# Ten-year survival of children born with congenital anomalies: a linked cohort EUROlinkCAT study

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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; 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 of 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 useful 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 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 Organization 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. To our knowledge, no studies from Western Europe summarizing and comparing survival of children with specific CAs aged beyond one year have been published. 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 records 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 registry and 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 was more informative as it 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 Revision*20 (ICD-10) or *Ninth Revision* (ICD-9) and categorized by CA group/subgroup (the organ system and the individual disorder affected), following the EUROCAT guidelines.21 Children with only minor anomalies, defined in EUROCAT as those which do not have serious medical, functional or cosmetic consequences for the child (eg, plagiocephaly), 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’ with a specified CA. 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 (live birth prevalence ≥1 per 10,000) and Down syndrome as the most common chromosomal anomaly (Supplemental Table 117).

## Statistical analysis

The statistical analysis consisted of two stages: firstly, all analyses on individual case data were performed by the registries locally – no individual case data were shared. 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 Registries uploaded aggregate tables and analytic results (ie, Kaplan-Meier survival estimates with 95% confidence intervals (CI) at individual time points (7 days, 28 days, 3 months, 6 months, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 years), the number at risk and the number of deaths in each time period for each CA subgroup) to the Central Results Repository at Ulster University, UK, using a secure web platform. The second stage involved pooling aggregated data and analytic results to produce combined 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 associated CAs which occur less frequently 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 to the group without any of these CAs.

Ten-year survival estimates with 95% CI for ‘Isolated’ and for ‘All’ groups were estimated and 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 contributing registries listed by mortality data source, ie, national/vital statistics (n=11) or mortality records only (n=2), the birth years included, birth population of each registry, the number of live births with CAs and the CA live birth prevalence. Overall, 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 1).

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 the majority of 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 estimates 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 by specific CA and the number of live births and deaths in the ‘Isolated’ group expressed as a proportion of the ‘All’ group. 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). Although for ‘any CA’ the proportion of ‘Isolated’ among all live births was 80%, this proportion among deaths was much lower (47.5%). The proportion of ‘Isolated’ among deaths varied by specific CA, being particularly high for severe CHD subgroups (eg, HLH, 82.0%).

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. Survival was higher in children in the ‘Isolated’ group for all specific CAs compared to the ‘All’ group. 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.

Pooled 1-year, 5-year and 10-year (where reported) survival of children born with specific isolated CAs in the Western European population was, on average, 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 of population-based studies.14,34 This is presumably due to a lower survival in earlier birth years reported in most studies, differences in the inclusion criteria (not all studies included isolated CAs only), improved prenatal diagnosis and consequent increase in TOPFA prevalence in more severe CAs over time and/or true differences in survival between different geographic locations. 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 mostly 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 program 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 long-term pooled survival estimates produced in our study are not representative of the whole Europe as participating regions are from high-income Western-European countries.

# CONCLUSIONS

The accuracy of estimated long-term survival of children born with specific CAs is ensured by the use of common protocol to data collection, standardisation, 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 of 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. Future multicenter studies of survival of children with CAs should be aware of challenges related to linkage and statistical issues, which can be overcome by using appropriate linkage mortality sources, data standardization and meta-analytic approaches to yield meaningful results. The geographical coverage should be widened in the future European studies to produce findings more representative and generalizable for Europe.

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# TABLE 1 Contributing European Surveillance of Congenital Anomalies (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)b

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Participating registries (full registry names)** | **Included birth years** | **Birth population coveredb** | **Number of all live births with CAs available for analysis** | **Live birth prevalence of all CAs per 10 000 live birthsb** |
| ***Registries which linked to national/vital statistics*** |  |  |
| Denmark: Funen | 2005-2014 | 50 093 | 1190 | 241.8 |
| Finland  | 2005-2014 | 594 212 | 24 554 | 454.7 |
| France: Parisa | 2005-2014 | 264 879 | 5734 | 218.6 |
| Italy: Emilia Romagna | 2008-2014 | 282 094 | 5589 | 204.8 |
| Italy: Tuscany | 2005-2014 | 299 869 | 4312 | 158.7 |
| Netherlands: Northern  | 2005-2014 | 173 671 | 3810 | 229.7 |
| Norway | 2005-2014 | 607 585 | 15 010 | 233.8 |
| UK: East Midlands and South Yorkshire  | 2005-2012 | 586 611 | 9274 | 161.9 |
| UK: Thames Valley | 2005-2013 | 270 327 | 3854 | 146.3 |
| UK: Wessex | 2005-2014 | 298 159 | 4015 | 147.3 |
| UK: Wales  | 2005-2014 | 347 032 | 10 341 | 291.2 |
| ***Registries which linked to mortality records*** |  |  |
| Malta | 2005-2014 | 41 155 | 1191 | 288.2 |
| Spain: Valencian Region  | 2007-2014 | 403 099 | 7389 | 180.1 |
| **Total**  |  | 4 218 786 | 96 263 |  |

a Civil registry and mortality registry

b extracted from the EUROCAT website: <https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence_en> (accessed on 05/02/2021)

# TABLE 2 Pooled survival estimates at selected age groups up to 10 years of age for children born with an isolated 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 isolated CAs in all live births and deaths with the specified CAs: 13 EUROCAT registries in nine Western European countries, 2005-2014

| **Congenital anomaly groups and subgroups** | **No. of live births**  | **No. of deaths up to 10 years** | **Survival estimates at 10 years of age (%)** | **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.