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Temporal and geographical variations in survival of children born with congenital anomalies in Europe: A multi-registry cohort study

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Abstract

Background: Congenital anomalies are a major cause of perinatal, neonatal and infant mortality.

Objectives: The aim was to investigate temporal changes and geographical variation in survival of children with major congenital anomalies (CA) in different European areas.

Methods: In this population-based linkage cohort study, 17 CA registries members of EUROCAT, the European network for the surveillance of CAs, successfully linked data on 115,219 live births with CAs to mortality records. Registries estimated Kaplan–Meier survival at 28 days and 5 years of age and fitted Cox's proportional hazards models comparing mortality at 1 year and 1–9 years of age for children born during 2005–2014 with those born during 1995–2004. The hazard ratios (HR) from each registry were combined centrally using a random-effects model. The 5-year survival conditional on having survived to 28 days of age was calculated.

Results: The overall risk of death by 1 year of age for children born with any major CA in 2005–2014 decreased compared to 1995–2004 (HR 0.68, 95% confidence interval [CI] 0.53, 0.89). Survival at 5 years of age ranged between registries from 97.6% to 87.0%. The lowest survival was observed for the registry of OMNI-Net (Ukraine) (87.0%, 95% CI 86.1, 87.9).

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Conclusions: Survival of children with CAs improved for births in 2005–2014 compared with 1995–2004. The use of CA registry data linked to mortality data enables investigation of survival of children with CAs. Factors such as defining major CAs, proportion of terminations of pregnancy for foetal anomaly, source of mortality data and linkage methods are important to consider in the design of future studies and in the interpretation of the results on survival of children with CAs.

KEYWORDS
cohort study, congenital anomalies, registry, survival

1 | BACKGROUND

Congenital anomalies (CAs) are a major cause of perinatal, neonatal and infant mortality worldwide.[1–3] In developed countries compared with developing countries, the relative contribution of CAs to infant mortality is higher due to the lower mortality from communicable diseases.[4–6] CAs are also a significant contributor to mortality of children under 5 years and in childhood.[7,8]Two recent systematic reviews and meta-analyses of population-based studies reported a general improvement in long-term survival of children with congenital heart defects (CHD)[9] and other specific CAs[10] over the last few decades. Despite reported improvements in long-term survival, CAs have an important role when interpreting the regional differences in neonatal, infant and child mortality reported across the European countries.[11–14] National statistics on the contribution of CAs to infant and child mortality are generally based on the analysis of the

underlying cause of death from death certificates. In Europe, deaths with a CA as the main cause are about 25% of all deaths of children aged less than 10 years.[15] However, for children with CAs, the analysis of the underlying cause of death from death certificates underestimates the mortality risk due to CA amongst these children.[16,17] Copeland et al. suggested that the most accurate way to analyse the mortality risk amongst children with CAs is to link births reported in CA registries to mortality data.[16]

Associations of survival with other factors, such as the occurrence of termination of pregnancy for foetal anomalies (TOPFA), should be investigated. In countries where termination of pregnancy is illegal (for example Malta), babies with lethal CAs may survive birth, succumbing soon after and inflating the mortality rates in the neonatal period.[18] However, when births with CAs are excluded, neonatal mortality in such countries is more in line with other countries.[19]

The aim of this EUROlinkCAT multicentre study was to investigate temporal changes and geographical variations in survival of children with CAs in different European areas by linking births reported in CA registries to mortality data[20] and to describe some methodological issues in studying survival of children with CAs in Europe.

Synopsis

Study questions

Is the survival of children born with congenital anomalies (CAs) improving? Are there geographical differences in survival of children born with CAs in Europe?

What's already known

CAs are a major cause of perinatal, neonatal and infant mortality worldwide. In Europe, deaths with a CA as the main cause are about 25% of all deaths of children aged less than 10 years. National statistics on the contribution of CAs to infant and child mortality are generally based on the analysis of the underlying cause of death from death certificates. However, for children with CAs, the analysis of the underlying cause of death from death certificates underestimates the mortality risk due to CA, suggesting that the most accurate way to analyse the mortality risk amongst children with CAs is to link births reported in CA registries to mortality data.

What this study adds

The linkage of congenital anomalies data from population-based registries to mortality records from national/vital statistics is an efficient and powerful method of analysing the survival of children born with CAs. Caution must be taken in the interpretation of variations in survival, which can be influenced by differences across registries in the exclusion/inclusion of less severe anomalies, the prevalence of prenatal screening and subsequent termination of pregnancies, the source of mortality data and linkage success.

2 | METHODS

2.1 | Cohort

This study was a European, population-based retrospective linkage cohort study. The cohort included all live births with major CAs collected and validated by population-based registries, which are members of EUROCAT, the European network for the surveillance of CAs.[21–23] Children with only minor anomalies according to the EUROCAT definitions were excluded.[24]

2.2 | Study design and setting

Participating registries linked their live born cases to mortality records. Eleven registries linked their data to vital statistics databases, which contain data on birth and death registrations. Six registries linked their data only to mortality databases. For registries linking to vital statistics databases, it was possible to determine the proportion of successful linkages, as any live births not identified in the database were linkage failures. However, when only a mortality database was used, a case without a death certificate could have been alive or could have been a linkage failure. A detailed description and results of the linkage process have been reported elsewhere.[25] A total of 17 registries in 12 different European countries successfully linked their live births with CA to mortality records. In only one registry (Malta), termination of pregnancy is illegal. All participating registries followed a common procedure of data collection, standardisation, quality control and statistical analyses, defined in the EUROlinkCAT protocol and reported in detail in a recent paper.[20] Data from each registry were locally analysed by the registry using common Stata syntax scripts, aggregate data and analytic results were then provided to a Central Results Repository based at Ulster University, UK.

