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

Svetlana V Glinianaia1, MD; Judith Rankin1, PhD; Anna Pierini2,3, BSc; Alessio Coi2, PhD; Michele Santoro2, MSc; Joachim Tan4, PhD; Abigail Reid4, MA; Ester Garne5, MD; Maria Loane6, PhD; Joanne Given6, PhD, MSc; Clara Cavero-Carbonell7, PhD; Hermien EK de Walle8, PhD; Miriam Gatt9, MD, MSc; Mika Gissler10, PhD; Anna Heino10, MSSc, MA; Babak Khoshnood11, MD, PhD; Kari Klungsøyr12,13, MD, PhD; Nathalie Lelong11, MSc; Amanda Neville14, BSc; Daniel S Thayer15, MDiv; David Tucker16, MPH; Stine K Urhøj5, PhD, MSc; Diana Wellesley17, FRCP; Oscar Zurriaga7, PhD; Joan K Morris4, PhD

**Affiliations**:

1Population Health Sciences Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom

2Unit of Epidemiology of Rare diseases and Congenital anomalies, Institute of Clinical Physiology, National Research Council, Pisa, Italy

3Fondazione Toscana Gabriele Monasterio, Pisa, Italy.

4Population Health Research Institute, St George’s, University of London, London, United Kingdom

5Pediatric Department, Hospital Lillebaelt, Kolding, Denmark

6Faculty of Life & Health Sciences, Ulster University, Northern Ireland, United Kingdom

7Rare Diseases Research Unit, Foundation for the Promotion of Health and Biomedical Research in the Valencian Region, Valencia, Spain

8Department of Genetics, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

9Malta Congenital Anomalies Registry, Department of Health Information and Research, Malta

10Information Services Department, THL Finnish Institute for Health and Welfare. Helsinki, Finland

11Université de Paris, Center of Research in Epidemiology and Statistics (CRESS), Obstetrical, Perinatal and Pediatric Epidemiology Research Team (EPOPé), INSERM, INRA, Paris, France

12Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway

13Division of Mental and Physical Health, Norwegian Institute of Public Health, Bergen, Norway

14Center for Clinical and Epidemiological Research, University of Ferrara, Ferrara, Italy

15Faculty of Health and Life Science, Swansea University, Swansea, United Kingdom

16Public Health Wales, Swansea, United Kingdom

17Wessex Clinical Genetics Service, Princess Anne Hospital, Southampton, United Kingdom

**Address correspondence to:** Svetlana V Glinianaia, Population Health Sciences Institute, Faculty of Medical Sciences, Newcastle University, Baddiley-Clark Building, Richardson Road, Newcastle upon Tyne, NE2 4AX, United Kingdom; Tel: +44 (0) 191 208 5891, [svetlana.glinianaia@ncl.ac.uk].

**Short title:** Survival of Children with Congenital Anomalies

**Conflict of Interest Disclosures**: The authors have no conflicts of interest relevant to this article to disclose.

**Funding/Support**: This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No. 733001 (Jan 2017 – Dec 2021) <https://ec.europa.eu/programmes/horizon2020/en>). 

**Role of the Funder/Sponsor:** The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, or review; and decision to submit the manuscript for publication. The views presented here are those of the authors only, and the European Commission is not responsible for any use that may be made of the information presented here.

**Abbreviations:** CA, congenital anomaly; CHD, congenital heart defect; CI, confidence interval; EUROCAT, European Surveillance of Congenital Anomalies; HLH, hypoplastic left heart; ICD-10, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision.

**Article summary**:

Through linkage of population-based European congenital anomaly registries’ and mortality databases, this study estimates 10-year survival of children born with 32 different structural congenital anomalies.

**What’s Known on This Subject**

Survival beyond infancy in children born with common congenital anomalies has been reported by individual studies, but long-term survival estimates for children with a wide range of specific congenital anomalies using standardized population-based multicenter data are lacking.

**What This Study Adds**

**This** population-based linked cohortstudy **from 13 regions within nine European countries (EUROlinkCAT) provided reliable survival estimates up to age 10 years for children with specific isolated and non-isolated structural congenital anomalies that are important for clinical practice and counseling.**

# Contributors' Statement:

Dr Glinianaia contributed to development of study methods, including data standardization and linkage, developed statistical analysis plan, performed the descriptive analysis, interpreted the results, drafted the initial manuscript, and reviewed and revised the manuscript.

Prof Rankin conceptualized and designed the study, contributed to obtaining funding, supervised the work, contributed to interpretation of the results, and reviewed and revised the manuscript.

