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

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abstract

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.

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WHAT'S KNOWN ON THIS SUBJECT: Survival beyond infancy in children born with common congenital anomalies (CAs) has been reported by individual studies, but long-term survival estimates for children with a wide range of specific CAs using standardized population-based multicenter data are lacking.

WHAT THIS STUDY ADDS: This population-based linked cohort study from 13 regions within 9 European countries (EUROlinkCAT) provided reliable survival estimates up to age 10 for children with specific isolated and nonisolated structural CAs that are important for clinical practice and counseling.

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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 years[5,6] and in older children[7] 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.[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] 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 Anomalies[15,16] (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 Revision[20] or 9th Revision, and categorized by CA group and subgroup (the organ system affected and the individual disorder)

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[a]	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 and vital statistics[b]				
Denmark: Funen[c]	2005–2014	50 093	1190	241.8 (228.3–255.8)
Finland[d]	2005–2014	594 212	24 554	454.7 (449.3–460.1)
France: Paris[c,e]	2005–2014	264 879	5734	218.6 (213.0–224.3)
Italy: Emilia Romagna[c]	2008–2014	282 094	5589	204.8 (199.6–210.2)
Italy: Tuscany[c]	2005–2014	299 869	4312	158.7 (154.2–163.3)
Netherlands: Northern[c]	2005–2014	173 671	3810	229.7 (222.7–237.0)
Norway[d]	2005–2014	607 585	15 010	233.8 (229.9–237.6)
United Kingdom				
East Midlands and South Yorkshire[c]	2005–2012	586 611	9274	161.9 (158.7–165.2)
Thames Valley[c]	2005–2013	270 327	3854	146.3 (141.7–150.9)
Wessex[c]	2005–2014	298 159	4015	147.3 (143.0–151.7)
Wales[c]	2005–2014	347 032	10 341	291.2 (285.5–296.9)
Registries which linked to mortality records[d]				
Malta[f]	2005–2014	41 155	1191	288.2 (272.0–305.1)
Spain: Valencian Region[c]	2007–2014	403 099	7389	180.1 (176.0–184.3)
Total	—	4 218 786	96 263	—

—, not applicable.
[a] Extracted from the EUROCAT Web site: https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence_en. Accessed May 2, 2021.
[b] National and vital statistics include birth and death registration data, and all live births will have a record.
[c] Regional registries.
[d] Mortality records only include death registration, and live births who remain alive will not have a record.
[e] Civil registry and mortality registry.
[f] National registries.

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 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[23,24] 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,[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 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.[25] Combescure

proposed the random-effects meta-analysis of survival curves by using the DerSimonian and Laird multivariate procedure[26] 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 (eg, 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,[2–10] 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.

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 3 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 because 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 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

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 9 Western European Countries, 2005 to 2014

Congenital Anomaly Groups and Subgroups	No. Live Births	No. Deaths Up to 10 y	Survival Estimates % (95% CI)				
			1 wk	4 wk	1 y	5 y	10 y
Any isolated anomaly[a]	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 microcephaly[b]	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 CHD[c]	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 wk)	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)
Anorectal 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)

TABLE 2 Continued

Congenital Anomaly Groups and Subgroups	No. Live Births	No. Deaths Up to 10 y	Survival Estimates % (95% CI) 1 wk	4 wk	1 y	5 y	10 y
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)

The number of live births or deaths for "any isolated 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 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 2 CA subgroups is because of rounding to 1 decimal place. 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.

[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 definition[41]).

[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, HLH, coarctation 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 4 and Morris et al[17] for more rare CHD).

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

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

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[a] 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 microcephaly[b]	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
CHD					
All CHD	34 874	2062	92.3 (90.2–94.5)	79.3	46.1
Severe CHD[c]	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
ASD	6427	332	94.5 (93.0–96.0)	71.5	35.8
AVSD	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 and 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
HLH	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 wk)	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
Anorectal atresia and stenosis	1097	91	92.7 (90.4–95.1)	39.4	8.8

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 Isolated[a] CAs (%) Within the "All" Group With Specified CAs	
				Live Births	Deaths
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

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 CHD may also be associated with severe CHD, 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.

[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 definition[41]).

[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, tricuspid atresia and stenosis, Ebstein anomaly, hypoplastic right heart, aortic valve atresia and stenosis, mitral valve anomalies, HLH, coarctation 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 al[17] for more rare CHD).

