Ten-Year Survival of Children With Congenital Anomalies: A European Cohort Study

Svetlana V. Glinianaia, MD, a Judith Rankin, PhD, b Anna Pierini, BSc, c Alessio Coi, PhD, d Michele Santoro, MSc, e Joachim Tan, PhD, f Abigail Reid, MA, g Esther Garne, MD, h Maria Loane, PhD, i Joanne Given, PhD, j Nathalie Lelongs, MSc, k Clara Cavero-Carbonell, PhD, l Hermien J. K. de Walle, PhD, m Miriam Gatt, MD, MSc, n Mika Gissler, MPH, o David Tucker, MPH, p Anna Heino, MSSc, MA, q Babak Khoshnood, MD, PhD, r Kari Klungsøyer, MD, PhD, s Nathalie Lelong, MSc, t Amanda J. Neville, BSc, u Daniel S. Thayer, MDiv, v David Tucker, MPH, w Stine K. Urhøj, PhD, MSc, x Diana Wellesley, FRCP, y Oscar Zurriaga, PhD, z Joan K. Morris, PhD

OBJECTIVES: To investigate the survival up to age 10 for children born alive with a major congenital anomaly (CA).

METHODS: This population-based linked cohort study (EUROlinkCAT) linked data on live births from 2005 to 2014 from 13 European CA registries with mortality data. Pooled Kaplan-Meier survival estimates up to age 10 were calculated for these children (77,054 children with isolated structural anomalies and 4011 children with Down syndrome).

RESULTS: The highest mortality of children with isolated structural CAs was within infancy, with survival of 97.3% (95% confidence interval [CI]: 96.6%–98.1%) and 96.9% (95% CI: 96.0%–97.7%) at age 1 and 10, respectively. The 10-year survival exceeded 90% for the majority of specific CAs (27 of 32), with considerable variations between CAs of different severity. Survival of children with a specific isolated anomaly was higher than in all children with the same anomaly when those with associated anomalies were included. For children with Down syndrome, the 10-year survival was significantly higher for those without associated cardiac or digestive system anomalies (97.6%; 95% CI: 96.5%–98.7%) compared with children with Down syndrome associated with a cardiac anomaly (92.3%; 95% CI: 89.4%–95.3%), digestive system anomaly (92.8%; 95% CI: 87.7%–98.2%), or both (88.6%; 95% CI: 83.2%–94.3%).

CONCLUSIONS: Ten-year survival of children born with congenital anomalies in Western Europe from 2005 to 2014 was relatively high. Reliable information on long-term survival of children born with specific CAs is of major importance for parents of these children and for the health care professionals involved in their care.
Congenital anomalies (CAs) are a major cause of perinatal, neonatal, and infant mortality in high-income countries, including the United States and Western European countries.1–4 Their contribution to mortality in children <5 years5,6 and in older children7 is also significant. Evidence from a 15-year time trend analysis (2001–2015) of preventable child mortality in 34 members of the Organization for Economic Co-operation and Development, including the United States, Canada, Japan, Australia, New Zealand, and Europe, showed that congenital heart defects (CHDs) were the second leading cause of mortality in infancy (<1 year), the leading cause of mortality in children aged 1 to 4 years, and the third cause in older children (5–14 years old).8 Globally, after a reduction of child mortality because of communicable diseases, the relative contribution of CAs to child mortality is increasing.5,9,10 Despite the global decline in infant and child mortality,9,11 a large variation in child death rates exists between countries, including Western Europe.12 Because of considerable length and costs of long-term follow-up studies, there is less research on survival beyond the first year of life, particularly for rare types of CAs. We found no published studies from Western Europe that summarized and compared survival of children with specific CAs aged beyond 1 year. Given that the significantly increased mortality of children born with CAs compared with the general population is not restricted to infancy,13,14 this research is of major public health importance.

