



# Risk factors for mortality in infancy and childhood in children with major congenital anomalies: A European population-based cohort study

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**Abstract**

**Background:** Preterm birth and young maternal age are known risk factors for infant and childhood mortality. There is limited knowledge of the impact of these risk factors in children born with major congenital anomalies (CAs), who have inherently higher risks of death compared with other children.

**Objectives:** To investigate the risk factors for mortality up to age 10 years in children born with specific major CAs.

**Methods:** This population-based cohort study involved 150,198 livebirths from 1995 to 2014 in 13 European CA registries linked to mortality data. Cox proportional hazards models estimated the association of gestational age, maternal age and child's sex with death <1 year and 1–9 years for the whole cohort and by CA subgroup. Hazard ratios (HR) from each registry were pooled using multivariate meta-analysis.

**Results:** Preterm birth had a dose–response association with mortality; compared with infants born at 37+ weeks gestation, those born at <28, 28–31 and 32–36 weeks had 14.88 (95% CI 12.57, 17.62), 8.39 (95% CI 7.16, 9.85) and 3.88 (95% CI 3.40, 4.43) times higher risk of death <1 year, respectively. The corresponding risks at 1–9 years were 4.99 (95% CI 2.94, 8.48), 3.09 (95% CI 2.28, 4.18) and 2.04 (95% CI 1.69, 2.46) times higher, respectively. Maternal age <20 years (versus 20–34 years) was a risk factor for death <1 year (HR 1.30, 95% CI 1.09, 1.54) and 1–9 years (HR 1.58, 95% CI 1.19, 2.10). Females had 1.22 (95% CI 1.07, 1.39) times higher risk of death between 1 and 9 years than males.

**Conclusion:** Preterm birth was associated with considerably higher infant and childhood mortality in children with CAs, comparable to estimates reported elsewhere for the background population. Additional risk factors included young maternal age and female sex. Information on risk factors could benefit clinical care and guide counselling of parents following CA diagnoses.

**KEYWORDS**

congenital anomalies, gestational age, maternal age, mortality, risk factors

**1 | BACKGROUND**

Major congenital anomalies (CA), also called birth defects, include structural defects and genetic syndromes, and occur in 2%–3% of livebirths in Europe and the USA.<sup>1,2</sup> CAs are a major cause of death during infancy and childhood, accounting for 21% of infant deaths in the USA<sup>3</sup>; in Europe, 26%, 16% and 9% of deaths at <1 year, 1–4 years and 5–9 years of age, respectively were due to CAs.<sup>4</sup> Although the survival of children with CAs has improved over time,<sup>5–7</sup> CAs remain an important risk factor for mortality in early life.

For children without CAs, preterm birth is a well-established risk factor for infant death. Children born very preterm at 28–30 weeks gestation had over 70 times higher odds of death during infancy and over twice the risk of death after 1 year of age, compared with children born at 37+ weeks.<sup>8</sup> The association of young maternal age with childhood mortality has also been reported for children without CAs.<sup>9,10</sup> There is limited literature concerning the risk factors for death in children with CAs. Analyses of data from the New

York State Congenital Malformations Registry from 1983 to 2006 identified several risk factors for mortality, amongst them child sex, preterm birth and maternal age.<sup>11,12</sup> Studies on children with congenital heart defects (CHDs) and Down syndrome in England have also found preterm birth to be associated with poorer survival up to early adulthood.<sup>5,13,14</sup>

EUROlinkCAT: Establishing a linked European Cohort of Children with Congenital Anomalies (2017–2022) was a multi-centre European project in which 13 population-based CA registries in EUROCAT (European network for the epidemiological surveillance of CAs)<sup>15,16</sup> linked their case data to vital statistics and mortality databases in order to investigate the survival of children with CAs.<sup>17</sup> This study aims to evaluate the association of known risk factors, including preterm birth and maternal age, with mortality during infancy and up to 10 years of age for children with major CAs. Pooling data from multiple registries across several European regions enables the association of these risk factors with mortality to be quantified more accurately for a range of CAs.



## 2 | METHODS

### 2.1 | Study design

This was a multi-centre retrospective data-linkage cohort study. All children born with a major CA between 1995 and 2014 in 13 population-based EUROCAT CA registries from 9 European countries were linked to mortality records up to their 10th birthday or 31/12/2015 (whichever was earlier). Fewer birthyears were included for registries which started after 1995 or ended data collection before 2014. Eleven registries linked to national or regional vital statistics (births, deaths and emigrations) and two could link to death registrations only; for the latter, a child was assumed alive if no death registration was found. For registries linking to vital statistics, birthyears in which under 85% of children were linked to their records were excluded from the study. Six registries linked over 96% of all their cases (>99% for five), whilst two Italian and three English registries had to exclude earlier years with insufficient linkage; after exclusion, the overall linkage rate ranged from 89% (Tuscany) to 97% (East Midlands and South Yorkshire (EMSY)). Further details of the data sources, linkage methods and inclusion criteria have been published previously.<sup>17-19</sup>