All live births with CA from 2005 to 2014 were included for all registries except for Emilia Romagna (Italy), Valencian Region (Spain), Thames Valley (UK), East Midlands and South Yorkshire (EMSY) (UK) and OMNI-Net (Ukraine), for which data were available for a shorter birth period (Table 1). All live births were linked to mortality records up to 2015, so that all live births had information on at least the first year's survival.

The CAs were classified according to the EUROCAT anomaly subgroups[24] and this paper reports on 'All anomalies', which includes all major CAs. Furthermore, we have investigated the major group of the 'isolated severe CHD', which includes the following specific subgroups: common arterial truncus, double outlet right ventricle, transposition of great vessels, single ventricle, atrioventricular septal defect, tetralogy of Fallot, pulmonary valve atresia, tricuspid

TABLE 1 Study period, linkage data source, number of live birth cases, live birth prevalence per 10,000 births, proportion of termination of pregnancy for foetal anomaly and proportion of linked live births, by registry

Registry	Birth years	Linkage	Number of LB cases	LB prevalence per 10,000 births[c]	% of TOPFA on total cases[c]	% of LB children linked
Belgium: Antwerp	2005–2014	MR	4459	212.2	12.3	NA
Denmark: Funen	2005–2014	VS	1190	241.8	20.8	100.0
Finland	2005–2014	VS	24,554	454.7	10.6	100.0
France: Paris	2005–2014	VS	5734	218.6	31.7	99.2
Germany: Saxony-Anhalt	2005–2014	MR	4667	270.8	11.0	NA
Italy: Emilia Romagna	2008–2014	VS	5589	204.8	16.4	92.1
Italy: Tuscany	2005–2014	VS	4312	158.7	22.6	88.8
Malta[b]	2005-2014	MR	1191	288.2	0	NA
Netherlands: Northern[a]	2005–2014	VS	3810	229.7	14.0	98.1
Norway	2005–2014	VS	15,010	233.8	14.0	100.0
Spain: Basque Country	2005–2014	MR	3586	171.4	32.6	NA
Spain: Valencian Region	2007–2014	MR	7839	180.1	20.8	NA
UK: Wales	2005–2014	VS	10,341	291.2	14.9	99.9
UK: Thames Valley	2005–2013	VS	3818	146.3	27.4	96.5
UK: Wessex	2005–2014	VS	4015	147.3	29.9	92.2
UK: East Midlands and South Yorkshire	2005–2012	VS	9269	161.9	21.1	97.4
Ukraine: OMNI-Net	2006–2014	MR	5835	204.7	13.8	NA
Total			115,219	231.1	17.6	

LB, live birth; TOPFA, terminations of pregnancy for foetal anomaly following prenatal diagnosis; NA, Not available as linkage only to mortality database; MR, registry linked to mortality record database; VS, registry linked to national/vital statistics database.

[a]For Netherlands: Northern, due to small number restrictions for all values the last digits are rounded to 0 or 5.

[b]In Malta termination of pregnancy is illegal.

[c]Extracted by EUROCAT website: https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence_en. Accessed March 21, 2021.

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. 'Isolated' means that the child had no associated anomalies in other organ systems or a genetic diagnosis.

2.3 | Outcomes

We considered the following outcomes: survival at 28 days and 5 years of age; 5-year survival conditional on having survived at 28 days; mortality hazard at 1 year and 1–9 years of age; Infant mortality (at <1 year of age) in children with CAs per 10,000 live births.

2.4 | Statistical analysis

For each CA subgroup, survival at specific ages was estimated by Kaplan–Meier survival analysis to account for the censoring that occurred. Survival estimates at 28 days and 5 years of age with 95% confidence intervals (CI) were calculated by registry. We derived the Kaplan–Meier survival estimates using the ln(−ln(S[t])) transformation, where the calculated 95% confidence intervals are symmetric on the ln(ln)) scale, but will not appear symmetric when transformed back to the proportions of children surviving. For the Antwerp (Belgium) registry, only deaths during the first year of life were available, so this registry was excluded from survival analysis beyond 1 year. Random-effects meta-analysis of the survival estimates at both age points were performed and the I^2 statistic was used to assess the between-registry heterogeneity.

For the nine registries with data on live births during 1995–2004, Cox's proportional hazards models were fitted to compare survival of children born in 1995–2004 with those in 2005–2014. As different factors may influence infant and childhood mortality, survival from birth to 1 year was analysed separately from survival from 1 year up to 10 years. Therefore, two hazard ratios (HRs) for mortality of children with CAs born during 2005–2014 compared with those born during 1995–2004 at 1 year and 1–9 years of age were estimated for each registry. The HRs were combined across registries using a random-effects meta-analysis.