This multicenter, population-based, linked cohort European study aimed to investigate the survival up to age 10 of children born with a major CA from 2005 to 2014 by linking data on live births from 13 European Surveillance of Congenital Anomalies15,16 (EUROCAT) registries to mortality data. This study was part of the EUROLinkCAT project that aimed to investigate the survival, morbidity, and educational outcomes of European children born with major CAs by linking live births with CAs to electronic administrative, health care, and education databases.17

METHODS
Setting and Population
Initially, 21 population-based EUROCAT registries agreed to participate in the EUROLinkCAT project.17 Three registries were unable to obtain linked data within the given time frame, whereas the data linkage in 3 other registries was not considered of sufficient quality.18 An additional registry (Belgium: Antwerp) was not included in this analysis because it did not provide death data beyond infancy and for some specific CAs because of their country’s restrictions on releasing small numbers. Survival of children from the only EUROCAT registry in Eastern Europe (Ukrainian OMNI-Net) was considerably lower compared with all other registries. Because childhood mortality is higher in Eastern than in Western Europe,19 and because OMNI-Net was the only registry from Eastern Europe, it was decided to limit the analysis to Western European registries.

All live-born children with a major CA born between January 1, 1995, and December 31, 2014, recorded in the 13 registries were linked to mortality sources up to the child’s 10th birthday or to December 31, 2015, whichever was earlier. Given observed increases in survival for births from 2005 to 2014 compared with 1995 to 2004 (Santoro M et al, submitted for publication on July 20, 2021) and improved linkage quality in the later decade,18 this study restricted the analysis to births between 2005 and 2014 (2007–2014 for the Valencian Region; 2008–2014 for Emilia Romagna) (Table 1) to provide the most up-to-date survival estimates.

Data Linkage
The EUROCAT registries have ethics permissions and procedures for routine surveillance, data collection, and transmission of anonymized data to a central database, according to national guidelines. Twelve CA registries sought local ethics approvals or other permissions to link their data with local mortality sources; 1 registry (Norway) obtained permission to use data they had already linked.

Registries linked their CA data to either national/vital statistics or to mortality records only. Linkage to national and vital statistics provided information on the vital status of all linked children (dead or alive) and, hence, a measure of successful linkage. Conversely, only registered deaths could be ascertained from mortality records; that is, children without death certificates were assumed to be alive, although it could have been a linkage failure. A detailed description of the linkage process and results is provided elsewhere.18 Data were only included in this paper from those registries where the linkage success was >85% for all years; for 5 registries, it was ≥99%.

Classification of Congenital Anomalies and Definitions
All major CAs were coded using the International Statistical Classification of Diseases and Related Health Problems, 10th Revision20 or 9th Revision, and categorized by CA group and subgroup (the organ system affected and the individual disorder).
following the EUROCAT guidelines. Children with only minor anomalies, defined in EUROCAT as those with lesser medical, functional, or cosmetic consequences for the child (eg, clinodactyly), were not included. For each CA subgroup, all children with the specified anomalies were included and those with an isolated anomaly only were identified, resulting in 2 groups for analysis: “All” and “Isolated.” An isolated CA was defined as a structural CA in one organ system only or as part of a known sequence (eg, renal agenesis with pulmonary hypoplasia). A child classified as having an isolated anomaly may be included in >1 anomaly subgroup within the same organ system (eg, esophageal atresia and anal atresia). The EUROCAT hierarchical computer algorithm for classification of major CAs was used without a manual clinical review of the identified potential multiple CAs. This article is focused on relatively common structural CAs in live births (live birth prevalence ≥1 per 10 000) and Down syndrome as the most common chromosomal anomaly (Supplemental Table 4).17

### Statistical Analysis

In addition to the standardized EUROCAT variables, a common data model was developed to standardize the local variables obtained from linkage. This enabled centrally written syntax scripts for checking the linkage quality and for the analysis of mortality data to be run by all registries.17 The statistical analysis consisted of 2 stages. First, the probability of survival at specific ages (7 days, 28 days, 3 months, 6 months, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 years) was calculated for each CA subgroup using Kaplan-Meier survival analysis, which takes into account the censoring of the data that occurred mainly because of the end of follow-up being December 31, 2015. This analysis was performed on individual case data by the registries locally using the centrally written syntax script. Registries then uploaded the Kaplan-Meier survival estimates with 95% confidence intervals (CIs), the number at risk, and the number of deaths at each age for each CA subgroup to the Central Results Repository at Ulster University, United Kingdom, using a secure Web platform. No individual case data were uploaded. The second stage involved pooling these data by meta-analysis to produce projectwide estimates.