### 2.2 | Classification of congenital anomalies

Major CAs are classified into subgroups using ICD-10-BPA or ICD-9-BPA (10th or 9th revision of the International statistical classification of diseases and related health problems with British Paediatric Association extension) codes in accordance with the EUROCAT Guide 1.4.<sup>16</sup> For this study, the CA subgroups analysed included: children with any major anomaly (all anomalies); selected "isolated" anomalies such as CHDs, congenital hydrocephalus, renal and gastrointestinal anomalies; Down syndrome. An isolated CA is defined as a structural CA in one organ system only. Specific cardiac anomalies (e.g. ventricular septal defect, VSD) are nested within the CHD subgroup, and severe cardiac anomalies (e.g. hypoplastic left heart) are nested within both severe CHD and CHD subgroups. The classification of isolated anomalies is performed by a EUROCAT computer algorithm.<sup>20</sup>

### 2.3 | Risk factors

Child's sex, gestational age and maternal age at birth are core variables collected as part of EUROCAT registration<sup>16</sup>; for some registries, selected variables were also available in the linked data. Data from the most complete source for each risk factor (i.e. the EUROCAT or the linked file which had at least 80% non-missing information recorded for the variable) were analysed. Risk factors were categorised as sex (male, female); gestational age in weeks (<28, 28-31, 32-36, 37+) and maternal age in years (<20, 20-34, 35+). Less than 0.01% of children were coded as indeterminate sex and were excluded from the analysis.

### Synopsis

#### Study questions

What is the influence of preterm birth on infant and childhood mortality in children born with major congenital anomalies (CAs) in Europe? Which are the other risk factors for death?

#### What's already known

Preterm birth greatly increases the risk of death in early life, with a distinct dose-response relationship. Major CAs are themselves risk factors for death, making the impact of gestational age less certain in these children.

#### What this study adds

Results from 13 European population-based registries showed that preterm birth increased the risk of death by up to 15-fold in infants with CAs; these risks reduced but persisted into childhood. Younger maternal age at birth and female sex were also moderately associated with increased mortality, particularly beyond infancy.

### 2.4 | Outcomes

Death under 1 year (0-364 days) and 1-9 years (365-3651 days) of age.

### 2.5 | Statistical analysis

As linked individual case data had to be processed within the requesting organisation, analysis was performed by each registry locally using centrally developed Stata scripts. Overall survival for all children with a major CA at 364 days and 3651 days was estimated using Kaplan-Meier analysis. Univariable Cox proportional hazards models estimated the hazard ratios (HRs) of death and 95% confidence intervals (95% CI) for each categorical risk factor compared to a reference level, for each CA subgroup in turn. For example, for gestational age, HRs were obtained for <28, 28-31, 32-36 versus 37+ (reference) weeks gestation. Separate models were fitted for deaths occurring at <1 year and 1-9 years, on the expectation that the HRs may be different in infancy and childhood.<sup>18</sup> Adjusted HRs were also estimated from multivariable models with sex, gestational age, maternal age and birth year (grouped as 1995-2004 and 2005-2014) as covariates, data permitting. Analytic results were submitted by each registry to a Central Results Repository via the project's file transfer portal and collated for meta-analysis. The script ran across all CA subgroups and age groups and output results, even when models failed to converge due to very small numbers of children. Absolute

values  $>20$  for the log HR and/or  $>3$  for its standard error were taken to indicate a lack of convergence and these estimates were excluded from the meta-analysis.

Meta-analysis for each risk factor was performed when there were at least two registries with sufficient valid HRs. The lowest category of gestational age ( $<28$  weeks) was only analysed for the "all anomalies" subgroup; for specific CA subgroups pooled estimates were obtained for the second and third lowest categories for gestational age.

Multivariate meta-analysis (MVMA) with random effects restricted maximum-likelihood and unstructured between-study covariance was used to pool the log HRs for risk factors with more than two levels (gestational age and maternal age). This accounts for the dependency between different levels of each risk factor, because the HRs for gestational age  $<28$ , 28–31 and 32–36 weeks were all compared with the same 37+ weeks reference group.<sup>21,22</sup> MVMA requires known within-study correlation which was not available from the submitted analytical results; instead, a representative value was derived from the estimated variances and covariances using individual participant data from the "all anomalies" subgroup in the English registries (available to first and last authors). Sensitivity analyses were carried out by assuming a range of values for the within-study correlation from 0 (no correlation) to 0.9 (highly correlated), to check that overall results did not change materially. Heterogeneity (total and level-specific) was quantified by Jackson–White–Riley statistics.<sup>23</sup> All analyses were performed using Stata version 17 (StataCorp LLC, Texas, USA).

## 2.6 | Missing data

Overall, the extent of missing data ranged from 1.6% for gestational age to  $<0.1\%$  for child's sex. For each registry, only consecutive years with less than 20% missing information for a risk factor were included in that specific analysis.<sup>19</sup> Most registries had  $<5\%$  missing data for all risk factors, except for four instances (maternal age: Wessex (11.6%), EMSY (8.4%); gestational age: EMSY (7.0%), North Netherlands (6.5%)). Due to low levels of missing data occurring in isolation, multiple imputation was not incorporated into the universal scripts for registry-level analyses. Details on the data available by the registry are given in supplemental tables (Tables S1 to S3).