Infant mortality (at <1 year of age) in children with CAs was calculated per 10,000 live births in the whole population births covered by each registry. Deaths occurring during the first 7 and 28 days of

life, were reported as a proportion of the number of deaths occurring during the first year for each registry. Finally, 5-year survival estimates conditional on having survived at 28 days with 95% CI were calculated for each registry.

Statistical analysis was performed in Stata (version 16.0, StataCorp LP, College Station, TX, USA).

2.5 | Missing data

Missing data in this study arose solely due to linkage not occurring. Eleven congenital anomaly registries linked to vital statistics databases and six of these had over 96% linkage success. For the remaining five registries all births in years in which the linkage success was lower than 85% were excluded. The registries who linked their data only to mortality databases were assumed to have linkage success above 85%. The Registry of Zagreb (Croatia) was unable to obtain identifiers for more than 20% of the children to link to the local death records and, therefore, was excluded from this study. A detailed description of the quality of linkage has published elsewhere.[25] Multiple imputation was not performed on any of the survival analysis as a failed linkage resulted in no covariates being available to use in the imputations.

2.6 | Ethics approval

The EUROCAT registries all have ethical and governance clearances and other permissions required according to their national guidelines for routine surveillance, data collection and transmission of anonymised data to a central database. Additional permissions to link their data to mortality or vital statistics and to transmit anonymous aggregate data and analytic results to a Central Results Repository (CRR) were obtained by each registry.

3 | RESULTS

A total of 17 EUROCAT registries from 12 European countries were included in the study and provided survival data for a total of 115,219 children born with a major CA (Table 1). The live birth prevalence of 'All anomalies' per 10,000 births ranged from 146.3 for the Thames Valley registry (UK) to 454.7 for the Finnish registry.

3.1 | Temporal variation

The risk of death at 1 year of age for live births with any major CA decreased significantly in most of the registries over time (Table 2). For Norway, there was no change over time and for Malta there was a slight increase in infant mortality in the 2005–2014 period. The overall risk of infant death decreased (HR 0.68, 95% CI 0.53, 0.89) as well as for deaths from 1–9 years of age (HR 0.75, 95% CI 0.62, 0.91). The small numbers of deaths after 1 year of age by registry resulted in wide confidence intervals.

For live births with isolated severe CHD (Table 2) with much higher mortality rates, a similar significant decrease in the risk of infant death was observed (HR 0.59, 95% CI 0.46, 0.74). A lower risk was evident for all the registries, except for Malta. For deaths between 1–9 years of age, the decrease in mortality was dagain similar to that observed for all anomalies.

3.2 | Differences in survival across registries

Survival estimates at 28 days and 5 years of age for all anomalies in the period 2005–2014 are reported in Table 3 and Figure S1. There was high heterogeneity of the estimates at 28 days and 5 years of age (I^2 = 97.8% and 99.0%, respectively). Saxony-Anhalt (Germany) and Finland were the registry with the highest survival estimates at 5 years. The lowest survival was observed for OMNI-Net (Ukraine; 87.0%, 95% CI 86.1, 87.9) and Malta (90.6%, 95% CI 88.7, 92.1), followed by the three English registries (i.e. Wessex, Thames Valley and East Midlands and South Yorkshire). The survival rates for the other registries were relatively similar varying within a difference of 3%.

For isolated severe CHD, the heterogeneity at 28 days and 5 years of age was high (I^2 = 93.4% and 95.6%, respectively). At 5 years of age, OMNI-Net (Ukraine) was the registry with the lowest survival (57.4%, 95% CI 52.1, 62.4), while Saxony-Anhalt (Germany) and Finland registries showed the highest survival of children with severe CHD.

Considering survival at 5 years of age for children with specific CA subgroups, such as isolated transposition of great vessels and isolated diaphragmatic hernia, we observed, as expected, a lower precision of the estimates in some registries due to the smaller numbers of events (Figure S2).

Table 4 shows the infant mortality of children with CAs expressed per 10,000 births in the whole population. The highest mortality rates were in Malta and OMNI-Net (Ukraine) (25.5 and 22.3 per 10,000 live births, respectively). The lowest values were observed for Tuscany (Italy) and Saxony-Anhalt (Germany) (4.1 and 5.8 per 10,000 live births, respectively).

3.3 | Conditional survival

For all the registries, the majority of deaths in infants with CAs occurred in the first 28 days of life. The proportion of deaths within the first 28 days of life amongst the infant deaths ranged from 52.9% in Funen (Denmark) to 73.3% in Malta (Table 4). For the 5-year conditional survival of all anomalies, OMNI-Net (Ukraine) had the lowest survival (93.3%, 95% CI 92.6, 93.9) and Saxony-Anhalt (Germany) and Finland those with the highest (Table 3, Figure S3). Similar to unconditional survival at 5 years, we observed a relatively low survival for the three English registries. For Malta and OMNI-Net (Ukraine), the 5-year conditional survival estimate largely increased compared

TABLE 2 Hazard Ratios (HR) with 95% Confidence Intervals (CI) for risk of infant death (<1 year) and deaths between 1–9 years of age for all anomalies and isolated severe Congenital Heart Defects (CHD) comparing birth year periods (2005–2014 with 1995–2004 [reference]) by registry