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 from 2005 to 2014 (n = 96 263 out of a birth population of 4 218 786) among 13 CA registries in Western Europe provided survival estimates for children up to age 10. The pooled 10-year survival was >90% for the majority of isolated CA subgroups (27 of 32), with considerable variation in survival among 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 with 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 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 increases in terminations of pregnancy for more severe CAs (https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence_en; 45.1 and 52.1 per 10 000 births in 1995–2004 and 2005–2014, respectively); and

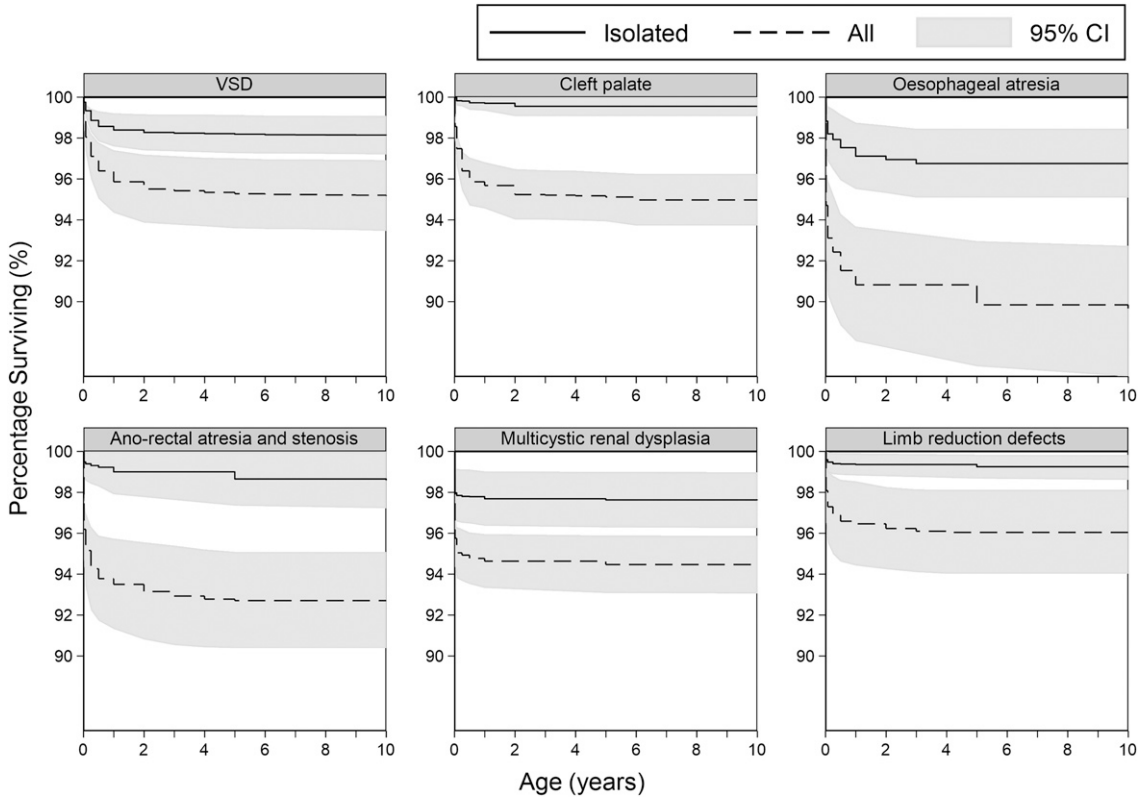

FIGURE 1

Survival estimates (with 95% CI) of children with selected subgroups of congenital anomalies for "Isolated" and "All" groups in 13 EUROCAT registries in 9 Western European countries, 2005 to 2014. For each anomaly 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 with a specified CA. 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.

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 studies[28,38–40] 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).[44,45] 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.[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 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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REFERENCES