## 2.7 | 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 for linkage to death registrations, analysis and transmission of aggregated numbers and estimates to a Central Results

Repository were obtained as required by each registry from their local authorities. Further details have been documented in an earlier publication.<sup>24</sup>

## 3 | RESULTS

A total of 150,198 children with major CAs from 13 EUROCAT registries were linked to vital statistics or mortality databases. The number of cases ranged from 2425 to 42,861 per registry with a median follow-up of 7.0 years (range 4.1–7.6 years). Overall, the median survival in the first year after birth was 95.1% and 93.8% by the end of 9 years of age (Table 1).

Table 2 shows the distribution of risk factors for all registries combined. Preterm birth was associated with mortality, with children born  $<32$  weeks accounting for 3.3% of births but 18.0% and 6.3% of deaths in the first year and between 1–9 years, respectively. Female children and those with mothers under 20 or over 34 years old at birth also made up disproportionately more deaths under 1 year and 1–9 years.

### 3.1 | All anomalies

Figure 1 plots the meta-analysis results for risk factors for death  $<1$  year and 1–9 years in children with any major CA. Preterm birth was the factor most strongly associated with increased risks of death, showing a dose–response relationship for both age groups. Children born preterm had up to 15 times higher risk of death  $<1$  year compared with births at 37+ weeks; these risks reduced after infancy but remained at least twofold greater up to age 9. The associations of child's sex and maternal age with mortality were more modest. Overall, females with a CA had a greater risk of death at 1–9 years than males, whilst maternal age  $<20$  and 35+ years were associated with increased risks of death at both ages, compared with 20–34 years; their impact appeared slightly greater at 1–9 years than  $<1$  year but the confidence intervals overlapped. Heterogeneity for all risk factors was moderate (61.5–64.0% except sex: 93.9%)  $<1$  year and low (7.0–17.1%) from 1 to 9 years (Tables S4 and S5). Adjusting for maternal age, gestational age, sex and birthyear simultaneously did not materially change the HRs estimated from models adjusting for each separately.

### 3.2 | Specific congenital anomaly subgroups

The results for gestational age for specific CA subgroups are given in Table 3, with the analysis being performed on a smaller number of registries due to insufficient sample sizes in some registries. A dose–response relationship between preterm birth and risk of death was observed across subgroups but there was variation in strength of

TABLE 1 Registries included, number of livebirths with a major congenital anomaly, length of follow-up and risk of death.

Registry	Included birthyears	Total livebirths	Mean follow-up, years	Risk of death, birth to 364 days, % (95% CI)	Risk of death, birth to 9 years (3651 days), % (95% CI)
Denmark, Funen <sup>a</sup>	1995–2014	2425	7.5	5.4 (4.6, 6.4)	6.2 (5.3, 7.3)
Finland	1995–2014	42,861	7.2	3.5 (3.3, 3.7)	4.3 (4.1, 4.5)
France, Paris	1995–2014	11,624	7.5	4.7 (4.3, 5.1)	5.3 (4.9, 5.7)
Italy, Emilia Romagna	2008–2014	5589	4.1	3.3 (2.9, 3.8)	<sup>b</sup>
Italy, Tuscany	2005–2014	4312	5.6	2.9 (2.4, 3.4)	3.7 (3.1, 4.4)
Malta <sup>c,d</sup>	1995–2014	2718	7.4	7.9 (7.0, 9.0)	9.0 (8.0, 10.1)
Netherlands, North <sup>a</sup>	1995–2014	8400	7.6	6.5 (6.0, 7.0)	7.6 (7.0, 8.2)
Norway	1999–2014	27,201	7.5	3.2 (3.0, 3.4)	3.9 (3.7, 4.1)
Spain, Valencian Region <sup>d</sup>	2007–2014	7389	4.9	4.9 (4.5, 5.4)	<sup>b</sup>
United Kingdom, Thames Valley	2005–2013	3854	5.1	6.7 (6.0, 7.6)	8.1 (7.3, 9.1)
United Kingdom, EMSY	2003–2012	11,288	6.6	6.9 (6.4, 7.4)	8.4 (7.9, 9.0)
United Kingdom, Wessex	2004–2014	4360	5.6	6.5 (5.8, 7.3)	8.3 (7.4, 9.3)
United Kingdom, Wales	1998–2014	18,177	7.0	3.8 (3.6, 4.1)	4.9 (4.6, 5.2)

Abbreviations: CI, confidence interval; EMSY, East Midlands and South Yorkshire.

<sup>a</sup>Counts rounded to nearest 5 due to statistical disclosure control.

<sup>b</sup>Not available.