### Meta-Analysis

The Kaplan-Meier survival estimates were combined in a random-effects meta-analysis to estimate the overall survival for each CA subgroup by modifying a method proposed by Combescure et al.17 Combescure

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**TABLE 1 Contributing EUROCAT Registries (Listed by Mortality Source), Birth Years and Population Covered, Number of All Live Births With Congenital Anomalies (CAs) Available for Analysis, and Live Birth Prevalence of All CA Cases (Per 10 000 Live Births)**

| Participating Population-Based Registries | Included Birth Years | Birth Population Covered | Number of All Live Births With CAs Available for Analysis | Live Birth Prevalence of All CAs Per 10 000 Live Births (95% CI) |
|------------------------------------------|----------------------|--------------------------|-----------------------------------------------------------|---------------------------------------------------------------|
| Registries which linked to national and vital statistics | | | | |
| Denmark: Funen | 2005–2014 | 50,093 | 1,190 | 241.8 (228.3–255.8) |
| Finland | 2005–2014 | 594,212 | 24,554 | 454.7 (448.3–460.1) |
| France: Paris | 2005–2014 | 264,879 | 5734 | 218.6 (213.0–224.3) |
| Italy: Emilia Romagna | 2008–2014 | 282,094 | 5589 | 204.8 (198.6–210.2) |
| Italy: Tuscany | 2005–2014 | 299,869 | 4312 | 158.7 (154.2–163.3) |
| Netherlands: Northern | 2005–2014 | 173,671 | 3810 | 229.7 (222.7–237.0) |
| Norway | 2005–2014 | 607,585 | 15,010 | 233.8 (229.3–237.6) |
| United Kingdom | | | | |
| East Midlands and South Yorkshire | 2005–2012 | 586,611 | 9274 | 161.9 (158.7–165.2) |
| Thames Valley | 2005–2013 | 270,327 | 3854 | 148.3 (141.7–150.9) |
| Wessex | 2005–2014 | 298,159 | 4015 | 147.3 (143.0–151.7) |
| Wales | 2005–2014 | 347,032 | 10,341 | 291.2 (285.5–296.9) |
| Registries which linked to mortality records | | | | |
| Malta | 2005–2014 | 41,155 | 1191 | 288.2 (272.0–305.1) |
| Spain: Valencian Region | 2007–2014 | 403,099 | 7388 | 180.1 (176.0–184.3) |
| Total | | 4,218,786 | 96,263 | |

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* Extracted from the EUROCAT Web site: https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence_en. Accessed May 2, 2021.
* Regional registries.
* Mortality records only include death registration, and live births who remain alive will not have a record.
* National registries.
proposed the random-effects meta-analysis of survival curves by using the DerSimonian and Laird multivariate procedure on arc-sine transformations of the conditional survival probabilities with a continuity correction of 0.25. However, when analyzed by individual CA subgroups, low numbers of cases in each registry and relatively low death rates for certain CA subgroups resulted in 100% survival for all registries for certain age years. By applying the method above, the model estimated a decrease in survival at these ages despite no deaths occurring, resulting in an underestimation of the overall survival. We therefore applied 3 adaptations. Firstly, instead of using the fixed continuity correction of 0.25 within the arc-sine transformation, a variable continuity correction equal to $1/n$ (the number of children alive at the start of the period) was used. This allowed the continuity correction to shrink with increasing sample sizes, while simultaneously reducing the overweighting of high survivals when sample sizes are small, which occurs because of the multivariate meta-analytic technique. This reduced the bias introduced into the country-level estimates when their samples sizes were $\geq 6$ children. Secondly, data were excluded from the analysis if there were $<6$ children alive with the specified anomaly in a registry at a certain age. This was required because even the variable $1/n$ continuity correction still introduced bias for sample sizes $<6$. Thirdly, if no deaths occurred in any of the registries after a certain age, the overall survival for the remaining ages was imputed as the survival rate for the previous time period. This is a logical assumption because no deaths had been observed. In scenarios where there were no deaths in any registry during specific ages (e.g., ages 3 and 4), but deaths did occur in later time periods, the meta-analyses were run on a reduced number of time points to limit the prevalence of the “no death” time periods. In these scenarios, instead of the 9 yearly time points, average survival was calculated between ages 1 to 5 and 6 to 10. This preserved the use of all the data but reduced the number of time points in which continuity corrections would introduce significant bias. All meta-analyses were performed using R software.

