ABSTRACT

Background Congenital anomalies (CAs) increase the risk of death during infancy and childhood. This study aimed to evaluate the accuracy of using death certificates to estimate the burden of CAs on mortality for children under 10 years old.

Methods Children born alive with a major CA between 1 January 1995 and 31 December 2014, from 13 population-based European CA registries were linked to mortality records up to their 10th birthday or 31 December 2015, whichever was earlier.

Results In total 4199 neonatal, 2100 postneonatal and 1087 deaths in children aged 1–9 years were reported. The underlying cause of death was a CA in 71% (95% CI 64% to 78%) of neonatal and 68% (95% CI 61% to 74%) of postneonatal infant deaths. For neonatal deaths the proportions varied by registry from 45% to 89% and by anomaly from 53% for Down syndrome to 94% for tetralogy of Fallot. In children aged 1–9, 49% (95% CI 42% to 57%) were attributed to a CA. Comparing mortality in children with anomalies to population mortality predicts that over 90% of all deaths at all ages are attributable to the anomalies. The specific CA was often not reported on the death certificate, even for lethal anomalies such as trisomy 13 (only 80% included the code for trisomy 13).

Conclusions Data on the underlying cause of death from death certificates alone are not sufficient to evaluate the burden of CAs on infant and childhood mortality across countries and over time. Linked data from CA registries and death certificates are necessary for obtaining accurate estimates.

BACKGROUND

The contribution of congenital anomalies (CAs) to causes of early death is increasing as mortality from other causes declines globally.1 The Global Burden of Disease study estimated that, worldwide in 2010, CAs accounted for 6.4% of neonatal deaths, 2.2% of postneonatal and 2.5% of deaths in children under 5 years of age.2 In comparison, in Europe from 2000 to 2015, CAs were estimated to account for 26% of all deaths in infants, 16% in children aged 1–4 and 9% in children aged 5–9.3

The above estimates of the burden of disease in populations have all been derived from data on the underlying cause of death recorded on death certificates. Such data are often used to monitor any changes in primary
Open access

Table 1  Number of deaths and percentage by age at death in children with a major congenital anomaly reported by participating EUROCAT registries and databases

<table>
<thead>
<tr>
<th>Participating registries</th>
<th>Included birth years</th>
<th>No of livebirths</th>
<th>% of all live births linked</th>
<th>Only underlying cause of death provided</th>
<th>No of deaths</th>
<th>Percentage of deaths (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Infants &lt;28 days</td>
<td>Infants 28–364 days</td>
</tr>
<tr>
<td>Denmark, Funen*</td>
<td>1995–2014</td>
<td>2 425</td>
<td>100.0</td>
<td></td>
<td>150</td>
<td>58</td>
</tr>
<tr>
<td>Finland</td>
<td>1995–2014</td>
<td>42 921</td>
<td>99.9</td>
<td></td>
<td>1 770</td>
<td>61</td>
</tr>
<tr>
<td>Italy, Emilia Romagna</td>
<td>2008–2014</td>
<td>5 589</td>
<td>91.4</td>
<td></td>
<td>204</td>
<td>52</td>
</tr>
<tr>
<td>Italy, Tuscany</td>
<td>2005–2014</td>
<td>4 312</td>
<td>87.2</td>
<td>Yes</td>
<td>148</td>
<td>48</td>
</tr>
<tr>
<td>Malta</td>
<td>1995–2014</td>
<td>2 718</td>
<td>91†</td>
<td></td>
<td>241</td>
<td>69</td>
</tr>
<tr>
<td>Northern Netherlands*</td>
<td>1995–2014</td>
<td>8 605</td>
<td>96.7</td>
<td>Yes</td>
<td>620</td>
<td>66</td>
</tr>
<tr>
<td>Norway</td>
<td>1999–2014</td>
<td>27 201</td>
<td>100.0</td>
<td></td>
<td>1 034</td>
<td>58</td>
</tr>
<tr>
<td>Spain, Basque Country</td>
<td>1995–2014</td>
<td>5 904</td>
<td>94†</td>
<td>Yes</td>
<td>411</td>
<td>52</td>
</tr>
<tr>
<td>Spain, Valencian Region</td>
<td>2007–2014</td>
<td>7 389</td>
<td>95†</td>
<td>Yes</td>
<td>416</td>
<td>58</td>
</tr>
<tr>
<td>UK, Thames Valley*</td>
<td>2005–2013</td>
<td>3 988</td>
<td>96.5</td>
<td></td>
<td>295</td>
<td>56</td>
</tr>
<tr>
<td>UK, EMSY*</td>
<td>2003–2012</td>
<td>11 587</td>
<td>97.3</td>
<td></td>
<td>910</td>
<td>52</td>
</tr>
<tr>
<td>UK, Wessex*</td>
<td>2004–2014</td>
<td>4 729</td>
<td>91.7</td>
<td></td>
<td>330</td>
<td>51</td>
</tr>
<tr>
<td>UK, Wales*</td>
<td>1998–2014</td>
<td>18 188</td>
<td>99.7</td>
<td></td>
<td>845</td>
<td>50</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>7 386</td>
<td>57</td>
<td>28</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