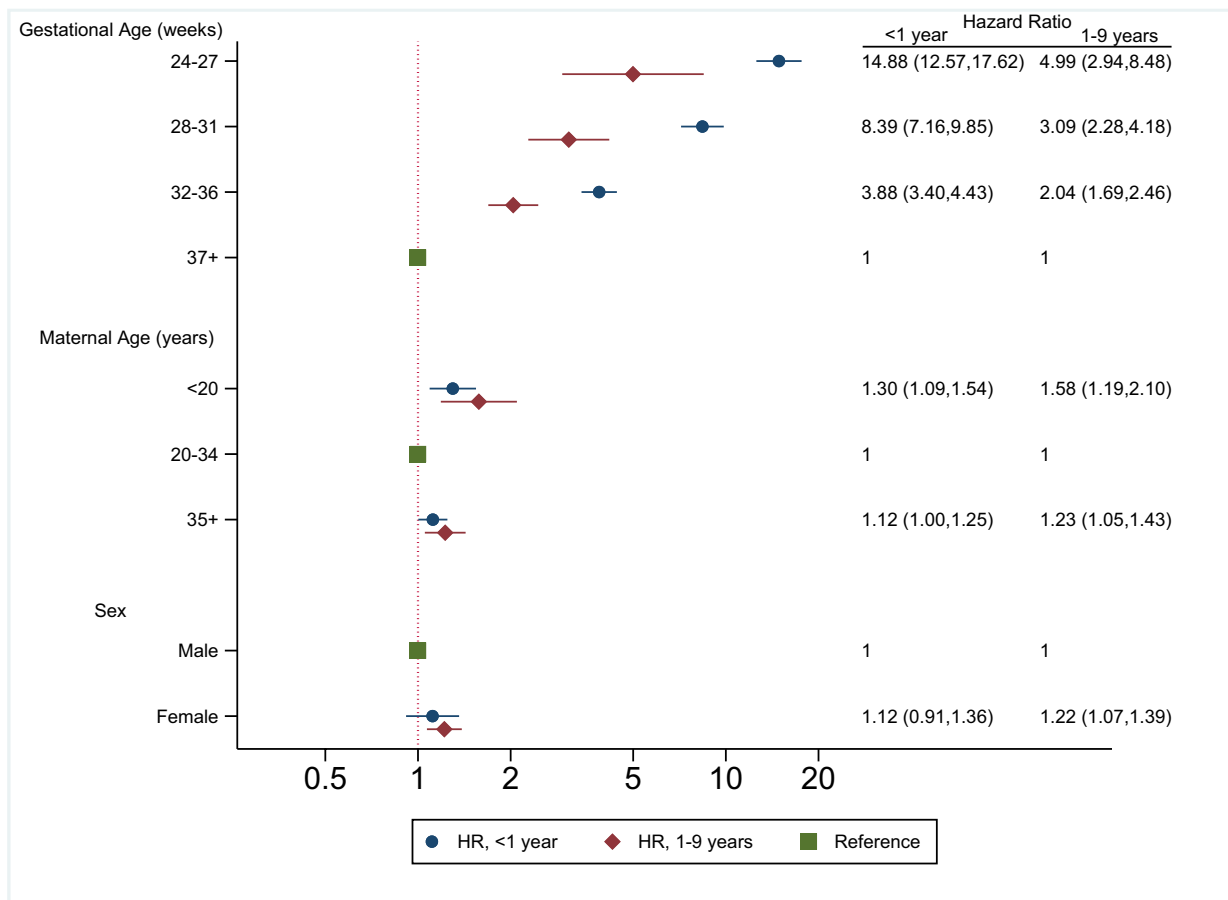
<sup>c</sup>Termination of pregnancy is illegal in Malta.

<sup>d</sup>Linked to mortality databases only.

TABLE 2 Distribution of children by risk factor category and outcome, all registries combined.

	Livebirths	Died <1 year	Died 1–9 years
	N (%)	N (%)	N (%)
TOTAL <sup>a</sup>	150,198 (100.0)	6478 (100.0)	1089 (100.0)
Birthyear			
1995–2004	53,915 (35.9)	2661 (41.1)	492 (45.2)
2005–2014	96,283 (64.1)	3817 (58.9)	597 (54.8)
Gestational age, weeks			
<28	1322 (0.9)	429 (6.6)	17 (1.6)
28–31	3610 (2.4)	740 (11.4)	51 (4.7)
32–36	17,833 (11.9)	1854 (28.6)	207 (19.0)
37+	124,972 (83.2)	3372 (52.1)	798 (73.3)
Missing/unknown	2461 (1.6)	63 (1.0)	31 (2.8)
Maternal age, years			
<20	5388 (3.6)	287 (4.4)	60 (5.5)
20–34	109,846 (73.1)	4558 (70.4)	746 (68.5)
35+	32,960 (21.9)	1558 (24.1)	255 (23.4)
Missing/unknown	2009 (1.3)	65 (1.0)	38 (3.5)
Child's sex			
Male	84,777 (56.4)	3534 (54.6)	576 (52.9)
Female	65,382 (43.5)	2924 (45.1)	528 (48.5)
Missing/unknown	39 (<0.1)	10 (0.2)	0 (0.0)

<sup>a</sup>Counts and percentages for Gestational age, Maternal age and Child's sex do not necessarily sum to TOTAL due to rounding of individual categories in the North Netherlands registry.