Sensitivity analyses were performed excluding each registry in turn to determine if the overall survival estimates differed significantly.

**Results**

Table 1 shows that 13 registries from 9 countries covering a population of 4,218,786 births from 2005 to 2014 provided survival data for 96,263 live births with a major CA.

Table 2 shows pooled survival estimates (with 95% CI) from ages 1 week to 10 years for children in the isolated group ($n = 77,054$) in 32 specific CA subgroups. Overall, 10-year survival of children with any isolated CA was 96.9% (95% CI: 96.0%–97.7%). As expected, the highest mortality was within the first year of life; survival did not substantially decline after the first year for most CA subgroups. There was considerable variation in survival among individual CA subgroups. Ten-year survival varied from 51.6% (95% CI: 44.9%–59.4%) for hypoplastic left heart (HLH) to 99.8% (95% CI: 99.6%–100.0%) for cleft lip with or without cleft palate. Overall, 10-year survival across Europe was >90% for all but 5 isolated CA subgroups analyzed (27 of 32).

Table 2 also shows survival for children with Down syndrome ($n = 4011$) with or without CHD or digestive system anomaly. Compared with the highest 10-year survival in children with Down syndrome without associated CHD or digestive system anomaly of 97.6% (95% CI: 96.5%–98.7%), survival was significantly lower when Down syndrome was associated with any CHD but not digestive system anomaly ($P < .001$), with any digestive system anomaly but not CHD ($P = .018$), and with both CHD and digestive system anomaly ($P < 0.001$).