	Deaths at <1 year		Deaths at age 1–9 years	
Registry[a]	Number live births	Hazard ratio (95% confidence interval)	Number alive at age 1	Hazard ratio (95% confidence interval)
All anomalies				
Belgium: Antwerp[b]	7853	0.90 (0.75, 1.07)	NA	NA
Denmark: Funen	2425	0.35(0.24, 0.52)	2285	0.36 (0.12, 1.12)
Finland	42,861	0.48 (0.43, 0.53)	41,333	0.58 (0.45, 0.75)
France: Paris	11,443	0.76 (0.64, 0.90)	10,886	0.93 (0.56, 1.56)
Malta[c]	2718	1.23 (0.94, 1.61)	2503	0.65 (0.27, 1.58)
Netherlands: Northern[d]	8400	0.53 (0.44, 0.63)	7850	1.08 (0.69, 1.69)
Norway[e]	27,201	1.03 (0.90, 1.18)	26,237	0.87 (0.63, 1.20)
Spain: Basque Country	5904	0.42 (0.34, 0.52	5540	0.60 (0.34, 1.07)
UK: Wales	18,177	0.92 (0.79, 1.07)	17,068	0.78 (0.56, 1.08)
Total	126,982	0.68 (0.53, 0.89)	113,702	0.75 (0.62, 0.91)
Severe CHD[f]				
Belgium: Antwerp[b]	415	0.40 (0.24, 0.68)	NA	NA
Denmark: Funen	160	0.44 (0.19, 0.99)	130	NC
Finland	2403	0.45 (0.35, 0.58)	2145	0.33 (0.12, 0.89)
France: Paris	574	0.86 (0.58, 1.27)	471	0.80 (0.19, 3.31)
Malta[c]	180	1.14 (0.60, 2.18)	143	NC
Netherlands: Northern[d]	555	0.84 (0.56, 1.26)	450	2.40 (0.83, 6.93)
Norway[e]	1221	0.46 (0.34, 0.63)	1058	1.22 (0.48, 3.11)
Spain: Basque Country	500	0.41 (0.28, 0.62)	394	0.26 (0.07, 0.95)
UK: Wales	968	0.74 (0.50, 1.09)	843	0.61 (0.22, 1.69)
Total	6976	0.59 (0.46, 0.74)	5634	0.72 (0.37, 1.41)

NC = not calculable because model not fitted due to too small numbers.

[a] Only registries with data available for 1995–2014 were included in this table.

[b] For Belgium: Antwerp registry, deaths during the first year of life were only available (NA = not available).

[c] In Malta termination of pregnancy is illegal.

[d] For Netherlands: Northern, due to small number restrictions for all values the last digits are rounded to 0 or 5.

[e] In Norway data available from 1999.

[f] Severe CHD included: 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.

to the unconditional survival (96.8% vs. 90.6% and 93.3% vs. 87.0%, respectively).

For isolated severe CHD, OMNI-Net (Ukraine) was the registry with the lowest survival estimate, although conditional survival compared with unconditional survival increased much more than in other registries (79.4% vs. 57.5%). Also in Malta, conditional survival compared with unconditional survival largely increased (93.5% vs. 78.3%).

In Figure 1, unconditional and conditional survival estimates were plotted showing a strong linear association between the two for all registries apart from Malta. For Finland and OMNI-Net (Ukraine) despite the survival estimates were the highest and lowest, they were both consistent with the association observed in the other registries.

Figure 2 shows the 5-year survival in children with a major CA compared with the prevalence of CAs per 10,000 births. No association between survival and prevalence is expected, hence Finland, Malta and Ukraine appear as potential outliers.

4 | COMMENT

4.1 | Principal findings

This study investigated survival across different European regions through the linkage of population-based CA registries data with mortality data for the period 2005–2014. The overall risk of death by 1 year of age for children born with any major CA in 2005–2014

TABLE 3 Survival estimates of children with a major congenital anomaly of 'All anomalies' and isolated severe Congenital Heart Defects (CHD), at 28 days, at 5 years and at 5 years conditional on surviving at 28 days, with 95% Confidence Intervals (95% CI), by registry (birth year period: 2005–2014)