1. Euro-Peristat Project. European Perinatal Health Report. Core indicators of the health and care of pregnant women and babies in Europe in 2015. Available at: https://europeristat.com/reports/8-our-publications.html. 2018. Accessed April 20, 2021
2. Heron M. Deaths: leading causes for 2017. *Natl Vital Stat Rep.* 2019;68(6):1–77
3. Office for National Statistics. Infant mortality (birth cohort) tables in England and Wales, 2017. Stillbirths and infant deaths (total by ethnicity): ONS cause groups in 2017, numbers (Table 16). Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/infantmortalitybirthcohorttablesinenglandandwales. 2020. Accessed February 09, 2021
4. Rosano A, Botto LD, Botting B, Mastroiacovo P. Infant mortality and congenital anomalies from 1950 to 1994: an international perspective. *J Epidemiol Community Health.* 2000;54(9):660–666
5. World Health Organization The Global Health Observatory. World health data platform. Distribution of causes of death among children aged < 5 years (%). Available at: https://www.who.int/data/gho/data/indicators/indicator-details/GHO/distribution-of-causes-of-death-among-children-aged-5-years-(-). 2017. Accessed April 20, 2021
6. GBD 2015 Child Mortality Collaborators. Global, regional, national, and selected subnational levels of stillbirths, neonatal, infant, and under-5 mortality, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet.* 2016;388(10053):1725–1774
7. Fraser J, Sidebotham P, Frederick J, Covington T, Mitchell EA. Learning from child death review in the USA, England, Australia, and New Zealand. *Lancet.* 2014;384(9946):894–903
8. Gianino MM, Lenzi J, Bonaudo M, et al. Patterns of amenable child mortality over time in 34 member countries of the Organisation for Economic Co-operation and Development (OECD): evidence from a 15-year time trend analysis (2001-2015). *BMJ Open.* 2019;9(5):e027909
9. World Health Organization. Chapter 4. Snapshot: child health. In: *Health in 2015: From MDGs, Millennium Development Goals, to SDGs, Sustainable Development Goals.* Switzerland: WHO; 2015
10. Hug L, Alexander M, You D, Alkema L. UN Inter-agency Group for Child Mortality Estimation. National, regional, and global levels and trends in neonatal mortality between 1990 and 2017, with scenario-based projections to 2030: a systematic analysis. *Lancet Glob Health.* 2019;7(6):e710–e720
11. Sartorius BKD, Sartorius K. Global infant mortality trends and attributable determinants – an ecological study using data from 192 countries for the period 1990–2011. *Popul Health Metr.* 2014;12:29
12. Wolfe I, Thompson M, Gill P, et al. Health services for children in western Europe. *Lancet.* 2013;381(9873):1224–1234
13. Berger KH, Zhu BP, Copeland G. Mortality throughout early childhood for Michigan children born with congenital anomalies, 1992-1998. *Birth Defects Res A Clin Mol Teratol.* 2003;67(9):656–661
14. Glinianaia SV, Morris JK, Best KE, et al. Long-term survival of children born with congenital anomalies: A systematic review and meta-analysis of population-based studies. *PLoS Med.* 2020;17(9):e1003356
15. Boyd PA, Haeusler M, Barisic I, Loane M, Garne E, Dolk H. Paper 1: The EUROCAT network–organization and processes. *Birth Defects Res A Clin Mol Teratol.* 2011;91(Suppl 1):S2–S15
16. Kinsner-Ovaskainen A, Lanzoni M, Garne E, et al. A sustainable solution for the activities of the European network for surveillance of congenital anomalies: EUROCAT as part of the EU Platform on Rare Diseases Registration. *Eur J Med Genet.* 2018;61(9):513–517

17. Morris JK, Garne E, Loane M, et al. EUROlinkCAT Consortium. EUROlinkCAT protocol for a European population-based data linkage study investigating the survival, morbidity and education of children with congenital anomalies. *BMJ Open*. 2021;11(6):e047859

18. Loane M, Given JE, Tan J, et al. Linking a European cohort of children born with congenital anomalies to vital statistics and mortality records: A EUROlinkCAT study. *PLoS One*. 2021;16(8):e0256535

19. Pitt MJ, Morris JK. European trends in mortality in children with congenital anomalies: 2000-2015. *Birth Defects Res*. 2021;113(12):958–967 [Part A]

20. World Health Organization. *Congenital Malformations, Deformations and Chromosomal Abnormalities (Q00-Q99). International Statistical Classification of Diseases and Related Health Problems: 10th Revision*. Geneva, Switzerland: World Health Organization; 2010

21. EUROCAT. Chapter 3.3. EUROCAT Subgroups of Congenital Anomalies (version 23.09.2016). In: *EUROCAT Guide 1.4: Instruction for the Registration of Congenital Anomalies (Last update version 20/12/2016)*. Newtownabbey, UK: EUROCAT Central Registry, University of Ulster; 2013

22. EUROCAT. Chapter 3.2. Minor Anomalies for Exclusion (version 14.10.14). *EUROCAT Guide 1.4: Instruction for the Registration of Congenital Anomalies (Last update version 20/12/2016)*. Newtownabbey, UK: EUROCAT Central Registry, University of Ulster; 2013

23. Garne E, Dolk H, Loane M, et al. EUROCAT Working Group. Paper 5: Surveillance of multiple congenital anomalies: implementation of a computer algorithm in European registers for classification of cases. *Birth Defects Res A Clin Mol Teratol*. 2011;91(1 Suppl 1):S44–S50

24. EUROCAT. Chapter 3.4. Multiple Congenital Anomaly Algorithm (version 19.11.2014). *EUROCAT Guide 1.4: Instruction for the Registration of Congenital Anomalies (Last update version 20/12/2016)*. Newtownabbey, UK: EUROCAT Central Registry, University of Ulster; 2013

25. Combescure C, Foucher Y, Jackson D. Meta-analysis of single-arm survival studies: a distribution-free approach for estimating summary survival curves with random effects. *Stat Med*. 2014;33(15):2521–2537

26. Jackson D, White IR, Thompson SG. Extending DerSimonian and Laird's methodology to perform multivariate random effects meta-analyses. *Stat Med*. 2010;29(12):1282–1297