In the sensitivity analysis, the pooled survival estimates were robust to the exclusion of data from individual registries for most
| Congenital Anomaly Groups and Subgroups | No. Live Births | No. Deaths Up to 10 y | Survival Estimates % (95% CI) |
|----------------------------------------|----------------|----------------------|-------------------------------|
| **Any isolated anomaly**<sup>a</sup>   | 77,054         | 2002                 | 98.8 (98.5–99.2)              |
| Nervous System                         |                |                      |                               |
| Spina bifida                           | 370            | 12                   | 98.3 (96.8–99.7)              |
| Congenital hydrocephalus (excluding spina bifida) | 767            | 59                   | 97.5 (95.7–99.4)              |
| Severe microcephaly<sup>b</sup>        | 361            | 19                   | 99.0 (97.6–100.0)             |
| Eye                                    |                |                      |                               |
| Congenital cataract                     | 560            | 4                    | 99.8 (99.5–100.0)             |
| Congenital Heart Defects (CHD)         |                |                      |                               |
| All CHD                                | 27,654         | 951                  | 98.8 (98.5–99.2)              |
| Severe CHD                             | 5952           | 718                  | 96.5 (95.7–97.3)              |
| Transposition of great vessels         | 1151           | 108                  | 97.5 (96.2–98.7)              |
| Ventricular septal defect              | 15,990         | 255                  | 99.8 (99.6–99.9)              |
| Atrial septal defect                   | 4594           | 119                  | 99.7 (99.5–99.9)              |
| Atrioventricular septal defect         | 484            | 70                   | 97.9 (96.5–99.3)              |
| Tetralogy of Fallot                    | 868            | 42                   | 99.6 (99.1–100.0)             |
| Pulmonary valve stenosis               | 1688           | 45                   | 99.9 (99.7–100.0)             |
| Aortic valve atresia/stenosis          | 576            | 58                   | 98.7 (97.4–100.0)             |
| Mitral valve anomalies                 | 453            | 52                   | 96.8 (94.7–98.0)              |
| Hypoplastic left heart                 | 515            | 237                  | 79.5 (70.5–89.7)              |
| Coarctation of aorta                   | 1450           | 101                  | 99.2 (98.6–99.8)              |
| Patent ductus arteriosus as only CHD in term infants (≥37 wk) | 1201           | 13                   | 99.8 (98.6–100.0)             |
| Respiratory system                     |                |                      |                               |
| Cystic adenomatous malformation of lung| 349            | 7                    | 99.1 (98.1–100.0)             |
| Orofacial clefts                       |                |                      |                               |
| Cleft lip with or without cleft palate | 2811           | 14                   | 99.9 (99.8–100.0)             |
| Digestive system                       |                |                      |                               |
| Esophageal atresia with or without tracheo-esophageal fistula | 451            | 22                   | 98.8 (97.6–100.0)             |
| Duodenal atresia or stenosis           | 270            | 6                    | 99.9 (99.4–100.0)             |
| Atresia or stenosis of other parts of small intestine | 282            | 17                   | 98.9 (97.7–100.0)             |
| Anorectal atresia and stenosis         | 432            | 8                    | 99.5 (98.7–100.0)             |
| Diaphragmatic hernia                   | 565            | 150                  | 81.4 (77.8–85.2)              |
| Abdominal wall                         |                |                      |                               |
| Gastroscisis                           | 945            | 31                   | 98.7 (97.7–99.8)              |
| Omphalole                            | 274            | 23                   | 97.4 (95.0–99.9)              |
specific CAs (within ±2.5%, but mostly within ±1%), except for severe microcephaly (Wales registry: 5.7%) and HLH (Finland registry: 3.6%) (Supplemental Table 5).

Table 3 shows 10-year survival estimates for children in the All group and the proportion of children with isolated CAs in all live births and deaths with the specified CAs. Of a total of 4214 deaths, 49% occurred in children with CHD and 30% in children with severe CHD; 5.9% of deaths occurred in children with diaphragmatic hernia. Tables 2 and 3 show that 5.4% of all deaths were in children with Down syndrome (226 of 4214). In Table 3, for “any CA,” although 80% of live births were in children with isolated CAs, only 47.5% of deaths occurred in these children, indicating the higher survival in children with an isolated CA (96.9%, Table 2) compared with All CA (94.8%, Table 3). The proportions of children with isolated CAs in all live births and all deaths differed by CA severity, being more similar for severe CAs (eg, HLH, atrioventricular septal defect, diaphragmatic hernia). This indicates that, for these anomalies, the death is most likely related to that specific CA, whereas in other CAs with large differences in proportions, the death is related to the associated anomalies and karyotype defect.