Registry	28-day-survival (95% CI)	5-year survival (95% CI)	5-year conditional survival (95% CI)
All anomalies			
Belgium: Antwerp[a]	96.4 (95.8, 96.9)	NA	NA
Denmark: Funen	98.5 (97.6, 99.0)	97.0 (95.8, 97.8)	98.4 (97.6, 99.0)
Finland	98.3 (98.1, 98.5)	97.2 (97.0, 97.4)	98.9 (98.8, 99.0)
France: Paris	97.2 (96.7, 97.6)	95.5 (94.9, 96.0)	98.3 (97.9, 98.6)
Germany: Saxony-Anhalt	98.7 (98.3, 99.0)	97.6 (97.1, 98.0)	98.9 (98.5, 99.1)
Italy: Emilia Romagna	98.1 (97.7, 98.4)	96.3 (95.7, 96.8)	98.1 (97.8, 98.5)
Italy: Tuscany	98.4 (97.9, 98.7)	96.6 (96.0, 97.1)	98.2 (97.7, 98.5)
Malta[c]	93.5 (92.0, 94.8)	90.6 (88.7, 92.1)	96.8 (95.6, 97.7)
Netherlands: Northern	96.9 (96.3, 97.4)	94.8 (94.0, 95.4)	97.8 (97.3, 98.3)
Norway	97.8 (97.6, 98.0)	96.3 (95.9, 96.6)	98.4 (98.2, 98.6)
Spain: Basque Country	97.7 (97.1, 98.1)	95.3 (94.5, 95.9)	97.6 (97.0, 98.0)
Spain: Valencian Region	96.7 (96.3, 97.1)	94.4 (93.8, 94.9)	97.5 (97.2, 97.9)
UK: Wales	97.8 (97.5, 98.1)	95.7 (95.3, 96.1)	97.8 (97.5, 98.1)
UK: Thames Valley	95.6 (94.9, 96.3)	91.9 (91.0, 92.8)	96.1 (95.4, 96.7)
UK: Wessex	96.1 (95.5, 96.7)	92.5 (91.6, 93.3)	96.2 (95.6, 96.8)
UK: East Midlands and South Yorkshire	95.7 (95.2, 96.1)	91.9 (91.4, 92.5)	96.1 (95.7, 96.5)
Ukraine: OMNI-Net	93.2 (92.6, 93.9)	87.0 (86.1, 87.9)	93.3 (92.6, 93.9)
Severe CHD[d]			
Belgium: Antwerp[a]	93.6 (89.5, 96.1)	NA	NA
Denmark: Funen	NA[b]	88.7 (78.7, 94.2)	NA[b]
Finland	94.8 (93.5, 96.0)	92.6 (91.0, 94.0)	97.7 (96.7, 98.4)
France: Paris	88.9 (84.5, 92.1)	81.9 (76.7, 86.1)	92.2 (88.1, 94.9)
Germany: Saxony-Anhalt	96.5 (93.7, 98.0)	94.6 (91.4, 96.6)	98.0 (95.6, 99.1)
Italy: Emilia Romagna	94.1 (91.2, 96.0)	89.2 (85.5, 91.9)	94.8 (92.1, 96.6)
Italy: Tuscany	95.6 (92.5, 97.4)	88.0 (83.7, 91.2)	92.0 (88.3, 94.6)
Malta[c]	83.7 (74.4, 89.8)	78.3 (68.4, 85.4)	93.5 (85.1, 97.2)
Netherlands: Northern	87.4 (82.0, 95.4)	79.5 (73.3, 84.4)	91.0 (87.2, 93.8)
Norway	93.9 (92.0, 95.4)	88.4 (85.9, 90.5)	94.1 (92.3, 95.6)
Spain: Basque Country	90.4 (86.1, 93.4)	85.3 (80.3, 89.1)	94.3 (90.6, 96.6)
Spain: Valencian Region	91.8 (89.0, 93.9)	85.4 (81.9, 88.3)	93.1 (90.3, 95.0)
UK: Wales	94.6 (92.4, 96.1)	89.2 (86.4, 91.5)	94.3 (92.1, 95.9)
UK: Thames Valley	90.3 (86.4, 93.1)	81.6 (76.7, 85.6)	90.4 (86.5, 93.2)
UK: Wessex	93.8 (90.9, 95.8)	86.5 (82.6, 89.5)	92.2 (88.9, 94.5)
UK: East Midlands and South Yorkshire	91.9 (89.8, 93.6)	82.6 (79.8, 85.1)	89.9 (87.5, 91.9)
Ukraine: OMNI-Net	72.3 (67.4, 76.7)	57.5 (52.1, 62.4)	79.4 (74.1, 83.8)

[a] For Belgium: Antwerp registry, deaths during the first year of life were only available (NA = not available).

[b] Data for Denmark: Funen could not be displayed due to small numbers (NA=not available).

[c] In Malta termination of pregnancy is illegal.

[d] Severe CHD included: 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.

TABLE 4 Infant deaths (<1 year) of children with a major congenital anomaly per 10,000 live births in the total population; deaths occurring during the first 28 and 7 days as a percentage of deaths occurring during the first year of life, by registry (birth year period: 2005–2014)

Registry	Number infant deaths	Infant deaths per 10,000 births	% deaths at 28 days (of infant deaths)	% deaths at 7 days (of infant deaths)
Denmark: Funen	34	6.8	52.9	41.2
Finland	593	10.0	70.5	57.0
France: Paris	231	8.7	69.3	48.5
Germany: Saxony-Anhalt	100	5.8	60.0	51.0
Italy: Emilia Romagna	185	6.6	57.3	36.8
Italy: Tuscany	124	4.1	57.3	38.7
Malta[a]	105	25.5	73.3	54.3
Netherlands: Northern[b]	170	9.8	70.6	38.2
Norway	491	8.1	66.6	45.6
Spain: Basque Country	146	7.1	57.5	30.8
Spain: Valencian Region	364	9.0	66.2	37.6
UK: Wales	381	11.0	59.3	38.6
UK: Thames Valley	254	9.4	64.6	43.7
UK: Wessex	256	8.6	60.2	37.1
UK: East Midlands and South Yorkshire	628	10.7	63.1	45.1
Ukraine: OMNI-Net	678	22.3	58.1	37.2

Data not available for Antwerp (Belgium).