*Numbers of deaths rounded to nearest multiple of 5 due to disclosure requirements.
†Estimated proportion as linkage was to mortality records only and completeness could not be directly estimated.
EMSY, East Midlands and South Yorkshire; EUROCAT, European Surveillance of Congenital Anomalies.

and secondary prevention over time\(^{1,4}\) and for international comparisons.\(^{6,7}\) However, the accuracy of cause of death on death certificates has often been questioned, and a US study concluded that linking CA registries to death certificates was necessary to provide a comprehensive picture of the full burden of CAs on mortality in infants and children.\(^{8}\) This EUROlinkCAT study linked live births with a major CA reported to 13 (European Surveillance of Congenital Anomalies, EUROCAT) (European network for the epidemiological surveillance of CAs) registries\(^9\) to national/regional databases on vital statistics/mortality up to their 10th birthday. The aim was to determine what the children with CAs died from and whether their CA was mentioned anywhere on the death certificate. This information should improve interpretation of mortality rates routinely reported for children with CAs in Europe.

**METHOD**

Thirteen population-based EUROCAT CA registries from eight countries linked their data on live born children with a major CA, born between 1 January 1995 and 31 December 2014, to mortality records up to the child’s 10th birthday or to 31 December 2015, whichever was earlier (Table 1). Ten registries linked to vital statistics containing civil registrations data (eg, births, deaths and emigrations) but three were able to link to death registrations only. Both deterministic and probabilistic linkage methods were used. Linkage rates were high, with eight registries linking over 95% of cases and only one registry linking less than 90% of the births. Additional details evaluating the linkage are provided elsewhere.\(^{10,11}\)

**Classification of anomalies**

The EUROCAT guide 1.4 specifies the coding of all major CAs into specific CA subgroups using ICD-10 (International Classification of Diseases, tenth revision) or ICD-9 (ninth revision) with the BP A (British Paediatric Association extension).\(^12\) A child is defined as having an isolated CA if (s)he has a CA in one organ system only or as part of a known sequence (eg, renal agenesis with pulmonary hypoplasia). A EUROCAT computer algorithm was used for classification of major CAs into isolated anomalies, multiple anomalies or genetic anomalies without a manual clinical review of the identified potential multiple CAs.\(^13\) The severe congenital heart defect (CHD) subgroup includes types of CHD’s selected due to their high mortality.\(^14\) Forty-six CA subgroups were analysed, including anomalies likely to be recorded as an
underlying cause of death (such as trisomy 13 or 18) and
anomalies less likely to be recorded on a death certificate
(such as limb reduction defects or hypospadias).

Classification of cause of death
All causes of death were recorded using ICD-10 or ICD-9.
Four registries were able to provide only the underlying
cause of death. Other registries were able to report in
addition to the underlying cause of death the primary/
immediate cause of death, contributing cause of death
and any other causes of death.

Deaths were categorised into neonatal (0–27 days),
postneonatal (28–364 days) and child (365–3651 days).
In England and Wales, the underlying cause for neonatal
deaths was not specified and each cause was classified as
related to infant, mother or either; main causes were
listed before other (secondary) causes. For this study, in
Wales, the first cause of death related to the infant was
taken to be the underlying cause of death. In England,
the first mention of a CA (if present) was taken to be the
underlying cause.

Seven categories of cause of neonatal and post-neonatal
deaths, based on a modified version of the UK Office for
National Statistics’ (ONS) classification of neonatal and
postneonatal causes of death were used in this study
(see online supplemental appendix A). The ‘All other
conditions’ group was very heterogeneous. It included
neoplasms, metabolic disorders, jaundice and endocrine
disorders, and external causes.

Similarly, the classification of cause of death for chil-

dren aged 1–9 in this study was based on the UK ONS
classification of causes of death and was divided into 13
categories (see online supplemental appendix B).

To determine the accuracy of the CA recorded on death
certificates, two paediatricians agreed a set of ICD-10 and
ICD-9 codes corresponding to an ‘exact match’ for the
child’s anomaly and a larger set of codes that were consid-
ered as an ‘acceptable match’ (see online supplemental
appendix C). For example, for a child with spina bifida
(ICD-10 code-Q05), if Q05 was on the death certificate
this was considered an exact code; if there were codes
for other neural tube defects Q00 (anecephaly) or Q01
(encephalocele) they were considered as acceptable
codes. All the available causes of death were searched to
determine if any exact or acceptable anomaly codes had
been specified.

Statistical analysis
The analysis variables from each of the 13 registries were
mapped and recoded to a common data model (full
details are given in Morris et al10) and analysed locally
using common Stata syntax scripts. Aggregate data from
each registry were submitted to a Central Results Reposi-
tory based at Ulster University, UK using a secure portal
where they were merged and uploaded to the study team
for analysis.

The predicted proportions of deaths in children with a
CA attributable to that anomaly was estimated from the
population mortality rate (published by WHO) for chil-
dren in the eight countries and the observed mortality
rate for children with the specific CA (from an earlier
EUROlinkCAT study16 as equal to (CA mortality—popu-
lation mortality)/CA mortality. For example, if the
mortality rate in children with anomalies is 10 times
greater than that in the population, then for every 10
deaths in a group of children with anomalies you would
expect only one death in a similar group of children
without anomalies. Therefore, it could be said that the
excess 9 deaths (10–1) were attributable to the anomaly,
or 90% when expressed as a proportion of all deaths in
children with anomalies (9/10). These were underesti-
mates as the population mortality included children with
CAs.