Survival curves are shown for children with more common
| CA Groups and Subgroups | Number of All Live Births | Number of All Deaths Up to 10 y | Survival Estimates at 10 y of Age % (95% CI) | Proportion of Children With Isolated CA (%) within the “All” Group With Specified CAs |
|-------------------------|--------------------------|-------------------------------|-----------------------------------------------|---------------------------------------------------------------------|
| Any anomaly             | 96,263                   | 4,214                         | 94.8 (93.7–95.9)                               | 80.0                                                                |
| Nervous system          |                          |                               |                                               |                                                                     |
| Spina bifida            | 576                      | 39                            | 93.5 (90.7–96.3)                               | 64.2                                                                |
| Congenital hydrocephalus (excluding spina bifida) | 1,269 | 159 | 86.9 (81.7–92.3) | 60.4 |
| Severe microcephaly     | 798                      | 102                           | 85.0 (80.2–90.2)                               | 45.2                                                                |
| Eye                     |                          |                               |                                               |                                                                     |
| Congenital cataract     | 691                      | 37                            | 94.6 (91.8–97.5)                               | 81.0                                                                |
| CHD                     |                          |                               |                                               |                                                                     |
| All CHD                 | 34,874                   | 2052                          | 92.3 (90.2–94.5)                               | 79.3                                                                |
| Severe CHD              | 8024                     | 1,245                         | 83.3 (80.8–85.8)                               | 72.3                                                                |
| Transposition of great vessels | 1263 | 140 | 89.9 (87.1–92.8) | 89.5 |
| Ventricular septal defect | 19,093                | 727                           | 95.2 (93.5–96.9)                               | 83.7                                                                |
| ASD                     | 6427                     | 332                           | 94.5 (93.0–96.0)                               | 71.5                                                                |
| AVSD                    | 1,352                    | 244                           | 82.5 (79.3–85.9)                               | 35.8                                                                |
| Tetralogy of Fallot     | 1,249                    | 115                           | 92.7 (90.4–95.1)                               | 69.5                                                                |
| Pulmonary valve stenosis | 20,64                    | 96                            | 96.4 (94.9–98.0)                               | 81.8                                                                |
| Aortic valve atresia and stenosis | 896 | 81 | 89.9 (87.2–92.8) | 82.8 |
| Mitral valve anomalies  | 628                      | 98                            | 85.0 (80.7–89.6)                               | 72.1                                                                |
| HLH                     | 605                      | 289                           | 49.6 (42.7–57.5)                               | 85.1                                                                |
| Coarctation of aorta    | 1,879                    | 186                           | 89.6 (87.4–91.8)                               | 77.2                                                                |
| Patent ductus arteriosus as only CHD in term infants (≥37 wk) | 1,723 | 51 | 97.2 (95.8–98.7) | 69.6 |
| Respiratory system      |                          |                               |                                               |                                                                     |
| Cystic adenomatous malformation of lung | 412 | 15 | 97.2 (95.2–99.1) | 84.7 |
| Orofacial clefts        |                          |                               |                                               |                                                                     |
| Cleft lip with or without cleft palate | 3,325 | 106 | 97.4 (96.6–98.2) | 84.5 |
| Cleft palate            | 2,752                    | 147                           | 95.0 (93.7–96.3)                               | 68.4                                                                |
| Digestive system        |                          |                               |                                               |                                                                     |
| Esophageal atresia with or without tracheo-esophageal fistula | 1,004 | 122 | 89.5 (86.3–92.7) | 44.9 |
| Duodenal atresia or stenosis | 582 | 39 | 93.6 (90.5–96.8) | 48.0 |
| Atresia or stenosis of other parts of small intestine | 408 | 32 | 94.1 (91.0–97.3) | 69.5 |
| Anorectal atresia and stenosis | 1,097 | 91 | 92.7 (90.4–95.1) | 39.4 |

*Table 3 Pooled Survival Estimates at 10 Years of Age for All Children With the Specified Structural Congenital Anomalies (‘All’ Group) and the Proportion of Children With Isolated CAs in All Live Births and All Deaths With the Specified CAs: 13 EUROCAT Registries in 9 Western European Countries, 2005 to 2014*
DISCUSSION

This linked cohort study using population-based data on live births from 2005 to 2014 (n = 98,263) of a birth cohort in Western Europe provided survival estimates for children up to age 10. The survival of children born with specific isolated CAs was higher in our study for spina bifida, CHDs, orofacial clefts, esophageal atresia, anorectal atresia or stenosis, diaphragmatic hernia, abdominal wall defects, and limb reduction defects compared with published population-based studies from Europe, the United States, and Australia,27–33 and 2 systematic reviews.14,34 The higher survival is expected, as first, the published studies cover earlier birth cohorts and survival has improved over time partly because of improvements in prenatal diagnosis and consequent increase in terminations of pregnancy for more severe CAs; and second, survival has improved over time partly because of improvements in neonatal care. The number of live births or deaths for "any anomaly" is not equal to the sum of those for each CA subgroup because some CAs may belong to >1 CA subgroup, for example, an individual OHD may also be associated with severe OHD, and any anomaly may include other subgroups not listed in this table. The number of deaths from the Netherlands: Northern registry were rounded to 0 or 5 because of small number restrictions and therefore were not included in the numbers of live births and deaths but were included in the survival estimates. ASD, atrial septal defect; AVSD, atrioventricular septal defect; HLH, coartation of aorta; aortic atresia/interrupted aortic arch; total anomalous pulmonary venous return (see the corresponding International Statistical Classification of Diseases and Related Health Problems codes in Supplemental Table 1 and Morris et al17 for more rare CAs).