**FIGURE 1** Association of all risk factors with mortality at <1 year and 1–9 years (all anomalies combined) estimated by multivariate meta-analysis using data from 13 registries.

effect, particularly for the very preterm category (28–31 weeks). For CHD and severe CHD, where all registries contributed results, the HRs for death at age <1 year were approximately 2–3 times lower (at every gestational age) than that for all anomalies. Preterm birth appears to be a particularly strong risk factor for mortality in children with Down syndrome for the 28–31 weeks category (Table 3). For CHD, severe CHD and Down syndrome, the HRs for death at 1–9 years remain elevated.

Table 4 shows that compared with maternal age 20–34 years, maternal age <20 years was associated with increased risks of death <1 year, particularly for hydrocephalus, VSD, pulmonary valve stenosis and coarctation of aorta. Maternal age 35+ years (compared with 20–34 years) was not observed to be associated with mortality at both ages for the individual CA subgroups.

For all the subgroups except CHD, no apparent association of death with child's sex was found (Table 5). For CHD, females had 24% (95% CI 16, 32) lower risk of death <1 year than males. The reverse was observed for severe CHD, where the risk of death was 67% (95% CI 17, 136) higher for females compared with males for 1–9 years. Results were not available for many CA subgroups after the first year.

A sensitivity analysis investigating the dependence of the MVMA results on the correlation of mortality between the

different risk factor levels within a registry found that varying the within-study correlation from 0 to 0.6 (the maximum observed in the individual data) did not materially change the overall HR estimates. A value of 0.2 (the mean of all possible correlations derived from the individual data) was used throughout as the within-study correlation.

## 4 | COMMENT

### 4.1 | Principal findings

Our study evaluated the association of gestational age, sex and maternal age with infant and childhood mortality in children with CAs. Preterm birth showed a strong dose–response association with increased mortality at both ages; compared with children born at term, very preterm children were up to 15 times more likely to die. The risks were generally lower for children with isolated structural anomalies than children with CAs overall, which includes those with genetic, chromosomal and multiple CAs. Additionally, females with CAs and children born to teenage mothers were found to be at slightly higher risk of death, particularly beyond the first year after birth.



TABLE 3 Association of gestational age with mortality, by selected congenital anomaly subgroup and child's age (unadjusted).

Anomaly	Total livebirths	Registries <sup>a</sup> (n)	Gestational Age, weeks		
			28–31	32–36	37+
Deaths <1 year			Hazard Ratio (95% CI)		
All anomalies <sup>a</sup>	147,737	13	8.39 (7.16, 9.85)	3.88 (3.40, 4.43)	1.00 (Reference)
Congenital hydrocephalus	557	5	4.76 (1.86, 12.19)	3.55 (1.81, 6.97)	1.00 (Reference)
CHD					
All CHD	39,721	13	3.16 (2.34, 4.25)	1.87 (1.47, 2.39)	1.00 (Reference)
Severe CHD	8602	13	2.99 (2.24, 3.99)	1.79 (1.45, 2.22)	1.00 (Reference)
VSD	21,238	10	6.76 (3.73, 12.26)	2.83 (1.81, 4.44)	1.00 (Reference)
ASD	3571	6	4.76 (1.85, 12.26)	2.58 (1.05, 6.31)	1.00 (Reference)
AVSD	206	3	2.73 (0.79, 9.38)	2.29 (0.80, 6.53)	1.00 (Reference)
Tetralogy of Fallot	148	2	13.42 (2.56, 70.25)	3.26 (0.78, 13.68)	1.00 (Reference)
Pulmonary valve stenosis	700	3	9.43 (3.04, 29.31)	1.91 (0.41, 8.96)	1.00 (Reference)
Aortic valve atresia/stenosis	581	3	10.67 (4.13, 27.57)	1.88 (0.89, 3.98)	1.00 (Reference)
Hypoplastic left heart	628	6	5.58 (2.92, 10.67)	1.81 (1.25, 2.63)	1.00 (Reference)
Coarctation of aorta	1566	6	6.32 (3.06, 13.03)	2.01 (1.21, 3.36)	1.00 (Reference)
Down syndrome	5215	9	7.99 (5.22, 12.24)	2.42 (1.82, 3.22)	1.00 (Reference)
Down syndrome with CHD	1759	4	9.62 (3.41, 27.20)	1.71 (1.03, 2.83)	1.00 (Reference)
Down syndrome without CHD/GI	1854	6	24.36 (10.75, 55.21)	4.47 (2.39, 8.35)	1.00 (Reference)
Deaths 1–9 years					
All anomalies	121,700	10	3.09 (2.28, 4.18)	2.04 (1.69, 2.46)	1.00 (Reference)
All CHD	23,553	4	2.37 (1.03, 5.44)	1.34 (0.77, 2.31)	1.00 (Reference)
Severe CHD	2397	2	7.87 (1.83, 33.85)	1.73 (0.60, 4.99)	1.00 (Reference)
Down syndrome	3300	4	5.73 (2.43, 13.48)	1.03 (0.53, 2.00)	1.00 (Reference)

Abbreviations: ASD, atrial septal defect; AVSD, atrioventricular septal defect; CHD, congenital heart defect; CI, confidence interval; GI, gastrointestinal anomalies; VSD, ventricular septal defect.