To estimate the overall proportion of each cause of
death specified as the underlying cause of death, multi-
level multinomial models were fitted with registry as a
random effect. The models were fitted in Stata using
the generalised structural equation model estimation
command (gsem) for each CA separately. The observed
information matrix was used to obtain the variance–co-
variance matrix of the estimates as it is the default method.
The same models were used to estimate the overall propor-
tion of death certificates with the exact and appropriate
CA codes. For the group of all anomalies, the proportion
of all neonatal deaths with CA as an underlying cause of
death was compared across the different registries in a
figure to illustrate the variation between registries, with
the exact method used to estimate the 95% CIs.

RESULTS
The 13 registries varied considerably in size due to the
differences in populations covered and years of data
available, from 1770 deaths in Finland to only 148 in
Tuscany (table 1). The majority of deaths reported
(57%) occurred in the neonatal period. Overall, 71% (95% CI
64% to 78%) of neonates who died had a CA coded as the
underlying cause of death. However, this
varied significantly according to registry from 89% in
Malta to 45% in Tuscany (Italy) and 46% in Wales (UK)
(figure 1). Registries providing only one cause of death
had a lower proportion specifying a CA as the underly-
ing cause of death. All registries, except for Wales, had under
7% or deaths attributed to immaturity. Wales had 15% of
such deaths, which together with the low proportion
of CAs, may be due to the Welsh coding of infant death
certificates (see the Methods section).

Figure 2 shows that the percentage of deaths with the
underlying cause of death coded as a CA was slightly
lower in the postneonatal period, 68% (95% CI 61% to
74%), and decreased to 49% (95% CI 42% to 57%) for
children who died between the ages of 1 and 9. Variations
by registry for the postneonatal period and for children


Downloaded from http://bmjpaedopen.bmj.com/ on September 15, 2023 by guest. Protected by copyright.
aged 1–9 were similar to those in figure 1 in the neonatal period (see online supplemental appendix D)

Table 2 provides the underlying cause of death for children with specific CAs. Deaths in neonates with severe CAs were likely to have the CA coded; for example, over 90% of deaths in neonates with trisomy 13, 18 or gastrochisis had an anomaly as the cause of death. Over 90% of births with cleft lip with or without cleft palate who died had CA as the cause of death, reflecting that these children were likely also to have had more severe anomalies, such as trisomy 13 or trisomy 18. For neonates with Down syndrome, 53% had an anomaly specified and 10% of deaths were due to immaturity. For neonates with Down syndrome, 53% had an anomaly specified and 10% of deaths were due to immaturity. The pattern was similar for all infant deaths. For children aged 1–9, other causes of death were more prominent: for several anomalies, over 10% of deaths were due to infections. For children with Down syndrome, 17% of deaths were due to neoplasms. Table 2 also shows the predicted proportion of deaths attributable to the anomalies as estimated by comparing the mortality in these children to the population mortality. These proportions were above 90% for all anomalies apart from for deaths in neonates with a ventricular septal defect, cleft lip with or without cleft palate or Down syndrome, and deaths in infants with a cleft lip with or without cleft palate or multicystic renal dysplasia.

Figure 3 shows the results for all causes (including underlying causes) of death to determine if any exact/acceptable CA codes were recorded for deaths up to age 10 years. As expected, no CA code indicating a limb reduction defect was provided for any of the 165 deaths among children with these anomalies. Five severe conditions (anecephaly, gastrochisis, diaphragmatic hernia, trisomy 13 and trisomy 18) had over 75% of exact codes recorded as cause of death. For other severe CAs (particularly CHDs), few

deaths were attributed to the anomaly. For example, tetralogy of Fallot had an exact or acceptable code recorded for just 50% of deaths. There were also coding issues with several CAs, such as bilateral renal agenesis and atresia of bile ducts, resulting in over 30% of codes being ‘acceptable codes’ rather than exact codes.

DISCUSSION

This study found that only 70% of infants dying with a major CA had the underlying cause of death recorded as a CA, with higher percentages for those with anomalies known to be associated with high mortality, such as 86% for infants with severe CHD. Children aged 1–9 years with a major CA were less likely to have underlying cause of death recorded as a CA (49%) with other causes such as infections, trauma and cancer being more prominent. By comparing the mortality rate for children with anomalies from an earlier EUROlinkCAT study to published population rates it was possible to estimate that over 90% of deaths in children with anomalies are attributable to their anomaly. These results are consistent with the estimates for infant deaths in other studies, but estimates have not been reported for deaths in later childhood. Our results show that if only the underlying cause of death on death certificates is analysed, the impact of CAs on mortality is considerably underestimated for all ages and all anomalies.