[a] In Malta termination of pregnancy is illegal.

[b] For Netherlands: Northern, due to small number restrictions for all values the last digits are rounded to 0 or 5.

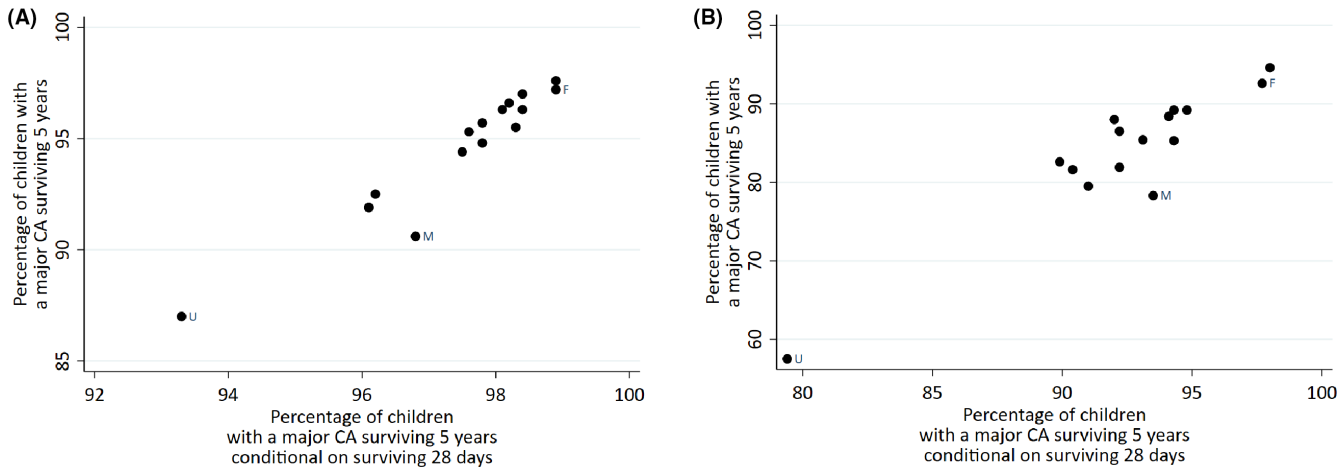

FIGURE 1 Five-year survival compared with 5-year survival conditional on having survived to 28 days in children with a major congenital anomaly (CA) (birth year period: 2005–2014). (A) 'All anomalies', (B) 'Severe congenital heart defects'
U = Ukraine: Omni-Net; M = Malta; F = Finland. Data of 'Severe congenital heart defects' for Denmark: Funen could not be displayed due to small numbers

decreased compared to 1995–2004. We observed a high variability in estimated survival across the European registries. Survival at 5 years of age across registries ranged between 97.6% and 87.0%.

4.2 | Strengths of the study

The main strength of this study is that population-based data from CA registries were linked to local mortality data sources and national/vital statistics using a standardised method developed within EUROlinkCAT project.[20] This can be considered the most accurate approach for investigating survival of children born with CAs. Another strength is the inclusion of specialist high-quality CA data as the EUROCAT registries all follow standard procedures of coding and classification of CAs. The study included data from 17 registries in 12 European countries and highlighted methodological issues, which may be useful in future epidemiological studies investigating survival of children with CAs.

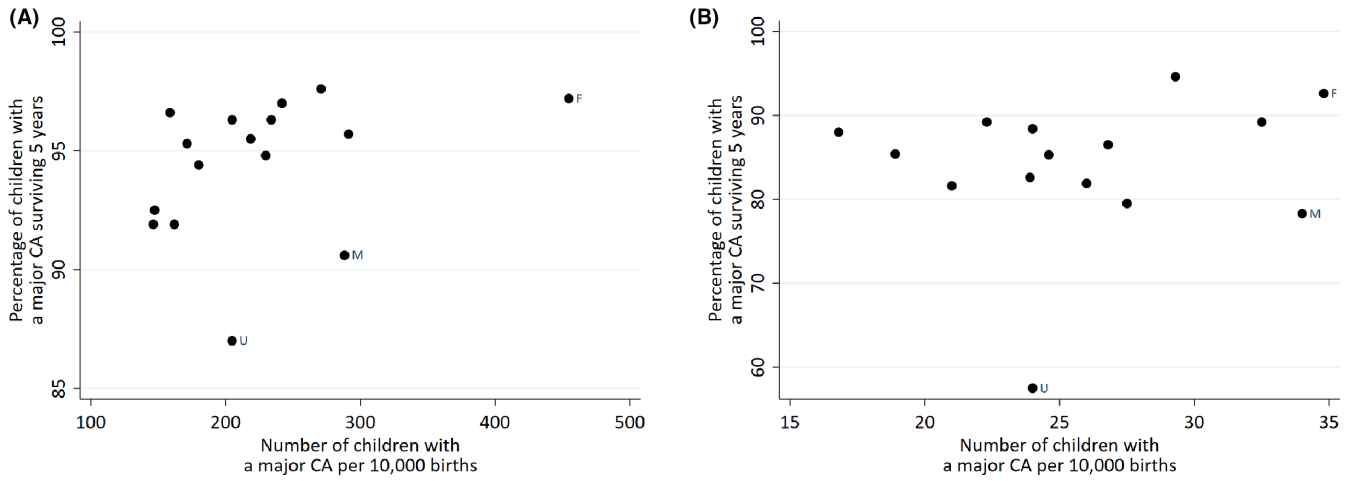

FIGURE 2 Five-year survival in children with a major congenital anomaly compared with the prevalence of children with a major congenital anomaly (CA) (birth year period: 2005–2014). (A) 'All anomalies', (B) 'Severe congenital heart defects'
U = Ukraine: Omni-Net; M = Malta; F = Finland