<sup>a</sup>Registries with no cases in a risk factor category, or without interpretable hazard ratios (e.g. due to deaths occurring in only 1 of 2 categories compared) would be excluded from the meta-analysis.

## 4.2 | Strengths of the study

By pooling data from 13 population-based CA registries across nine European countries linked to national/regional mortality databases, this study has provided accurate and representative estimates of the association between a number of risk factors and mortality for children with a wide range of isolated CAs and Down syndrome at different ages in Europe. The EUROCAT network of registries use clinical expertise and standardised methods for coding specific CA subgroups, ensuring consistency and homogeneity of disease severity in the study cohort. The majority of registries linked to vital statistics databases, which provided detailed information on follow-up duration and outcomes. Overall mortality was broadly comparable across countries except for Malta, whose absolute ban on terminations of pregnancy results in more babies with very severe CAs being born alive. The quality of data on risk factors in the analysis was very good overall (only one registry had >10% missing data in one risk factor), which minimised potential bias from excluded cases.

## 4.3 | Limitations of the data

Due to restrictions on sharing of individual-level data, all regression models had to be pre-specified via centrally developed syntax scripts for registries to run. It was not possible to perform different analyses if the assumption of proportional hazards was not met for different anomalies in different registries. This was mitigated by separating outcomes into <1 year and 1–9 years, as mortality decreases markedly after infancy,<sup>18,25</sup> and proportional hazards are more likely to hold within each period. Further age divisions (e.g. 1–4 and 5–9 years), particularly for individual CAs, would not have been feasible given that relatively few deaths occur in childhood.

The sparsity of data resulting from categorisation of risk factors on small samples also meant that only a limited number of models yielded interpretable results, particularly for 1–9 years. There was insufficient data to perform multivariable analysis to adjust for potential confounders for specific anomalies; however, adjusted estimates for all CAs combined, which additionally controlled for period effects, showed little departure from unadjusted estimates,

TABLE 4 Association of maternal age with mortality, by child's age and congenital anomaly subgroup.

Anomaly	Total livebirths	Registries <sup>b</sup> (n)	Maternal age, years		
			<20	20–34	35+
Deaths <1 year			Unadjusted Hazard Ratio (95% CI)		
All anomalies	148,194	13	1.30 (1.09, 1.54)	1.00 (Reference)	1.12 (1.00, 1.25)
Congenital hydrocephalus	256	2	3.81 (1.32, 10.99)	1.00 (Reference)	1.22 (0.34, 4.38)
CHD					
All CHD	39,477	12	1.40 (1.05, 1.87)	1.00 (Reference)	0.92 (0.75, 1.13)
Severe CHD	7601	10	1.31 (0.98, 1.76)	1.00 (Reference)	0.90 (0.66, 1.22)
VSD	18,866	8	2.42 (1.16, 5.06)	1.00 (Reference)	0.86 (0.62, 1.22)
ASD	5289	5	1.94 (0.89, 4.23)	1.00 (Reference)	0.97 (0.59, 1.59)
AVSD	227	3	1.35 (0.38, 4.79)	1.00 (Reference)	1.79 (0.79, 4.03)
Tetralogy of Fallot	185	2	4.62 (0.46, 46.48)	1.00 (Reference)	1.58 (0.41, 6.11)
Pulmonary valve stenosis	719	3	7.55 (1.58, 36.05)	1.00 (Reference)	1.91 (0.56, 6.57)
Aortic valve atresia/stenosis	<sup>a</sup>				
Hypoplastic left heart	671	7	1.38 (0.89, 2.13)	1.00 (Reference)	0.76 (0.57, 1.01)
Coarctation of aorta	461	3	4.14 (1.10, 15.51)	1.00 (Reference)	1.98 (0.42, 9.46)
Down syndrome	2047	5	2.16 (0.96, 4.84)	1.00 (Reference)	0.79 (0.56, 1.13)
Down syndrome with CHD	681	3	2.38 (0.66, 8.57)	1.00 (Reference)	0.69 (0.41, 1.19)
Deaths 1–9 years					
All anomalies	127,512	11	1.58 (1.19, 2.10)	1.00 (Reference)	1.23 (1.05, 1.43)
All CHD	27,452	5	2.81 (1.05, 7.53)	1.00 (Reference)	1.16 (0.74, 1.83)
Severe CHD	3836	4	2.59 (0.97, 6.89)	1.00 (Reference)	1.05 (0.37, 2.97)
Down syndrome	1890	2	2.07 (0.43, 10.07)	1.00 (Reference)	0.74 (0.31, 1.73)

Abbreviations: ASD, atrial septal defect; AVSD, atrioventricular septal defect; CHD, congenital heart defect; CI, confidence interval; GI, gastrointestinal anomalies; VSD, ventricular septal defect.

<sup>a</sup>Insufficient data for meta-analysis.