Dr Pierini conceptualized and designed the study, contributed to obtaining funding, contributed to interpretation of the results, and critically reviewed the manuscript for important intellectual content.

Drs Coi and Santoro contributed to the data analysis and interpretation of the results, and critically reviewed the manuscript for important intellectual content.

Dr Tan contributed to development of study methods, including data standardization and data linkage, development of statistical analysis plan***,*** writing analysis programs,data analysis and interpretation of the results, and critically reviewed the manuscript for important intellectual content.

Ms Reid wrote analysis programs and contributed to data analysis, interpretation of the results, and critically reviewed the manuscript for important intellectual content.

Dr Garne contributed to obtaining funding, development of study methods, including data standardization and data linkage, to interpretation of the results, and critically reviewed the manuscript for important intellectual content.

Dr Loane contributed to obtaining funding, was responsible for data standardization and management of data linkage by the participating data providers, contributed to data analysis and interpretation of the results, and critically reviewed the manuscript for important intellectual content.

Dr Given contributed to development of study methods, including data standardization and data linkage, to interpretation of the results, and critically reviewed the manuscript for important intellectual content.

Drs Cavero-Carbonell, de Walle, Gatt, Khoshnood, Urhøj, Zurriaga, Professors Gissler, Klungsøyr, Mses Heino, Lelong, Neville, Wellesley and Mr Thayer and Mr Tucker were responsible for data linkage and standardization for their registries’ data and running centrally written syntax scripts for local analyses, and critically reviewed the manuscript for important intellectual content.

Prof Morris conceptualized and designed the study, obtained funding, developed study methods, including data standardization and linkage, supervised writing analysis programs, performed statistical analysis, supervised the work, drafted the initial manuscript, and reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for major aspects of the work.

# ABSTRACT

**Objectives:** To investigate the survival up to age 10 years for children born alive with a major congenital anomaly.

**METHODs:** Thispopulation-based linked cohort study (EUROlinkCAT) linked data on live births during 2005-2014 from 13 European congenital anomaly registries with mortality data. Pooled Kaplan-Meier survival estimates up to 10 years of age were calculated for these children (77,054 children with isolated structural anomalies and 4,011 children with Down syndrome).

**Results:** The highest mortality of children with isolated structural congenital anomalies was within infancy, with survival of 97.3% (95% CI: 96.6-98.1) and 96.9% (95% CI: 96.0-97.7) at age 1 and 10 years, respectively. The 10-year survival exceeded 90% for the majority of specific congenital anomalies (27/32), with considerable variations between congenital anomalies 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 to 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 during 2005-2014 was relatively high. Reliable information on long-term survival of children born with specific congenital anomalies 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 USA and Western European countires.1-4 Their contribution to mortality in children under 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 Organisation for Economic Co-operation and Development, including the USA, 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 1-4 years and the third cause in older children (5-14 years old).8 Globally, following a reduction of child mortality due to communicable diseases, the relative contribution of CAs to child mortality is increasing.6,9,10 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 Due to 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 one year. Given that the significantly increased mortality of children born with CAs compared to 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 10 years of age of children born with a major CA during 2005-2014 by linking data on live births from 13 EUROCAT (European network for the epidemiological surveillance of CAs15,16) 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, healthcare 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, while the data linkage in three other registries was not considered of sufficient quality.18 A further registry (Belgium: Antwerp) was not included in this analysis as it did not provide death data beyond infancy and for some specific CAs due to 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 to all other registries. As childhood mortality is higher in Eastern than in Western Europe,19 and as 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 1st January 1995 and 31st December 2014 recorded in the 13 registries were linked to mortality sources up to the child’s 10th birthday or to 31st December 2015, whichever was earlier. Given observed increases in survival for births in 2005-2014 compared with 1995-2004 (Santoro M et al, submitted for publication on 20.07.2021) and improved linkage quality in the later decade,18 this study restricted the analysis to births between 2005-2014 (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; one 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/vital statistics provided information on the vital status of all linked children (dead/alive) and hence a measure of successful linkage. Conversely, only registered deaths could be ascertained from mortality records, ie, 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 over 85% for all years; for five 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, Tenth Revision20 (ICD-10) or Ninth Revision (ICD-9) and categorized by CA group/subgroup (the organ system affected and the individual disorder), following the EUROCAT guidelines.21 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.22 For each CA subgroup, all children with the specified anomalies were included and those with an isolated anomaly only were identified resulting in two 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 more than one anomaly subgroup within the same organ system (eg, esophageal atresia and anal atresia). The EUROCAT hierarchical computer algorithm for classification of major CAs was used23,24 without a manual clinical review of the identified potential multiple CAs.