4.3 | Limitations of the data

Poor linkage success could bias the survival estimates and hence data from individual registries were only included if the linkage was above 85% and for most registries it was above 95%. Loss to follow-up due to emigration could also induce bias. However, in our study populations, the proportion of births lost to follow-up was under 2% for most of the registries, although it was higher for the UK registries (under 10%).[25] A limitation for the investigation of geographical differences is the lack of representation of registries from throughout Europe, with some areas poorly represented, particularly Eastern Europe.

Although the participating registries were all members of an established network that employs common guidelines of registration,[24] some differences in exclusion/inclusion criteria exist, which may have impacted on survival estimates. However, analysing more specific subgroups of CAs can overcome differences in inclusion/exclusion criteria.

4.4 | Interpretation

4.4.1 | Temporal variation

The risk of mortality was lower for all anomalies live births during the period 2005–2014 compared to those in 1995–2004, in particular for infant mortality. This result is consistent with the improvement in survival of children with specific CAs in different countries, including Europe, reported in a recent systematic review.[10]

As TOPFA is associated with severe CAs, its occurrence influences the size and the characteristics of the cohort of live born children investigated in a survival study. A previous study estimated that prevalence of TOPFA accounted for 75.5% of the between-country variation in perinatal mortality in EUROCAT registries[26] Seven of the nine registries able to compare mortality in birth year periods 2005–2014 and 1995–2004 did experience an increase in TOPFA rates between the two time periods (TOPFA rates from the EUROCAT website[27]) and there was a clear association with the decreased hazard ratios (Table 2) and the increased TOPFA rates across these two time periods (Figure S4). In Malta, no change in TOPFA rates occurred as TOPFA is not permitted by law in this country and the mortality did not decrease over time. Funen (Denmark) was the registry with the highest decrease in infant mortality in 2005–2014 compared to 1995–2004 (HR 0.35, 95% CI 0.24, 0.52) and one of the highest increases in TOPFA rates. This may be explained by the impact of the Danish national prenatal screening program implemented in 2005 and offered to all pregnant women free of charge.[28,29] Screening programmes are known to increase the prenatal detection of major CAs with an impact on the rate of TOPFA for the most severe cases and a consequent decrease in infant mortality.[30] Prenatal detection might also improve outcomes of livebirths, especially for some CAs, as it enables prenatal therapy where available and facilitates a more effective clinical management of neonates in tertiary care centres.

The decrease in mortality may also be an underestimate as deaths within the first few days of life were more likely to be missed in the linkage process and that the quality of linkage improved over time.[25] It is, therefore, likely that the true survival in the first birth cohort is lower than that observed and hence that the true improvements in survival are greater.

Since survival has improved over time, when comparing survival between different areas it is essential to use similar birth cohorts and that data from the most recent cohorts only should be used to estimate current survival rates for children with CAs. This ensures greater robustness of the results and less potential for bias.

4.4.2 | Geographical differences

We observed a high variability in estimated survival across the registries, which may be due to a number of factors. First, the quality

of linkage to mortality records may influence survival estimates, as deaths occurring in the first few days of life have been shown to be less likely to be linked. The linkage was less complete for the Italian and English registries in this study possibly resulting in an overestimation of survival. Saxony-Anhalt (Germany) was only able to manually link their births to death registrations, which did not allow an estimate of linkage rates to be obtained. However, the manual linkage may result in missed deaths and may explain the extremely high survival observed. Malta also manually linked their births to death registrations, but due to Malta being an island with a relatively small and stable population, there was more confidence that all deaths had been linked.

Second, we examined survival for all anomalies, which includes a wide range of heterogeneous conditions. EUROCAT issues coding guidelines concerning classifying the CAs. However, the classification of children with CAs is likely to vary between registries, particularly for affiliate registries that only submit aggregate data to EUROCAT and whose individual case data cannot be examined to confirm consistency of coding. We observed high rates of survival for Finland (an affiliate registry), which cannot be due to linkage problems as the quality of the linkage with national vital statistics was 100%. In this case, the total live birth prevalence observed for the Finnish registry was much higher than for the other registries (Table 1), possibly due to the inclusion of more children with less severe CAs. Figure 2 indicates this may be the explanation as both the 5-year survival and the live birth prevalence in Finland were very high. When analysing specific CA subgroups where the inclusion of less severe cases was unlikely, such as diaphragmatic hernia or transposition of great vessels, the survival estimates were more similar to the other registries (Figure S2). Conversely, the low survival for all anomalies observed for the three English registries may be explained by a low live birth prevalence possibly due to underreporting of less severe anomalies. Considering the results of the group of isolated severe CHDs or specific subgroups, the survival estimates for the English registries were similar to those of the other registries. Expressing the mortality of cases with CAs per 10,000 population births, rather than per birth with a CA, provided further insight into both the heterogeneity of `All anomalies' and differences in linkage quality. The infant mortality of cases with CAs in Finland was similar to most of the other registries, confirming that the high survival estimate was partially explained by the inclusion in the cohort of more children with less severe CAs. Registries with a lower level of linkage quality had the lowest mortality rates (i.e. Italian registries and Saxony-Anhalt (Germany)), confirming that poor linkage can bias mortality/survival estimates because early deaths are more likely not to be linked.