27. Bakker MK, Kancherla V, Canfield MA, et al. Analysis of mortality among neonates and children with spina bifida: an international registry-based study, 2001–2012. *Paediatr Perinat Epidemiol*. 2019;33(6):436–448

28. Wang Y, Hu J, Druschel CM, Kirby RS. Twenty-five-year survival of children with birth defects in New York State: a population-based study. *Birth Defects Res A Clin Mol Teratol*. 2011;91(12):995–1003

29. Tennant PW, Pearce MS, Bythell M, Rankin J. 20-year survival of children born with congenital anomalies: a population-based study. *Lancet*. 2010;375(9715):649–656

30. Schneuer FJ, Bell JC, Shand AW, Walker K, Badawi N, Nassar N. Five-year survival of infants with major congenital anomalies: a registry based study. *Acta Paediatr*. 2019;108(11):2008–2018

31. Dastgiri S, Gilmour WH, Stone DH. Survival of children born with congenital anomalies. *Arch Dis Child*. 2003;88(5):391–394

32. Wang Y, Liu G, Canfield MA, et al. National Birth Defects Prevention Network. Racial/ethnic differences in survival of United States children with birth defects: a population-based study. *J Pediatr*. 2015;166(4):819–26.e1, 2

33. Nembhard WN, Salemi JL, Ethen MK, Fixler DE, Dimaggio A, Canfield MA. Racial/Ethnic disparities in risk of early childhood mortality among children with congenital heart defects. *Pediatrics*. 2011;127(5):e1128–e1138

34. Best KE, Rankin J. Long-term survival of individuals born with congenital heart disease: a systematic review and meta-analysis. *J Am Heart Assoc*. 2016;5(6):e002846

35. EUROSTAT. Fetal, peri- and neonatal mortality rates by country of occurrence, 2011–2015. Available at: https://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=hlth_cd_aperrto&lang=en. 2021. April 21, 2021

36. EUROSTAT. Infant mortality halved between 1998 and 2018. Available at: https://ec.europa.eu/eurostat/web/products-eurostat-news/-/DDN-20200309-1#:~:text=In%20the%20EU%20in%202018,per%201%20000%20live%20births. 2020. Accessed April 22, 2021

37. You D, Hug L, Chen Y. United Nations Inter-agency Group for Child Mortality Estimation. *(UN IGME). Levels and trends in child mortality. Report 2014: United Nations Children's Fund*. New York: UNICEF; 2014

38. Halliday J, Collins V, Riley M, Youssef D, Muggli E. Has prenatal screening influenced the prevalence of comorbidities associated with Down syndrome and subsequent survival rates? *Pediatrics*. 2009;123(1):256–261

39. Kucik JE, Shin M, Siffel C, Marengo L, Correa A. Congenital Anomaly Multistate Prevalence and Survival Collaborative. Trends in survival among children with Down syndrome in 10 regions of the United States. *Pediatrics*. 2013;131(1):e27–e36

40. Rankin J, Tennant PW, Bythell M, Pearce MS. Predictors of survival in children born with Down syndrome: a registry-based study. *Pediatrics*. 2012;129(6):e1373–e1381

41. Brodwall K, Greve G, Leirgul E, et al. The five-year survival of children with Down syndrome in Norway 1994-2009 differed by associated congenital heart defects and extracardiac malformations. *Acta Paediatr*. 2018;107(5):845–853

42. Glasson EJ, Jacques A, Wong K, Bourke J, Leonard H. Improved survival in Down syndrome over the last 60 years and the impact of perinatal factors in recent decades. *J Pediatr*. 2016;169:214–20.e1

43. Chua GT, Tung KTS, Wong ICK, et al. Mortality among children with Down syndrome in Hong Kong: a population-based cohort study from birth. *J Pediatr*. 2020;218:138–145

44. Morris JK, Rankin J, Garne E, et al. Prevalence of microcephaly in Europe: population based study. *BMJ*. 2016;354:i4721

45. EUROCAT. Chapter 3.6. EUROCAT Description of the Congenital Anomaly Subgroups (version 19.11.2014). *EUROCAT Guide 1.4: Instruction for the Registration of Congenital Anomalies (Last update version 20/12/2016)*. Newtownabbey, UK: EUROCAT Central Registry, University of Ulster; 2013

46. Hautala J, Gissler M, Ritvanen A, et al. The implementation of a nationwide anomaly screening programme improves prenatal detection of major cardiac defects: an 11-year national population-based cohort study. *BJOG*. 2019;126(7):864–873

47. Tworetzky W, McElhinney DB, Reddy VM, Brook MM, Hanley FL, Silverman NH. Improved surgical outcome after fetal diagnosis of hypoplastic left heart syndrome. *Circulation*. 2001;103(9):1269–1273