Under-reporting is to be expected as it is not always clear if the CA is the underlying cause of death. For example, a child may die from an infection and it is difficult to distinguish if the CA is the underlying cause or not as the CA does increase the risk of severe infections, making infection either more likely or more severe. Similarly, many anomalies are associated with an increased risk of preterm birth. However, all registries apart from Wales, appeared to be consistent in assigning cause of death as the CA rather than the morbidity associated with being born preterm. Similar under-reporting of mortality and morbidity for children with chronic conditions has also been reported from healthcare databases.

In addition to the under-reporting on death certificates, estimating the full burden of CAs will require including data on stillbirths, miscarriages and terminations of pregnancy for CAs.

Another important finding was that if a CA was mentioned on the death certificate, it may not have been the exact code. For example, for CHDs a general code indicating a heart defect was often provided rather than the code for the specific cardiac defect. Care must be taken when analysing data from death certificates if there

Figure 2. The distribution of causes of death in children with a major congenital anomaly (CA) according to the recorded underlying cause of death by age at death.

Deaths were attributed to the anomaly. For example, tetralogy of Fallot had an exact or acceptable code recorded for just 50% of deaths. There were also coding issues with several CAs, such as bilateral renal agenesis and atresia of bile ducts, resulting in over 30% of codes being ‘acceptable codes’ rather than exact codes.

DISCUSSION

This study found that only 70% of infants dying with a major CA had the underlying cause of death recorded as a CA, with higher percentages for those with anomalies known to be associated with high mortality, such as 86% for infants with severe CHD. Children aged 1–9 years with a major CA were less likely to have underlying cause of death recorded as a CA (49%) with other causes such as infections, trauma and cancer being more prominent. By comparing the mortality rate for children with anomalies from an earlier EUROlinkCAT study to published population rates it was possible to estimate that over 90% of deaths in children with anomalies are attributable to their anomaly. These results are consistent with the estimates for infant deaths in other studies, but estimates have not been reported for deaths in later childhood. Our results show that if only the underlying cause of death on death certificates is analysed, the impact of CAs on mortality is considerably underestimated for all ages and all anomalies.

Under-reporting is to be expected as it is not always clear if the CA is the underlying cause of death. For example, a child may die from an infection and it is difficult to distinguish if the CA is the underlying cause or not as the CA does increase the risk of severe infections, making infection either more likely or more severe. Similarly, many anomalies are associated with an increased risk of preterm birth. However, all registries apart from Wales, appeared to be consistent in assigning cause of death as the CA rather than the morbidity associated with being born preterm. Similar under-reporting of mortality and morbidity for children with chronic conditions has also been reported from healthcare databases.

In addition to the under-reporting on death certificates, estimating the full burden of CAs will require including data on stillbirths, miscarriages and terminations of pregnancy for CAs.

Another important finding was that if a CA was mentioned on the death certificate, it may not have been the exact code. For example, for CHDs a general code indicating a heart defect was often provided rather than the code for the specific cardiac defect. Care must be taken when analysing data from death certificates if there
Table 2  Percentages of children with congenital anomalies (CA) with 95% CI according to underlying cause of death by age at death (anomalies with <10 deaths occurring are not included)