TABLE 3

Continued

| CA Groups and Subgroups | Number of All Live Births | Number of All Deaths Up to 10 y | Survival Estimates at 10 y of Age % (95% CI) | Proportion of Children With Isolateda CAs (%) Within the “All” Group With Specified CAs | Live Births | Deaths |
|-------------------------|---------------------------|-------------------------------|---------------------------------------------|-------------------------------------------------------------------------------------------------|-------------|--------|
| Diaphragmatic hernia     | 830                       | 249                           | 71.1 (67.4–75.0)                             | 48.1                                                                               | 60.2        |        |
| Abdominal wall           |                           |                               |                                             |                                                                                     |             |        |
| Gastrochisis             | 1056                      | 48                            | 96.0 (93.9–98.2)                             | 89.5                                                                               | 64.6        |        |
| Omphalocele              | 516                       | 90                            | 85.9 (79.5–88.5)                             | 53.1                                                                               | 25.8        |        |
| Urinary system           |                           |                               |                                             |                                                                                     |             |        |
| Multicystic renal dysplasia | 1277                  | 79                            | 94.5 (93.1–95.9)                             | 83.8                                                                               | 36.7        |        |
| Congenital hydronephrosis| 5699                      | 124                           | 98.1 (97.7–98.6)                             | 84.4                                                                               | 23.4        |        |
| Genital                  |                           |                               |                                             |                                                                                     |             |        |
| Hypospadia               | 8574                      | 87                            | 99.0 (98.6–99.3)                             | 85.0                                                                               | 31.0        |        |
| Limb                     | 1572                      | 84                            | 96.0 (94.0–98.1)                             | 54.8                                                                               | 13.1        |        |
| Musculoskeletal          |                           |                               |                                             |                                                                                     |             |        |
| Craniosynostosis         | 1257                      | 31                            | 97.9 (96.6–99.1)                             | 72.3                                                                               | 19.4        |        |

The number of live births or deaths for "any anomaly" is not equal to the sum of those for each CA subgroup because some CAs may belong to >1 CA subgroup, for example, an individual OHD may also be associated with severe OHD, and any anomaly may include other subgroups not listed in this table. The number of deaths from the Netherlands: Northern registry were rounded to 0 or 5 because of small number restrictions and therefore were not included in the numbers of live births and deaths but were included in the survival estimates. ASD, atrial septal defect; AVSD, atrioventricular septal defect; HLH, coartation of aorta; aortic atresia/interrupted aortic arch; total anomalous pulmonary venous return (see the corresponding International Statistical Classification of Diseases and Related Health Problems codes in Supplemental Table 1 and Morris et al17 for more rare CAs).

a For each anomaly subgroup, all children with the specified anomalies were included and those with an isolated anomaly only were identified. An isolated CA is defined as a structural CA in 1 organ system only or if coexisting anomalies were a consequence of a single primary anomaly.

b Reduction in the size of the brain with a head circumference >3 SDs below the mean for sex, gestational age, and ethnic origin (EUROCAT definition41).