This paper 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 117).

## Statistical analysis

In addition to the standardized EUROCAT variables,17 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 two 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 due to the end of follow up being 31st December 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 (CI), the number at risk and the number of deaths at each age for each CA subgroup to the Central Results Repository at Ulster University, UK, using a secure web platform - no individual case data were uploaded. The second stage involved pooling these data by meta-analysis to produce project-wide 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.25 Combescure proposed the random-effects meta-analysis of survival curves by using the DerSimonian and Laird multivariate procedure26 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 three 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 due to the multivariate meta-analytic technique. This reduced the bias introduced into the country-level estimates when their samples sizes were six children and above. Secondly, data were excluded from the analysis if there were less than six children alive with the specified anomaly in a registry at a certain age. This was required as even the variable 1/n continuity correction still introduced bias for sample sizes below six. 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 as no deaths had been observed. In scenarios where there were no deaths in any registry during specific ages (for example 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 nine yearly time points (2-10) average survival was calculated between ages 1-5 and 6-10. 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.

**Comparison of 10-year survival between different congenital anomaly groups**

Four independent categories of children with Down syndrome were analyzed: those without associated CHD or digestive system anomaly, those with only a CHD, those with only a digestive system anomaly and those with both (other less common associated CAs were not considered). The 10-year survival estimates for each registry were analyzed using a random-effects meta-analysis comparing the three Down syndrome groups with an associated CHD and/or digestive system anomaly with the group without any of these CAs.

Ten-year survival estimates with 95% CI for ‘Isolated’ and for ‘All’ groups were plotted for selected CAs. No formal statistical tests were performed as the ‘All’ group included children in the ‘Isolated’ group.

Stata v16 (StataCorp LLC, 2019) was used for the above comparisons.

# RESULTS

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

Table 2 shows pooled survival estimates (with 95% CI) from 1 week to 10 years of age 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 between 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/without cleft palate. Overall, 10-year survival across Europe was over 90% for all but five isolated CA subgroups analyzed (27/32).

Table 2 also shows survival for children with Down syndrome (n=4011) with or without CHD or digestive system anomaly. Compared to 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*<0.001), with any digestive system anomaly but not CHD (*P*=0.018), 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 specific CAs (within ±2.5%, but mostly within ±1%), except for severe microcephaly (Wales registry: 5.7%) and HLH (Finland registry: 3.6%) (SupplementalTable 2).

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 (226/4214). 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, while in other CAs with large differences in proportions, the death is related to the associated anomalies/karyotype defect.

Survival curves are shown for children with more common selected CAs from different organ systems in the ‘Isolated’ and ‘All’ groups, clearly demonstrating the higher survival for children in the ‘Isolated’ group (Fig 1).

# DISCUSSION

This linked cohort study using population-based data on live births during 2005-2014 (n=96,263 from a birth population of 4,218,786) from 13 CA registries from Western Europe provided survival estimates for children up to age 10 years. The pooled 10-year survival was over 90% for the majority of isolated CA subgroups (27/32), with considerable variation in survival between specific CAs of different severity. Presence of associated anomalies considerably reduced survival in children with specific CAs. For children with Down syndrome, the 10-year survival was significantly higher for children without associated CHD or digestive system anomalies compared to children with these anomalies.

Survival of children born with specific isolated CAs was higher in our study for spina bifida, CHDs, orofacial clefts, esophageal atresia, anorectal atresia/stenosis, diaphragmatic hernia, abdominal wall defects and limb reduction defects compared to published population-based studies from Europe, USA and Australia27-33 and two 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 due to improvements in prenatal diagnosis and consequent increases in terminations of pregnancy for more severe CAs ([https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence\_en -](https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence_en%20-) 45.1 and 52.1 per 10,000 births in 1995-2004 and 2005-2014, respectively), and second, some studies were not restricted to isolated anomalies. True differences in survival between different countries are also likely. A recent smaller Australian study analyzing 1- and 5-year survival for births in 2004-2009 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 to 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 to earlier studies28,38-40 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 to 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/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 datasets and analytic results. This enabled the establishment of a large cohort of children with CAs from 13 regions of nine 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 from 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 due to barriers to gaining ethical approval, low linkage quality or lack of survival data beyond one year. Despite relatively high linkage success, lack of 100% linkage in all registries may have resulted in an overestimate of the survival due to 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 due to a less stringent definition of severe microcephaly in Wales (<5th percentile instead of EUROCAT definition of <−3SD).44,45 Higher survival of children with HLH in Finland may be due to higher prenatal detection rates resulting in improved survival after the full implementation of the national ultrasound screening programme from 2010.46,47

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.23

No formal comparison of 10-year survival between the isolated and non-isolated CAs could be performed as the ‘Isolated’ and the ‘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 due to 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.