<table>
<thead>
<tr>
<th>Anomaly</th>
<th>No deaths (100%)</th>
<th>CA</th>
<th>Infections</th>
<th>Immaturity</th>
<th>Other</th>
<th>Missing cause of death</th>
<th>Predicted proportion attributable to the CA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal deaths</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All anomalies</td>
<td>4199</td>
<td>71 (64 to 78)</td>
<td>1 (1 to 2)</td>
<td>7 (6 to 9)</td>
<td>11 (8 to 14)</td>
<td>9 (7 to 12)</td>
<td>93</td>
</tr>
<tr>
<td>Spina Bifida (isolated cases with or without hydrocephalus)</td>
<td>19</td>
<td>79 (39 to 95)</td>
<td>0 (0 to 0)</td>
<td>11 (3 to 22)</td>
<td>5 (1 to 19)</td>
<td>5 (1 to 19)</td>
<td>97</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>138</td>
<td>64 (43 to 80)</td>
<td>1 (0 to 4)</td>
<td>7 (4 to 12)</td>
<td>14 (8 to 20)</td>
<td>14 (8 to 20)</td>
<td>97</td>
</tr>
<tr>
<td>Congenital heart defects (CHD)</td>
<td>1937</td>
<td>79 (71 to 86)</td>
<td>1 (1 to 2)</td>
<td>3 (2 to 5)</td>
<td>9 (7 to 13)</td>
<td>7 (5 to 9)</td>
<td>94</td>
</tr>
<tr>
<td>Severe CHD</td>
<td>1254</td>
<td>86 (78 to 91)</td>
<td>0 (0 to 1)</td>
<td>2 (1 to 3)</td>
<td>6 (4 to 9)</td>
<td>7 (4 to 10)</td>
<td>98</td>
</tr>
<tr>
<td>Transposition of great vessels (as only severe CHD)</td>
<td>106</td>
<td>91 (66 to 98)</td>
<td>1 (0 to 5)</td>
<td>2 (0 to 7)</td>
<td>4 (1 to 12)</td>
<td>3 (1 to 10)</td>
<td>97</td>
</tr>
<tr>
<td>VSD (without severe CHD)</td>
<td>291</td>
<td>75 (58 to 86)</td>
<td>2 (1 to 5)</td>
<td>5 (3 to 9)</td>
<td>13 (8 to 19)</td>
<td>5 (3 to 9)</td>
<td>89</td>
</tr>
<tr>
<td>ASD (without severe CHD)</td>
<td>153</td>
<td>68 (45 to 84)</td>
<td>4 (1 to 8)</td>
<td>9 (4 to 15)</td>
<td>14 (7 to 22)</td>
<td>6 (3 to 12)</td>
<td>90</td>
</tr>
<tr>
<td>AVSD</td>
<td>153</td>
<td>85 (65 to 94)</td>
<td>0 (0 to 0)</td>
<td>5 (2 to 11)</td>
<td>6 (2 to 14)</td>
<td>5 (2 to 11)</td>
<td>97</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>63</td>
<td>94 (78 to 98)</td>
<td>0 (0 to 0)</td>
<td>0 (0 to 0)</td>
<td>5 (2 to 13)</td>
<td>2 (0 to 10)</td>
<td>94</td>
</tr>
<tr>
<td>Coarctation of aorta</td>
<td>188</td>
<td>87 (75 to 93)</td>
<td>0 (0 to 0)</td>
<td>2 (1 to 5)</td>
<td>7 (4 to 12)</td>
<td>4 (2 to 8)</td>
<td>96</td>
</tr>
<tr>
<td>Cleft lip with or without cleft palate</td>
<td>128</td>
<td>91 (71 to 98)</td>
<td>0 (0 to 0)</td>
<td>4 (1 to 13)</td>
<td>2 (1 to 8)</td>
<td>2 (0 to 7)</td>
<td>89</td>
</tr>
<tr>
<td>Cleft palate</td>
<td>121</td>
<td>68 (46 to 83)</td>
<td>1 (0 to 5)</td>
<td>12 (6 to 18)</td>
<td>11 (6 to 17)</td>
<td>9 (5 to 15)</td>
<td>92</td>
</tr>
<tr>
<td>Oesophageal atresia</td>
<td>110</td>
<td>82 (64 to 92)</td>
<td>0 (0 to 0)</td>
<td>5 (2 to 10)</td>
<td>6 (3 to 12)</td>
<td>7 (3 to 14)</td>
<td>97</td>
</tr>
<tr>
<td>Diaphragmatic hernia (isolated cases)</td>
<td>186</td>
<td>89 (76 to 96)</td>
<td>0 (0 to 0)</td>
<td>2 (1 to 5)</td>
<td>2 (1 to 6)</td>
<td>6 (3 to 13)</td>
<td>99</td>
</tr>
<tr>
<td>Gastrochisis (isolated cases)</td>
<td>25</td>
<td>92 (61 to 99)</td>
<td>4 (1 to 20)</td>
<td>0 (0 to 0)</td>
<td>0 (0 to 0)</td>
<td>4 (1 to 20)</td>
<td>94</td>
</tr>
<tr>
<td>Multicystic renal dysplasia</td>
<td>92</td>
<td>67 (42 to 85)</td>
<td>1 (0 to 6)</td>
<td>9 (4 to 15)</td>
<td>10 (5 to 17)</td>
<td>13 (6 to 20)</td>
<td>96</td>
</tr>
<tr>
<td>Down syndrome</td>
<td>102</td>
<td>53 (33 to 72)</td>
<td>4 (2 to 7)</td>
<td>10 (6 to 15)</td>
<td>26 (17 to 34)</td>
<td>7 (8 to 11)</td>
<td>82</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>156</td>
<td>90 (76 to 96)</td>
<td>0 (0 to 0)</td>
<td>1 (0 to 5)</td>
<td>2 (1 to 6)</td>
<td>6 (3 to 13)</td>
<td>100</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>330</td>
<td>93 (80 to 98)</td>
<td>0 (0 to 0)</td>
<td>1 (0 to 4)</td>
<td>1 (0 to 4)</td>
<td>5 (2 to 12)</td>
<td>100</td>
</tr>
<tr>
<td>Postneonatal deaths</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All anomalies</td>
<td>2100</td>
<td>68 (61 to 74)</td>
<td>5 (4 to 6)</td>
<td>4 (3 to 5)</td>
<td>20 (16 to 22)</td>
<td>4 (3 to 5)</td>
<td>94</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>85</td>
<td>55 (38 to 70)</td>
<td>7 (4 to 11)</td>
<td>6 (3 to 10)</td>
<td>29 (22 to 34)</td>
<td>2 (1 to 7)</td>
<td>98</td>
</tr>
</tbody>
</table>