c Severe CHD included the following CHD subgroups: common arterial trunk, double outlet right ventricle, transposition of great vessels, single ventricle, atrioventricular septal defect, tetralogy of Fallot, pulmonary valve atresia, tris-cuspid atresia and stenosis, Ebstein anomaly, hypoplastic right heart, aortic valve atresia and stenosis, mitral valve anomalies, HLH, coartation of aorta, aortic atresia/interrupted aortic arch, total anomalous pulmonary venous return (see the corresponding International Statistical Classification of Diseases and Related Health Problems codes in Supplemental Table 1 and Morris et al17 for more rare CAs).
second, some studies were not restricted to isolated anomalies. True differences in survival among different countries are also likely. A recent smaller Australian study analyzing 1- and 5-year survival for births from 2004 to 2009 reported comparable survival estimates for all isolated CAs and for some specific subgroups such as severe CHD and diaphragmatic hernia.30 Despite relatively high survival estimates at 4 weeks, 1 year, and 5 years for children born with isolated CAs reported in our paper, overall, they are still much lower compared with the average survival in the general European population of children at corresponding ages.35–37

Five- and 10-year survival of children with Down syndrome was also higher in our study compared with earlier studies26,38–40 and comparable to more recent ones.30,41,42 Presence of associated CHD in children with Down syndrome is an acknowledged risk factor for reduced long-term survival,14,39–43 although a significant improvement in survival of these children over time was recently reported.14 This European study also reports a significantly reduced survival of children with Down syndrome associated with CHD and/or digestive system anomalies compared with those without.

**Strengths**

This study has several strengths. We used high-quality data from specialist population-based registries of CAs that were linked to official mortality data sources, including data from national and vital statistics for 11 of 13 registries. Standardized approaches to data collection, coding, and classification in EUROCAT registries were enhanced by standardization of linked mortality data, creation of standardized syntax scripts, and generation of combined data sets and analytic results. This enabled the establishment of a large cohort of children with CAs in 13 regions of 9 Western European countries, increasing statistical power for the analysis of specific CAs and, thereby, the reliability of our findings. We developed a novel meta-analytic approach of analyzing survival data from several small samples to reduce bias arising as a result of the use of more standard techniques, which rely on the asymptotic
properties of estimates from larger samples.

**Limitations**

We were not able to include as many registries as originally planned because of barriers to gaining ethical approval, low linkage quality, or lack of survival data beyond 1 year. Despite relatively high linkage success, lack of 100% linkage in all registries may have resulted in an overestimate of the survival because of missed deaths. An overestimate of the pooled survival for children with severe microcephaly revealed by the sensitivity analysis after exclusion of the Wales registry may be because of a less stringent definition of severe microcephaly in Wales (<5th percentile instead of EUROCAT definition of <–3 SD). Higher survival of children with HLH in Finland may be because of higher prenatal detection rates, resulting in improved survival after the full implementation of the national ultrasound screening program from 2010.

The classification of CA into isolated and multiple CA was computer-based only, without manual expert review of the potential multiple CA cases, which could have resulted in some isolated CAs being misclassified as multiple CAs.

No formal comparison of 10-year survival among the isolated and nonisolated CAs could be performed because the Isolated and All groups were not mutually exclusive.

The participating registries do not cover all births in Western European countries, but we consider our results to be representative of Western Europe.

**CONCLUSIONS**

The accuracy of estimated long-term survival of children born with specific CAs is ensured by the use of common protocol for data collection, standardization, quality control, and registry-specific statistical analyses, as well as the development of the novel meta-analytic approach. Reliable information on long-term survival of children born with specific CAs is of major importance for counseling parents facing a prenatal diagnosis of CA, families living with a child affected by a CA, and for the health professionals involved in their care. The timely diagnosis of associated anomalies is essential for parental counseling because of their association with reduced survival. The geographical coverage should be widened in future European studies to produce findings that are more representative and generalizable for all of Europe.

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**ABBREVIATIONS**

CA: congenital anomaly  
CHD: congenital heart defect  
CI: confidence interval  
EUROCAT: European Surveillance of Congenital Anomalies  
HLH: hypoplastic left heart
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Address correspondence to Svetlana V. Glinianaia, MD, Faculty of Medical Sciences, Population Health Sciences Institute, Newcastle University, Baddiley-Clark Building, Richardson Road, Newcastle upon Tyne, NE2 4AX, United Kingdom. E-mail: svetlana.glinianaia@ncl.ac.uk

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