# Acknowledgements

We are very grateful to all other EUROlinkCAT contributors to this paper for their work on the project (data linkage and standardization, running syntax scripts): Drs L. Renée Lutke and Nicole Siemensma-Mühlenberg (University Medical Center Groningen, Groningen, The Netherlands); Sandra Moreno Marro, Laia Barrachina Bonet and Laura García Villodre (Foundation for the Promotion of Health and Biomedical Research in the Valencian Region, Valencia, Spain); Dr Sonja Kiuru-Kuhlefelt and Tuuli Puroharju (THL Finnish Institute for Health and Welfare. Helsinki, Finland); Drs Gianni Astolfi, Aurora Puccini, Annarita Armaroli (Center for Clinical and Epidemiological Research, University of Ferrara, Ferrara, Italy); Nathalie Bertille and Makan Rahshenas (INSERM, Paris, France); Professor Sue Jordan (Swansea University, Wales, United Kingdom); Professor Elizabeth Draper (University of Leicester, Leicester, United Kingdom); Professor Jenny Kurinczuk (University of Oxford, Oxford, United Kingdom). We also thank Mr Hugh Claridge for the project management.

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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)a

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Participating population-based registries** | **Included birth years** | **Birth population covereda** | **Number of all live births with CAs available for analysis** | **Live birth prevalence of all CAs per 10 000 live births (95% CI)a** |
| ***Registries which linked to national/vital statisticsb*** |  |  |
| Denmark: Funenc | 2005-2014 | 50 093 | 1190 | 241.8 (228.3-255.8) |
| Finlandd  | 2005-2014 | 594 212 | 24 554 | 454.7 (449.3-460.1) |
| France: Parisc,e | 2005-2014 | 264 879 | 5734 | 218.6 (213.0-224.3) |
| Italy: Emilia Romagnac | 2008-2014 | 282 094 | 5589 | 204.8 (199.6-210.2) |
| Italy: Tuscanyc | 2005-2014 | 299 869 | 4312 | 158.7 (154.2-163.3) |
| Netherlands: Northernc  | 2005-2014 | 173 671 | 3810 | 229.7 (222.7-237.0) |
| Norwayd | 2005-2014 | 607 585 | 15 010 | 233.8 (229.9-237.6) |
| UK: East Midlands and South Yorkshirec | 2005-2012 | 586 611 | 9274 | 161.9 (158.7-165.2) |
| UK: Thames Valleyc | 2005-2013 | 270 327 | 3854 | 146.3 (141.7-150.9) |
| UK: Wessexc | 2005-2014 | 298 159 | 4015 | 147.3 (143.0-151.7) |
| UK: Walesc  | 2005-2014 | 347 032 | 10 341 | 291.2 (285.5-296.9) |
| ***Registries which linked to mortality recordsd*** |  |  |
| Maltad | 2005-2014 | 41 155 | 1191 | 288.2 (272.0-305.1) |
| Spain: Valencian Regionc  | 2007-2014 | 403 099 | 7389 | 180.1 (176.0-184.3) |
| **Total**  |  | 4 218 786 | 96 263 |  |

a Extracted from the EUROCAT (European network of population-based registries for the epidemiological surveillance of congenital anomalies) website: <https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence_en> (accessed on 05/02/2021);

b National/vital statistics include birth and death registration data and all live births will have a record;

c Regional registries;

d National registries;

e Civil registry and mortality registry;

f Mortality records only include death registration and live births who remain alive will not have a record.

95% CI, 95% confidence interval.