<sup>b</sup>Registries with no cases in a risk factor category, or without interpretable hazard ratios (e.g. due to deaths occurring in only 1 of 2 categories compared) would be excluded from the meta-analysis.

which gives reassurance to our results. The association with other risk factors, such as socio-economic status and ethnicity, has not been explored.<sup>26</sup> Due to the absence of data in many registries, the complexities of standardising proxy measures of socio-economic deprivation and the heterogeneity of racial/ethnic categories across Europe, these are topics to be addressed in future work.

#### 4.4 | Interpretation

A Swedish study estimated that compared to 39+ weeks gestation, children born preterm at 22–27, 28–33 and 34–36 weeks had 66.1 (95% CI 63.1, 69.3), 8.7 (95% CI 8.3, 9.0) and 2.6 (95% CI 2.5, 2.7) times higher risks of death, respectively, up to mid-adulthood.<sup>27</sup> Sensitivity analyses excluding children with CAs only slightly altered these results. Our results show similar dose–response relationships in children with CAs, but direct comparison of magnitudes requires caution due to the different reference categories and follow-up periods (partially mitigated as most deaths occur during infancy). The relative risks of death in the lowest gestational

age categories do appear less extreme in children with CAs versus those without.

A French study reported that preterm birth is less strongly associated with mortality in children with CHD than in children from the general population, citing disease severity having a more dominant effect on survival as an explanation.<sup>28</sup> A US study found that the association between CAs and infant mortality strengthened dramatically as gestational age (and birthweight) increased from very low towards normal,<sup>29</sup> but this is a different comparison as our study evaluated the effect of preterm birth on survival amongst children with the same CA. Since CAs are themselves associated with preterm birth,<sup>30,31</sup> the size of effect will depend on the underlying causal pathways between disease severity and low gestational age for the specific CA. Another possibility is that proportionally far fewer very preterm babies with major CAs will be born alive, compared to babies without CAs.

A recent study using linked administrative data of over 21,000 children with severe CHD showed that compared with gestational age  $\geq 39$  weeks, the adjusted HRs for under-five mortality for 24–31, 32–36 and 37–38 weeks were 3.66 (95% CI 3.12, 4.29), 2.51 (95%



**TABLE 5** Association of child's sex with mortality, comparing females to males (reference), by child's age and congenital anomaly subgroup (unadjusted).

Anomaly	<1 year		1-9 years	
	Cases	HR (95% CI)	Cases	HR (95% CI)
All anomalies	150,159	1.12 (0.91, 1.36)	142,402	1.22 (1.07, 1.39)
Congenital hydrocephalus	773	1.15 (0.66, 2.01)	576	0.99 (0.42, 2.35)
Microcephaly	302	0.90 (0.30, 2.69)	161	0.58 (0.04, 8.13)
<b>CHD</b>				
All CHD	40,973	0.76 (0.68, 0.84)	39,234	1.11 (0.84, 1.46)
Severe CHD	8923	1.09 (0.96, 1.24)	7410	1.67 (1.17, 2.36)
Transposition of great vessels	988	1.23 (0.60, 2.52)	345	1.17 (0.35, 3.86)
VSD	23,457	0.80 (0.62, 1.02)	18,287	1.03 (0.63, 1.69)
ASD	7740	0.79 (0.59, 1.05)	5738	1.05 (0.50, 2.20)
AVSD	698	0.67 (0.44, 1.01)	362	1.29 (0.45, 3.65)
Tetralogy of Fallot	884	1.13 (0.60, 2.11)	282	1.01 (0.22, 4.62)
Pulmonary valve stenosis	1838	0.66 (0.36, 1.19)	901	0.62 (0.13, 3.00)
Aortic valve atresia/ stenosis	770	1.21 (0.68, 2.17)	<sup>a</sup>	
Mitral valve anomalies	593	0.62 (0.34, 1.15)	<sup>a</sup>	
Hypoplastic left heart	854	1.17 (0.93, 1.48)	313	2.17 (0.98, 4.82)
Coarctation of aorta	2189	1.09 (0.79, 1.49)	1323	2.17 (0.78, 6.09)
PDA as only CHD in term infants (≥37 weeks)	1131	1.05 (0.28, 3.92)	<sup>a</sup>	
Cystic adenomatous malformation of lung	159	0.82 (0.13, 5.01)	<sup>a</sup>	
Cleft lip with or without palate	2623	1.68 (0.56, 5.04)	<sup>a</sup>	
Cleft palate	431	0.98 (0.27, 3.54)	<sup>a</sup>	
Oesophageal atresia with or without tracheo-oesophageal fistula	393	1.19 (0.44, 3.25)	<sup>a</sup>	
Duodenal atresia or stenosis	184	0.52 (0.08, 3.16)	<sup>a</sup>	
Atresia or stenosis of other parts of small intestine	207	1.54 (0.49, 4.87)	<sup>a</sup>	
Diaphragmatic hernia	642	1.15 (0.85, 1.55)	<sup>a</sup>	
Gastroschisis	755	0.91 (0.34, 2.43)	<sup>a</sup>	
Omphalocele	246	0.82 (0.35, 1.95)	<sup>a</sup>	
Multicystic renal dysplasia	1180	0.99 (0.45, 2.19)	<sup>a</sup>	
Congenital hydronephrosis	2959	1.46 (0.61, 3.48)	<sup>a</sup>	
Limb reduction defects	574	0.75 (0.22, 2.56)	<sup>a</sup>	
Down syndrome	6039	1.09 (0.79, 1.50)	5448	0.88 (0.52, 1.49)
Down syndrome without CHD/GI	2613	1.11 (0.87, 1.40)	1819	1.06 (0.73, 1.55)
Down syndrome with CHD	2586	0.92 (0.59, 1.45)	2093	0.91 (0.43, 1.93)

Abbreviations: ASD, atrial septal defect; AVSD, atrioventricular septal defect; CHD, congenital heart defect; CI, confidence interval; GI, gastrointestinal anomalies; HR, hazard ratio; PDA, patent ductus arteriosus; VSD, ventricular septal defect.

