst sleeping alone and more than two thirds were found prone. Prone sleeping is a major risk factor for SIDS and advice to avoid the prone position has resulted in substantial reductions in SIDS deaths worldwide. [15] The proportion of SUDC infants found prone in this study was 68%, substantially more than for SIDS (23%). Two thirds of SUDC were from families of lower socioeconomic groups, and fewer cases occurred during the warmer months of the year. It is thought that the previous predominance of SIDS during colder months may have been a reflection of reduced susceptibility to infection during the warmer months of the year and this may also be true for SUDC. [1, 14, 16] The higher prevalence of SUDC occurring at weekends is also true of SIDS, a trend that has continued despite the overall drop in SIDS rates and is possibly a consequence of change in environment or routine [17, 18]

SUDC share other similarities with SIDS; similar proportions of both groups had symptoms in the 48hrs prior to death and had visited their GP with illness in the week preceding death. The proportion of SUDC that were low birthweight and/or premature was also high and much greater than national average figures (6% and 5% respectively). [19] This is of interest considering that such a large proportion of SUDC were found prone; previous SIDS research has shown that mild illness significantly increases the risk of death if the infant is sleeping prone and it is possible that a similar interaction occurs in older children. [20] Other similarities included the proportion of young mothers, high parity and the proportion of infants initiated breastfeeding.
Despite the similarities with SIDS there were also some important differences, particularly in relation to the last sleep environment. Whereas half of SIDS deaths occur while bed-sharing, the vast majority of SUDC children in this study were solitary sleepers. [21] Another important difference was the proportion of mothers that smoked during pregnancy; with the decline in prone sleeping, maternal smoking during pregnancy is now the major risk factor for SIDS, with a population attributable risk of 49%. [1] Although this observation must be confirmed by larger studies, the relatively low level of maternal smoking among SUDC families in comparison to SIDS (72% vs 38%) may indicate that maternal smoking may be less important as a risk factor for SUDC than it is for SIDS and that different mechanisms of death are involved. SUDC deaths may not represent a single underlying cause but may comprise a collection of deaths from various unknown causes, some of which like SIDS may be associated with maternal smoking and some of which may not.

The observation of a high incidence of a history of febrile seizures among SUDC relative to SIDS (<1%) and the general paediatric population (2-5%) is in agreement with previously published reports. [23-26]. Kinney et al. described neuropathological abnormalities in the hippocampus and temporal lobe in a large proportion of SUDC. [26] Many of these findings (including hippocampal sclerosis, gliosis, hippocampal asymmetry) are also seen in temporal lobe epilepsy and the authors postulated that a potential new entity may account for the majority of SUDC in toddlers, defined by sleep related death in the prone position, individual/family history of febrile seizures and hippocampal anomalies. While the results of the Irish dataset are important in confirming a high prevalence of seizures among SUDC, such detailed neuropathological examination as described by Kinney et al. is not currently possible,
in part due to the lack of standardisation of neuropathological sampling. As such our data is not proof of a causative association between febrile seizures and sudden death and considering the rarity of SUDC, it must be stressed that the overall risk of death is very low and that febrile seizure is a common condition with a benign outcome for the vast majority of children. [23-25] Investigation of a proposed association between febrile seizures and SIDS has not been supported. [27, 28]

The reason for the increase in SUDC in recent years is unclear. The possibility of a diagnostic shift must be considered i.e. whether frequency of other causes of sudden death, that are not immediately identifiable have changed accordingly during the same period. There is currently no standardized approach to the investigation of sudden unexpected deaths in Ireland and a death scene investigation is not mandatory. Additionally there has been variation between centres in Ireland in terms of organ sampling for histology, formal neuropathological examination and ancillary testing (bacteriology, virology, metabolic investigations, other) in SUDC cases. This practice is already changing. Traditionally, there has been a heavy onus on the pathologist to identify a cause of death and therefore of identifying minor abnormalities as the cause of death, in the absence of any clearly significant abnormality and this practice is now changing. It is also possible that fewer additional investigations are carried out due to a reluctance of hospitals to retain additional tissue samples in light of the recent organ retention controversy. [29] This highlights once again the importance of a standardized multidisciplinary approach to the investigation of sudden unexpected deaths. Inaccurate classification of deaths produces misleading statistics, limiting the ability to identify associated risk factors. [30] This can have serious consequences where the death is due to an inherited disorder that may cause multiple deaths within families and raises potential child protection issues where there is failure to
differentiate between natural and unnatural deaths. Diagnostic accuracy can be improved by standardisation of protocols including a full autopsy, review of the clinical history and a death scene investigation. [31, 32] Previous audits of the autopsy procedure in Ireland demonstrated the need for specialist paediatric pathologists in the investigation of sudden unexpected deaths in infancy/childhood in order to increase the likelihood of establishing a cause of death [34, 35].

Conclusions
We concluded from this study that while SUDC share some characteristics with SIDS, there are also some important differences, suggesting that in at least some cases there may be different cause of death mechanisms at play. Standardization of definitions, protocols and procedures for investigating and reporting sudden unexpected deaths is urgently required in order that efficient future studies are conducted.

Study Limitations
The non standardized approach to investigation of SUDC during the time period of this study means that criteria for assigning deaths as unexplained may have changed over time, increasing the possibility of variation among cases. There is currently no standardized approach to the autopsy examination of sudden unexpected deaths in Ireland and there is variation amongst pathologists in terms of organ sampling and ancillary testing, and the authors acknowledge this limitation. The small sample size of SUDC data for some variables limits the ability to detect statistically significant differences and there is additional bias introduced by the retrospective collection of data.
The lack of epidemiological data on SIDS post 2003 also introduces potential bias. However, restricting SUDC data to years 1994-2003 did not alter the results and conclusions remain unchanged.

Conflict/competing interest statement:
The authors state that there are no conflicts of interest. The authors had full access to all the data in the study and had the final responsibility for the decision to submit for publication. All authors have viewed the ICJME conflicts of interest form and have nothing to declare.

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Contributorship statement:
CmG contributed to study design, data analysis and writing of the manuscript. Mo'R contributed to study design, statistical analysis and review of the manuscript. JC, AT and DD contributed to interpretation of data and review of the manuscript. KH contributed to data collection. TM contributed to study design and review of the manuscript.

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What we already known on this topic;
• SUDC is rare
• Previous reports on SUDC described a male predominance of cases, a large proportion found prone and a high incidence of individual/family history of febrile seizures.

What this study adds;
• Although rare, the incidence of SUDC in Ireland has increased in recent years, accounting for 9% of deaths in children aged 1-4yrs between 2006 and 2008.
• Although SUDC deaths share some characteristics with SIDS there are also some important differences.
• Unlike SIDS, of which almost half of cases occur while bed-sharing with adults, the majority of SUDC cases are solitary sleepers.
• Maternal smoking is less prevalent among SUDC cases than SIDS.
• This study confirms previous reports of a high incidence of febrile seizures and being found prone among SUDC cases.
References