# TABLE 2 Pooled survival estimates at selected age groups up to 10 years of age for children born with an isolated structural congenital anomaly (‘Isolated’ group) or Down syndrome in 13 EUROCAT registries in nine Western European countries, 2005-2014

|  |  |  | **Survival estimates % (95% CI)** |
| --- | --- | --- | --- |
| **Congenital anomaly groups and subgroups** | **No. of live births** | **No. of deaths up to 10 years** | **1 week** | **4 weeks** | **1 year** | **5 years** | **10 years** |
| **Any isolated anomalya** | 77 054 | 2002 | 98.8 (98.5-99.2) | 98.2 (97.7-98.7) | 97.3 (96.6-98.1) | 97.0 (96.1-97.8) | 96.9 (96.0-97.7) |
| ***Nervous System*** |  |  |  |  |  |  |  |
| Spina bifida | 370 | 12 | 98.3 (96.8-99.7) | 98.1 (96.6-99.6) | 97.4 (95.5-99.3) | 96.7 (94.5-98.9) | 96.6 (94.4-98.9) |
| Congenital hydrocephalus (excluding spina bifida) | 767 | 59 | 97.5 (95.7-99.4) | 97.2 (95.1-99.3) | 95.2 (92.2-98.3) | 94.1 (90.4-98.0) | 92.9 (88.2-97.9) |
| Severe microcephalyb | 361 | 19 | 99.0 (97.6-100.0) | 98.4 (96.7-100.0) | 97.2 (94.5-100.0) | 96.5 (93.5-99.7) | 95.7 (92.2-99.4) |
| ***Eye*** |  |  |  |  |  |  |  |
| Congenital cataract | 560 | 4 | 99.8 (99.5-100.0) | 99.8 (99.3-100.0) | 99.6 (99.0-100.0) | 99.3 (98.4-100.0) | 99.3 (98.4-100.0) |
| ***Congenital Heart Defects (CHD)*** |  |  |  |  |  |  |  |
| All CHD | 27 654 | 951 | 98.8 (98.5-99.2) | 97.6 (96.8-98.4) | 95.9 (94.4-97.3) | 95.4 (93.8-97.1) | 95.3 (93.7-97.0) |
| Severe CHDc | 5932 | 718 | 96.5 (95.7-97.3) | 92.7 (91.4-94.1) | 88.2 (86.1-90.3) | 87.1 (84.8-89.5) | 86.7 (84.3-89.3) |
| Transposition of great vessels | 1131 | 108 | 97.5 (96.2-98.7) | 94.4 (92.1-96.7) | 92.5 (89.9-95.3) | 91.9 (88.9-95.0) | 91.7 (88.7-94.9) |
| Ventricular septal defect | 15 990 | 255 | 99.8 (99.6-99.9) | 99.3 (99.0-99.7) | 98.4 (97.6-99.2) | 98.2 (97.3-99.1) | 98.1 (97.2-99.1) |
| Atrial septal defect | 4594 | 119 | 99.7 (99.5-99.9) | 99.2 (98.6-99.7) | 98.2 (97.2-99.1) | 97.9 (96.8-98.9) | 97.7 (96.7-98.8) |
| Atrioventricular septal defect | 484 | 70 | 97.9 (96.5-99.3) | 95.6 (93.4-97.8) | 89.9 (86.3-93.6) | 87.7 (83.3-92.3) | 87.0 (82.5-91.8) |
| Tetralogy of Fallot | 868 | 42 | 99.6 (99.1-100.0) | 99.3 (98.8-99.9) | 97.6 (96.3-99.0) | 96.7 (95.2-98.2) | 96.6 (95.1-98.2) |
| Pulmonary valve stenosis | 1688 | 45 | 99.9 (99.7-100.0) | 99.5 (99.0-99.9) | 98.8 (97.9-99.7) | 98.5 (97.6-99.4) | 98.4 (97.5-99.3) |
| Aortic valve atresia/stenosis | 576 | 58 | 98.7 (97.4-100.0) | 96.4 (94.3-98.6) | 92.2 (89.3-95.2) | 91.3 (88.0-94.6) | 91.2 (87.9-94.6) |
| Mitral valve anomalies | 453 | 52 | 96.8 (94.7-99.0) | 95.4 (92.4-98.5) | 90.5 (87.0-94.1) | 89.5 (85.6-93.7) | 89.5 (85.6-93.7) |
| Hypoplastic left heart | 515 | 237 | 79.5 (70.5-89.7) | 64.0 (55.7-73.5) | 54.0 (46.9-62.3) | 51.8 (45.0-59.6) | 51.6 (44.9-59.4) |
| Coarctation of aorta | 1450 | 101 | 99.2 (98.6-99.8) | 96.6 (95.3-97.8) | 94.2 (92.3-96.2) | 93.4 (91.2-95.7) | 93.3 (91.1-95.6) |
| Patent ductus arteriosus as only CHD in term infants (≥37 weeks) | 1201 | 13 | 99.8 (99.6-100.0) | 99.8 (99.5-100.0) | 99.2 (98.4-99.9) | 98.9 (98.0-99.8) | 98.9 (98.0-99.8) |
| ***Respiratory system*** |  |  |  |  |  |  |  |