Continued
Table 2

<table>
<thead>
<tr>
<th>Anomaly</th>
<th>No deaths (100%)</th>
<th>CA</th>
<th>Infections</th>
<th>Immaturity</th>
<th>Other</th>
<th>Missing cause of death</th>
<th>Predicted proportion attributable to the CA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital heart defect</td>
<td>1329</td>
<td>75 (68 to 82)</td>
<td>4 (3 to 6)</td>
<td>3 (2 to 4)</td>
<td>15 (11 to 18)</td>
<td>3 (2 to 4)</td>
<td>97</td>
</tr>
<tr>
<td>Severe CHD</td>
<td>773</td>
<td>87 (79 to 93)</td>
<td>3 (2 to 5)</td>
<td>1 (0 to 2)</td>
<td>6 (4 to 10)</td>
<td>3 (2 to 6)</td>
<td>99</td>
</tr>
<tr>
<td>Transposition of great vessels (as only severe CHD)</td>
<td>27</td>
<td>100 (100 to 100)</td>
<td>0 (0 to 0)</td>
<td>0 (0 to 0)</td>
<td>0 (0 to 0)</td>
<td>0 (0 to 0)</td>
<td>97</td>
</tr>
<tr>
<td>VSD (without severe CHD)</td>
<td>289</td>
<td>67 (55 to 77)</td>
<td>5 (3 to 8)</td>
<td>5 (3 to 8)</td>
<td>20 (15 to 25)</td>
<td>2 (1 to 4)</td>
<td>96</td>
</tr>
<tr>
<td>ASD (without severe CHD)</td>
<td>169</td>
<td>56 (41 to 69)</td>
<td>2 (1 to 5)</td>
<td>8 (5 to 11)</td>
<td>30 (23 to 35)</td>
<td>4 (2 to 7)</td>
<td>96</td>
</tr>
<tr>
<td>AVSD</td>
<td>199</td>
<td>84 (67 to 93)</td>
<td>4 (2 to 7)</td>
<td>1 (0 to 3)</td>
<td>9 (5 to 16)</td>
<td>3 (1 to 6)</td>
<td>99</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>85</td>
<td>98 (66 to 100)</td>
<td>1 (0 to 9)</td>
<td>0 (0 to 6)</td>
<td>1 (0 to 12)</td>
<td>0 (0 to 6)</td>
<td>97</td>
</tr>
<tr>
<td>Coarctation of aorta</td>
<td>130</td>
<td>86 (67 to 95)</td>
<td>5 (2 to 11)</td>
<td>0 (0 to 0)</td>
<td>6 (2 to 12)</td>
<td>4 (1 to 10)</td>
<td>98</td>
</tr>
<tr>
<td>Cleft lip with or without cleft palate</td>
<td>53</td>
<td>66 (45 to 80)</td>
<td>2 (0 to 9)</td>
<td>0 (0 to 0)</td>
<td>26 (17 to 33)</td>
<td>6 (2 to 12)</td>
<td>88</td>
</tr>
<tr>
<td>Cleft palate</td>
<td>76</td>
<td>70 (49 to 84)</td>
<td>3 (1 to 8)</td>
<td>3 (1 to 8)</td>
<td>16 (10 to 21)</td>
<td>9 (5 to 15)</td>
<td>95</td>
</tr>
<tr>
<td>Oesophageal atresia</td>
<td>45</td>
<td>66 (39 to 84)</td>
<td>5 (1 to 11)</td>
<td>0 (0 to 0)</td>
<td>26 (17 to 33)</td>
<td>9 (4 to 16)</td>
<td>97</td>
</tr>
<tr>
<td>Diaphragmatic hernia (isolated cases)</td>
<td>12</td>
<td>83 (39 to 98)</td>
<td>8 (1 to 30)</td>
<td>0 (0 to 0)</td>
<td>8 (1 to 30)</td>
<td>0 (0 to 0)</td>
<td>97</td>
</tr>
<tr>
<td>Gastrochisis (isolated cases)</td>
<td>20</td>
<td>82 (31 to 98)</td>
<td>5 (1 to 17)</td>
<td>5 (1 to 17)</td>
<td>5 (1 to 17)</td>
<td>5 (1 to 17)</td>
<td>94</td>
</tr>
<tr>
<td>Multicystic renal dysplasia</td>
<td>11</td>
<td>41 (5 to 90)</td>
<td>0 (0 to 0)</td>
<td>24 (4 to 41)</td>
<td>36 (6 to 54)</td>
<td>0 (0 to 0)</td>
<td>72</td>
</tr>
<tr>
<td>Down syndrome</td>
<td>165</td>
<td>71 (53 to 84)</td>
<td>6 (3 to 10)</td>
<td>5 (2 to 8)</td>
<td>16 (9 to 23)</td>
<td>2 (1 to 5)</td>
<td>96</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>35</td>
<td>94 (69 to 99)</td>
<td>0 (0 to 0)</td>
<td>0 (0 to 0)</td>
<td>3 (0 to 15)</td>
<td>3 (0 to 15)</td>
<td>100</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>136</td>
<td>93 (77 to 98)</td>
<td>0 (0 to 0)</td>
<td>1 (0 to 5)</td>
<td>1 (0 to 6)</td>
<td>5 (2 to 13)</td>
<td>100</td>
</tr>
</tbody>
</table>

Child deaths (1–9 years)