Finally, there may be true variations in survival. For the OMNI-Net (Ukraine) registry, the only registry from Eastern Europe, we observed the lowest survival estimates in all the analyses. These results are consistent with the high infant mortality in the general population of Ukraine[11,31] and mortality for CAs.[12] A high risk of mortality under 5 years of age has also been reported for all Eastern Europe.[32] Both the low survival at 28 days and the low five year survival conditional on survival at 28 days (Table 3) indicate that programs in Ukraine concerned with the care of children with CAs may need greater attention.

The lower survival estimates for Malta were expected, since TOPFA is illegal in this country and this results in a higher mortality in the first week/month of life, in particular for severe CAs.[19] When further survival is estimated for live births with CA surviving the first month of life, the 5-year survival significantly improved and became comparable to that of other countries (Figures 1 and S3), again demonstrating that the observed lower survival is likely to be due to the inclusion of live births unlikely to survive beyond the first month of life, that are likely to be TOPFAs in other registries.

A previous study suggested that prenatal diagnoses rates may also account for between-country variations in perinatal mortality in EUROCAT registries[26] as prenatal diagnosis may enable earlier and more effective treatment to occur.

4.4.3 | Methodological issues and recommendations

This study has demonstrated that the linkage of CA data from population-based registries to mortality records from national/vital statistics is an efficient and powerful method of analysing the survival of children born with CAs. A prospective cohort study design using a process of ad-hoc data collection is resource intensive and time-consuming and it would be very difficult to achieve for studies on large cohorts of children with CAs.

Many factors influence the observed survival of children with CAs, including differences across registries in the exclusion/inclusion of less severe anomalies, the prevalence of prenatal screening and subsequent TOPFA, the source of mortality data, linkage success and amount of lost to follow-up may influence the results. All these factors should be considered when interpreting observed geographic and temporal differences. Survival conditional on the first month of life can also provide important additional information. It enables better understanding of the effect of differences in TOPFA rates for the most severe cases with high fatality in the first weeks of life.

Survival following a congenital anomaly is more meaningful when analysed for specific CAs rather than for all anomalies. However, if survival in children with a specific CA is analysed, the numbers of children from each registry are so small that sampling error limits the interpretation of any differences between registries). More precise survival estimates of individual CAs, even if rare, can be calculated pooling data from different registries using a meta-analytical approach as performed in studies of the EUROlinkCAT project.[33,34] Therefore, the purpose of this study was to examine potential sources of bias in sufficiently large samples, to establish recommendations for future meta-analyses across registries.

It is hoped that the assessment of survival of CAs across different geographic areas, after a careful evaluation of the impact of the methodological factors described above, may provide useful information for making inferences about the quality of care provided to children born with CAs. However, additional factors not measured in detail in this study, such as socio-economic inequalities in child mortality,[13,35,36] may also need to be considered.

5 | CONCLUSIONS

This study showed that the use of CA registry data linked to mortality data from national/vital statistics is a useful source of information to monitor the impact of existing policies at European and regional level, to support future optimisation of health care policies and to motivate further research questions. Survival improved in the most recent period (2005–2014). We observed a relatively high variability between registries; however, caution must be taken in the interpretation of differences in survival, with a particular focus on differences across registries in the exclusion/inclusion of less severe anomalies, the prevalence of prenatal screening and subsequent TOPFA, the source of mortality data and linkage success. Future studies should include more areas to widen the geographical coverage and produce findings, which are more representative and generalisable at a European level adopting linkage method such as those presented here.

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CONFLICT OF INTEREST

None declared.

ROLE OF THE FUNDER/SPONSOR

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.

AUTHORS' CONTRIBUTIONS

Santoro, Coi and Morris had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Morris, Santoro, Coi, Pierini, Glinianaia and Rankin involved in concept and design. Loane, Given, Santoro, Coi, Morris, Tan and Reid involved in the development of study methods, including data standardisation and linkage, development of statistical analysis plan, writing analysis programs and statistical analysis. All authors involved in data acquisition, interpretation of the results, critical revision of the manuscript for important intellectual content and approved the final manuscript as submitted and agree to be accountable for major aspects of the work. Santoro and Morris involved in drafting of the manuscript. Morris, Rankin, Pierini, Loane, Garne obtained funding. Morris involved in supervision.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the participating registries of congenital anomalies, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors for scientifically valid requests and with permission of the participating registries of congenital anomalies.

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