| Cystic adenomatous malformation of lung | 349 | 7 | 99.1 (98.1-100.0) | 98.7 (97.5-99.9) | 98.7 (97.5-99.9) | 98.7 (97.5-99.9) | 98.7 (97.5-99.9) |
| ***Orofacial clefts*** |  |  |  |  |  |  |  |
| Cleft lip with or without cleft palate | 2811 | 14 | 99.9 (99.8-100.0) | 99.9 (99.8-100.0) | 99.8 (99.6-100.0) | 99.8 (99.6-100.0) | 99.8 (99.6-100.0) |
| Cleft palate | 1882 | 15 | 100.0 (99.9-100.0) | 99.8 (99.6-100.0) | 99.7 (99.3-100.0) | 99.6 (99.1-100.0) | 99.6 (99.1-100.0) |
| ***Digestive system*** |  |  |  |  |  |  |  |
| Esophageal atresia with or without tracheo-esophageal fistula | 451 | 22 | 98.8 (97.6-100.0) | 98.2 (96.9-99.6) | 97.1 (95.5-98.8) | 96.8 (95.1-98.5) | 96.8 (95.1-98.5) |
| Duodenal atresia or stenosis | 270 | 6 | 99.9 (99.4-100.0) | 99.5 (98.7-100.0) | 98.2 (96.6-99.8) | 97.9 (96.2-99.6) | 97.7 (95.9-99.7) |
| Atresia or stenosis of other parts of small intestine | 282 | 17 | 98.9 (97.7-100.0) | 98.2 (96.6-99.8) | 96.5 (94.3-98.7) | 95.9 (93.6-98.3) | 95.6 (92.5-98.9) |
| Ano-rectal atresia and stenosis | 432 | 8 | 99.5 (98.7-100.0) | 99.4 (98.6-100.0) | 99.0 (97.9-100.0) | 98.7 (97.3-100.0) | 98.6 (97.2-100.0) |
| Diaphragmatic hernia | 565 | 150 | 81.4 (77.8-85.2) | 76.2 (72.3-80.2) | 74.5 (70.4-78.9) | 74.3 (70.1-78.7) | 74.2 (70.0-78.7) |
| ***Abdominal wall*** |  |  |  |  |  |  |  |
| Gastroschisis | 945 | 31 | 98.7 (97.7-99.8) | 98.4 (97.1-99.7) | 97.3 (95.6-99.0) | 97.2 (95.5-98.9) | 97.2 (95.5-98.9) |
| Omphalocele | 274 | 23 | 97.4 (95.0-99.9) | 95.8 (93.1-98.4) | 93.1 (89.6-96.6) | 92.7 (89.1-96.4) | 92.7 (89.1-96.4) |
| ***Urinary system*** |  |  |  |  |  |  |  |
| Multicystic renal dysplasia | 1070 | 29 | 98.0 (96.7-99.2) | 97.8 (96.6-99.1) | 97.7 (96.4-99.0) | 97.6 (96.3-99.0) | 97.6 (96.3-99.0) |
| Congenital hydronephrosis | 4812 | 29 | 99.9 (99.8-100.0) | 99.9 (99.8-100.0) | 99.8 (99.6-100.0) | 99.7 (99.5-99.9) | 99.7 (99.5-99.9) |
| ***Genital*** |  |  |  |  |  |  |  |
| Hypospadias | 5586 | 27 | 99.9 (99.9-100.0) | 99.9 (99.8-100.0) | 99.8 (99.7-99.9) | 99.8 (99.6-99.9) | 99.8 (99.6-99.9) |
| *Limb* |  |  |  |  |  |  |  |
| Limb reduction defects | 862 | 11 | 99.6 (99.2-100.0) | 99.5 (99.0-100.0) | 99.4 (98.8-99.9) | 99.3 (98.7-99.8) | 99.2 (98.6-99.8) |
| ***Musculoskeletal*** |  |  |  |  |  |  |  |
| Craniosynostosis | 909 | 6 | 100.0 (99.9-100.0) | 100.0 (99.8-100.0) | 99.6 (99.3-100.0) | 99.6 (99.2-100.0) | 99.6 (99.2-100.0) |
|  |  |  |  |  |  |  |  |
| **Chromosomal**  |  |  |  |  |  |  |  |
| Down syndrome | 4011 | 226 | 99.3 (99.0-99.7) | 98.7 (98.2-99.1) | 96.2 (95.1-97.3) | 94.5 (93.1-96.0) | 94.3 (92.8-95.9) |
| Down syndrome with CHD and digestive system anomaly  | 180 | 23 | 99.8 (99.0-100.0) | 97.4 (95.0-99.9) | 93.8 (90.1-97.6) | 88.7 (83.4-94.3) | 88.6 (83.2-94.3) |
| Down syndrome with any CHD, but not digestive system anomaly | 1728 | 121 | 99.6 (99.3-100.0) | 99.2 (98.7-99.7) | 94.8 (92.9-96.8) | 92.9 (90.3-95.5) | 92.3 (89.4-95.3) |
| Down syndrome with any digestive system anomaly, but not CHD | 140 | 8 | 98.4 (96.2-100.0) | 96.9 (93.9-99.9) | 94.2 (90.2-98.3) | 93.1 (88.7-97.8) | 92.8 (87.7-98.2) |
| Down syndrome without CHD and digestive system anomaly | 1963 | 74 | 99.3 (98.7-100.0) | 98.8 (98.2-99.5) | 98.4 (97.6-99.3) | 97.7 (96.7-98.8) | 97.6 (96.5-98.7) |