<table>
<thead>
<tr>
<th>Anomaly</th>
<th>No deaths 1–9 years (100%)</th>
<th>CA</th>
<th>Infections</th>
<th>Neoplasms</th>
<th>Nervous</th>
<th>Other</th>
<th>Missing cause of death</th>
<th>Predicted proportion attributable to the CA</th>
</tr>
</thead>
<tbody>
<tr>
<td>All anomalies</td>
<td>1087</td>
<td>49 (42 to 57)</td>
<td>9 (8 to 10)</td>
<td>5 (4 to 6)</td>
<td>9 (8 to 11)</td>
<td>23 (21 to 26)</td>
<td>4 (3 to 5)</td>
<td>99</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>66</td>
<td>49 (25 to 73)</td>
<td>13 (7 to 18)</td>
<td>7 (3 to 11)</td>
<td>10 (5 to 15)</td>
<td>17 (10 to 21)</td>
<td>5 (2 to 10)</td>
<td>100</td>
</tr>
<tr>
<td>Congenital heart defect</td>
<td>474</td>
<td>63 (54 to 72)</td>
<td>8 (6 to 10)</td>
<td>3 (2 to 4)</td>
<td>4 (3 to 5)</td>
<td>19 (16 to 22)</td>
<td>3 (2 to 5)</td>
<td>99</td>
</tr>
<tr>
<td>Severe CHD</td>
<td>258</td>
<td>79 (67 to 87)</td>
<td>5 (3 to 8)</td>
<td>1 (0 to 3)</td>
<td>2 (1 to 4)</td>
<td>10 (7 to 13)</td>
<td>3 (2 to 6)</td>
<td>100</td>
</tr>
<tr>
<td>VSD (without severe CHD)</td>
<td>100</td>
<td>48 (31 to 66)</td>
<td>13 (9 to 17)</td>
<td>6 (3 to 10)</td>
<td>6 (3 to 10)</td>
<td>24 (18 to 27)</td>
<td>2 (1 to 6)</td>
<td>99</td>
</tr>
<tr>
<td>ASD (without severe CHD)</td>
<td>81</td>
<td>44 (28 to 61)</td>
<td>10 (6 to 13)</td>
<td>7 (4 to 11)</td>
<td>2 (1 to 6)</td>
<td>31 (25 to 32)</td>
<td>5 (2 to 9)</td>
<td>99</td>
</tr>
<tr>
<td>AVSD</td>
<td>70</td>
<td>79 (60 to 90)</td>
<td>6 (2 to 12)</td>
<td>0 (0 to 0)</td>
<td>0 (0 to 0)</td>
<td>11 (6 to 18)</td>
<td>4 (2 to 10)</td>
<td>99</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>51</td>
<td>71 (42 to 87)</td>
<td>10 (5 to 15)</td>
<td>2 (0 to 8)</td>
<td>2 (0 to 8)</td>
<td>12 (6 to 17)</td>
<td>4 (1 to 10)</td>
<td>100</td>
</tr>
</tbody>
</table>

Continued
A study in the USA, using information from death certificates, estimated that trisomy 18 and CHD were the two most common causes of infant death due to CAs in term born infants, accounting for 11% and 15% of CA deaths, respectively. In our study, the comparable figures using the diagnosed anomalies of the infants (not the anomalies recorded on the death certificates) are 8% for trisomy 18 and 32% for severe CHD. Inaccuracies on death certificates are expected with the accuracy depending on the person completing the form. The 60% of exact codes for children with a CHD in our study is similar to the 70% recorded by a recent study from the USA on infants with CHD. As the study was conducted by standardising the data in all registries and then providing syntax scripts to analyse it, it was not possible to redefine more meaningful categories. In addition, four registries were only able to provide one cause of death, which may not have been the underlying cause of death.

Strengths

The strength of this study is that it included data from 13 population-based CA registries in six European countries. The analysis of linked cases enabled direct comparisons of the recorded anomaly codes on the death certificates with the CA diagnosis reported in the CA registries, assumed to be the gold standard. Earlier analyses of EUROCAT data enabled attributable proportions to be estimated for the same CAs.

Limitations

A limitation of the study is that a child may have several anomalies and the one of interest may not be the underlying cause of death. Another limitation was the cause of death for infants was categorised into only seven categories resulting in the ‘all other conditions’ being heterogeneous including neoplasms, metabolic disorders, infections, jaundice and endocrine disorders. This unfortunately limits the interpretation of the data as it was not possible to redefine more meaningful categories. In addition, four registries were only able to provide one cause of death, which may not have been the underlying cause of death. A limitation of the study is that a child may have several anomalies and the one of interest may not be the underlying cause of death. Another limitation was the cause of death for infants was categorised into only seven categories resulting in the ‘all other conditions’ being heterogeneous including neoplasms, metabolic disorders, infections, jaundice and endocrine disorders. This unfortunately limits the interpretation of the data as it was not possible to redefine more meaningful categories. In addition, four registries were only able to provide one cause of death, which may not have been the underlying cause of death.
CONCLUSION

Data on the underlying cause of death from death certificates alone are not sufficient to evaluate the burden of CAs on infant and childhood mortality across countries and over time. Linked data from CA registries and death certificates are necessary for obtaining accurate estimates.