CHD, congenital heart defect; CI, confidence interval.

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

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

c Severe CHD included the following CHD subgroups: common arterial truncus, double outlet right ventricle, transposition of great vessels, single ventricle, atrioventricular septal defect, tetralogy of Fallot, pulmonary valve atresia, triscuspid atresia and stenosis, Ebstein anomaly, hypoplastic right heart, aortic valve atresia/stenosis, mitral valve anomalies, hypoplastic left heart, coarctation of aorta, aortic atresia/interrupted aortic arch, total anomalous pulmonary venous return (see the corresponding ICD codes in Supplemental Table 1 and Morris et al17 for more rare CHD).

The number of live births or deaths for ‘any isolated anomaly’ is not equal to the sum of those for each congenital anomaly subgroup as some congenital anomalies may belong to more than one congenital anomaly subgroup, eg, an individual CHD may also be associated with severe CHD, and ‘any isolated anomaly’ may include other subgroups not listed in this table.

The survival estimate of 100% at 1 week for two congenital anomaly subgroups is because of rounding to one decimal place.

Deaths from the Netherlands: Northern registry were rounded to 0 or 5 due to small number restrictions and therefore were not included in the numbers of live births and deaths but were included in the survival estimates.

#

# TABLE 3 Pooled survival estimates at 10 years of age for all children with the specified structural congenital anomalies (CAs) (‘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 nine Western European countries, 2005-2014

| **Congenital anomaly groups and subgroups** | **No. of all live births**  | **No. of all deaths up to 10 years** | **Survival estimates at 10 years of age % (95% CI)** | **Proportion of children with isolateda CAs (%) within the ‘All’ group with specified CAs** |
| --- | --- | --- | --- | --- |
|  |  |  |  | **Live births** | **Deaths** |
| **Any anomaly** | 96 263 | 4214 | 94.8 (93.7-95.9) | 80.0 | 47.5 |
| ***Nervous System*** |  |  |  |  |  |
| Spina bifida | 576 | 39 | 93.5 (90.7-96.3) | 64.2 | 30.8 |
| Congenital hydrocephalus (excluding spina bifida) | 1269 | 159 | 86.9 (81.7-92.3) | 60.4 | 37.1 |
| Severe microcephalyb | 798 | 102 | 85.0 (80.2-90.2) | 45.2 | 18.6 |
| ***Eye*** |  |  |  |  |  |
| Congenital cataract | 691 | 37 | 94.6 (91.8-97.5) | 81.0 | 10.8 |
| ***Congenital Heart Defects (CHD)*** |  |  |  |  |  |
| All CHD | 34 874 | 2062 | 92.3 (90.2-94.5) | 79.3 | 46.1 |
| Severe CHDc | 8204 | 1245 | 83.3 (80.8-85.8) | 72.3 | 57.7 |
| Transposition of great vessels | 1263 | 140 | 89.9 (87.1-92.8) | 89.5 | 77.1 |
| Ventricular septal defect | 19 093 | 727 | 95.2 (93.5-96.9) | 83.7 | 35.1 |
| Atrial septal defect | 6427 | 332 | 94.5 (93.0-96.0) | 71.5 | 35.8 |
| Atrioventricular septal defect | 1352 | 244 | 82.5 (79.3-85.9) | 35.8 | 28.7 |
| Tetralogy of Fallot | 1249 | 115 | 92.7 (90.4-95.1) | 69.5 | 36.5 |
| Pulmonary valve stenosis | 2064 | 96 | 96.4 (94.8-98.0) | 81.8 | 46.9 |
| Aortic valve atresia/stenosis | 696 | 81 | 89.9 (87.2-92.8) | 82.8 | 71.6 |
| Mitral valve anomalies | 628 | 98 | 85.0 (80.7-89.6) | 72.1 | 53.1 |
| Hypoplastic left heart | 605 | 289 | 49.6 (42.7-57.5) | 85.1 | 82.0 |
| Coarctation of aorta | 1879 | 186 | 89.6 (87.4-91.8) | 77.2 | 54.3 |
| Patent ductus arteriosus as only CHD in term infants (≥37 weeks) | 1725 | 51 | 97.2 (95.8-98.7) | 69.6 | 25.5 |
| ***Respiratory system*** |  |  |  |  |  |
| Cystic adenomatous malformation of lung | 412 | 15 | 97.2 (95.2-99.1) | 84.7 | 46.7 |
| ***Orofacial clefts*** |  |  |  |  |  |
| Cleft lip with or without cleft palate | 3325 | 106 | 97.4 (96.6-98.2) | 84.5 | 13.2 |
| Cleft palate | 2752 | 147 | 95.0 (93.7-96.3) | 68.4 | 10.2 |
| ***Digestive system*** |  |  |  |  |  |
| Esophageal atresia with or without tracheo-esophageal fistula | 1004 | 122 | 89.5 (86.3-92.7) | 44.9 | 18.0 |
| Duodenal atresia or stenosis | 562 | 39 | 93.6 (90.5-96.8) | 48.0 | 15.4 |
| Atresia or stenosis of other parts of small intestine | 406 | 32 | 94.1 (91.0-97.3) | 69.5 | 53.1 |
| Ano-rectal atresia and stenosis | 1097 | 91 | 92.7 (90.4-95.1) | 39.4 | 8.8 |
| Diaphragmatic hernia | 830 | 249 | 71.1 (67.4-75.0) | 68.1 | 60.2 |
| ***Abdominal wall*** |  |  |  |  |  |
| Gastroschisis | 1056 | 48 | 96.0 (93.9-98.2) | 89.5 | 64.6 |
| Omphalocele | 516 | 90 | 83.9 (79.5-88.5) | 53.1 | 25.6 |
| ***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*** |  |  |  |  |  |
| Hypospadias | 6574 | 87 | 99.0 (98.6-99.3) | 85.0 | 31.0 |
| ***Limb*** |  |  |  |  |  |
| Limb reduction defects | 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 |

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

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

CHD, congenital heart defect.

c Severe CHD included the following CHD subgroups: common arterial truncus, double outlet right ventricle, transposition of great vessels, single ventricle, atrioventricular septal defect, tetralogy of Fallot, pulmonary valve atresia, triscuspid atresia and stenosis, Ebstein anomaly, hypoplastic right heart, aortic valve atresia/stenosis, mitral valve anomalies, hypoplastic left heart, coarctation of aorta, aortic atresia/interrupted aortic arch, total anomalous pulmonary venous return (see the corresponding ICD codes in Supplemental Table 1 and Morris et al17 for more rare CHD).

The number of live births or deaths for ‘any anomaly’ is not equal to the sum of those for each congenital anomaly subgroup as some congenital anomalies may belong to more than one congenital anomaly subgroup, eg, an individual CHD may also be associated with severe CHD, and ‘any anomaly’ may include other subgroups not listed in this table.

Deaths from the Netherlands: Northern registry were rounded to 0 or 5 due to small number restrictions and therefore were not included in the numbers of live births and deaths but were included in the survival estimates.

# Figure legends

**FIGURE 1** Survival estimates (with 95% CI) of children with selected subgroups of congenital anomalies for ‘Isolated’ and ‘All’ groups in 13 EUROCAT registries in nine Western European countries, 2005-2014

**Note:** For each anomaly subgroup, all children with the specified anomalies were included and those with an isolated anomaly only were identified resulting in two groups for analysis: ‘All’ and ‘Isolated’ with a specified CA. An isolated congenital anomaly is defined as a structural congenital anomaly in one organ system only or if co-existing anomalies were a consequence of a single primary anomaly.

# Supplemental information

**Supplemental Table 1.** EUROCAT congenital anomaly subgroups in EUROlinkCAT.

**Supplemental Table 2.** Results of the sensitivity analysis: survival estimates and the difference in survival compared to the survival for all registries after the exclusion of each registry in turn, 13 EUROCAT registries in nine European countries, 2005-2014.