Author affiliations

1Malformation Monitoring Centre Saxony-Anhalt, Medical Faculty, Otto von Guericke Universität Magdeburg, Magdeburg, Germany
2Population Health Research Institute, St George’s University of London, London, UK
3Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, UK
4Fondazione Toscana Gabriele Monasterio, Pisa, Italy
5Unit of Epidemiology of Rare Diseases and Congenital Anomalies, Institute of Clinical Physiology National Research Council, Pisa, Italy
6Department of Paediatrics and Adolescent Medicine, Lillebaelt Hospital - University Hospital of Southern Denmark, Kolding, Denmark
7Centre for Maternal, Fetal and Infant Research, Institute of Nursing and Health Research, Ulster University, Belfast, UK
8Health Division of Gipuzkoa, Biodonostia Health Research Institute, Donostia-San Sebastian, Spain
9OMNI-Net for Children International Charitable Fund, Rivne Regional Medical Diagnostic Center, Rivne, Ukraine
10Neonatal Intensive Care Unit, Paediatric Section, IMER Registry (Emilia Romagna Registry of Birth Defects), Dep. of Medical Sciences, University of Ferrara, Ferrara, Italy
11Centre of Excellence for Reproductive and Regenerative Medicine, Children’s Hospital Zagreb, Medical School University of Zagreb, Zagreb, Croatia
12Rare Diseases Research Join Unit, Foundation for the Promotion of Health and Biomedical Research and Universitat de Valencia, Valencia, Spain
13Department of Genetics, Groningen University, Groningen, The Netherlands
14Malta Congenital Anomalies Register, Directorate for Health Information and Research, Ta’Picċà, Malta
15Department of Knowledge Brokers, THL Finnish Institute for Health and Welfare, Helsinki, Finland

Figure 3  Anomaly codes on death certificates for children with a major congenital anomaly dying before their 10th birthday according to the acceptability of the ICD-9/ICD-10 code recorded (number of deaths). CHD, congenital heart defect; GA, gestational age; PDA, patent ductus arteriosus; ICD-9/ICD-10, version 9/10 of the International Classification of Diseases.

- Pulmonary valve stenosis (33)
- Limb reduction defects (165)
- Pulmonary valve atresia (109)
- Congenital hydronephrosis (206)
- PDA as only CHD in term infants (GA +37 weeks) (77)
- Atrial septal defect (403)
- Double outlet right ventricle (109)
- Coarctation of aorta (98)
- Cleft palate (238)
- Single ventricle (98)
- Cleft lip with or without cleft palate (193)
- Mitral valve anomalies (177)
- Craniosynostosis (50)
- Ventricular Septal Defect (740)
- Severe microcephaly (194)
- Hydrocephalus (289)
- Anorectal atresia and stenosis (142)
- Hypoplastic right heart (37)
- Total anomalous pulmonary venous return (112)
- Coarctation of aorta (362)
- Multicystic renal dysplasia (109)
- Desmoplastic atresia (178)
- Aortic valve atresia/stenosis (156)
- Duodenal atresia or stenosis (65)
- Atrioventricular septal defect (422)
- Cystic adenomatous malformation of lung (17)
- Hirschsprung’s disease (10)
- Bilateral renal agenesis (155)
- Atresia of bile ducts (59)
- Tetralogy of Fallot (199)
- Encephalocoele (50)
- Omphalocele (143)
- Atrioventricular/atrioventricular (85)
- Down syndrome (365)
- Common arterial truncus (106)
- Trans. of great vessels (143)
- Hypoplastic left heart (590)
- Congenital Heart Defects (3780)
- Spina Bifida (28)
- Diaphragmatic hernia (201)
- Anencephaly (123)
- Trisomy 18 (483)
- Trisomy 13 (195)
- Gastroschisis (51)
Contributors JT, Arltssmann, SVG, JR, ML, JM and EG conceptualised and designed the study, coordinated and supervised data collection, carried out the initial analyses, drafted the initial manuscript and reviewed and revised the manuscript. AP, MS, AC, JG and AReid designed the data collection instruments, the initial analyses, drafted the initial manuscript and reviewed and revised the manuscript. JT, JT, and license their derivative works on different terms, provided the original work is

AJN, DST, DGW, LY and OZ collected data, and critically reviewed the manuscript. AP, MS, AC, JG and AReid designed the data collection instruments, the initial analyses, drafted the initial manuscript and reviewed and revised the manuscript. AP, MS, AC, JG and AReid designed the data collection instruments, the initial analyses, drafted the initial manuscript and reviewed and revised the manuscript.

Funding This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No. 733001.

Disclaimer The views presented here are those of the authors only

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval All EUROCAT registries obtained ethical, governance and other permissions for the data linkage according to their national legislations and arrangements. University of Ulster obtained Ethics permission for the Central Results Repository on 15 September 2017 (Institute of Nursing and Health Research Ethics Filter Committee, number FCNUR-17-0000).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The aggregate data that support the findings of this study are available from the authors for scientifically valid requests and with permission of the participating registries of congenital anomalies. To apply for the data, please see https://www.eurocat.cc/contactinformationanddatarequest.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs

Anke Rissmann http://orcid.org/0000-0002-9437-2790
Joachim Tan http://orcid.org/0000-0003-0462-4761
Ingeborg Barisic http://orcid.org/0000-0002-9805-6747
Clara Caverio-Carboneb http://orcid.org/0000-0002-4856-6456
Stine Kjaer Uinho http://orcid.org/0000-0002-2069-9723
Joan Morris http://orcid.org/0000-0002-7164-612X

REFERENCES