<sup>a</sup>Insufficient data for meta-analysis.

CI 2.24, 2.81) and 1.68 (95% CI 1.53, 2.85), respectively.<sup>5</sup> Previous analyses of children with any CHD in Northern England showed that the HR for death up to 20 years, comparing very preterm (<32 weeks gestation) and moderately preterm (32–36 weeks) versus term (37–41 weeks) births were 6.85 (95% CI 5.11, 9.18) and 1.87 (95% CI 1.54, 2.27), respectively.<sup>13</sup> We have separately analysed deaths <1 year and 1–9 years, but after allowing for this and the different gestational age categories used, our results appear compatible with those reported by others.

A data linkage study in Sweden on children born 1973–2012 also found young maternal age (<20 years compared to 25–29 years) to be associated with offspring mortality (follow-up ranged from 1 to 40 years); the adjusted HRs for non-accidental (diseases) and accidental deaths were 1.14 (95% CI 1.04, 1.24) and 1.96 (95% CI 1.71, 2.25), respectively.<sup>32</sup> Similar results were reported by the New York State study, with an adjusted HR of 1.15 (95% CI 1.06, 1.25) for maternal age <20 years compared with 30–34 years.<sup>11</sup> We also observed that children with CAs whose mothers were aged <20 years had an increased risk of death, and the effect was greater at 1–9 years than <1 year; the association was slightly reduced but remained after adjusting for gestational age, sex and birthyear. It is possible that whilst morbidity and complications of CAs are the dominant contributors to mortality in infancy, the relative lack of resources in younger mothers may influence survival during a child's later years. Lower educational level and household incomes, which are correlated with young maternal age, have been shown to be associated with mortality in childhood and adolescence.<sup>33</sup>

This study also found that for the cohort as a whole, females were at increased risk of death at 1–9 years of age compared with males. This could partially be explained by the inclusion of non-lethal CAs such as hypospadias which only affect males, but also appears to be driven by the higher risk of death for females with severe CHD. Our results are similar to those reported by Wang et al.<sup>11</sup> A UK study on survival of children with serious CHD (defined as structural heart malformations requiring intervention or resulting in death during the first year after birth) up to age 15 years also showed that females had higher adjusted risks of death compared to males (HR: 1.25, 95% CI 1.06, 1.47)<sup>34</sup>; differences in disease severity and better cardiac or lung function in males were cited as possible explanations. Other studies of children admitted to paediatric intensive care units in Europe and the US—many of whom will be children with CAs and other co-morbidities—have reported similar increased risks of death for females compared with males.<sup>35–37</sup> This contrasts with the gender-specific mortality rates in the background population, which are consistently higher for males compared to females from birth to 9 years in Europe and North America.<sup>38</sup>

## 5 | CONCLUSIONS

This study has shown that the associations of preterm birth with mortality in children with CAs are broadly comparable to those

estimated by studies based on the background birth population. The increased risks of death reduce after the first year, but they remain elevated at age 1–9 years. Clinically, these findings not only underscore the need for close monitoring of the health of children who are more at risk, but also the importance of risk assessment when considering induced delivery following a prenatal diagnosis. This study has added to the body of evidence that young maternal age, as well as female sex, are additional risk factors for early mortality, particularly after infancy. This highlights the importance of ensuring that appropriate support is identified and made available to this group of parents and their children, to minimise any risks of death.

## AUTHOR CONTRIBUTIONS

Tan 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. Concept and design: Tan, Morris, Glinianaia, Rankin. Development of study methods, including standardisation of congenital anomalies, development of statistical analysis plan, writing analysis programs and statistical analysis: Tan, Morris, Loane, Given, Brigden, Glinianaia, Rankin. Data acquisition and interpretation of the results: All authors. Drafting of the manuscript: Tan, Morris. Critical revision of the manuscript for important intellectual content: All authors. Obtained funding: Morris, Rankin, Pierini, Loane, Garne. Supervision: Morris. All authors approved the final manuscript as submitted, and agree to be accountable for major aspects of the work.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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## DATA AVAILABILITY STATEMENT

The study data are available from the authors for scientifically valid requests and with the permission of the participating registries. Some registries have time-limited licences for their linked data and may not be able to provide data as requested. <https://www.eurolinkcat.eu/contactinformationanddatarequests>.

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## REFERENCES

- Dolk H, Loane M, Garne E. The prevalence of congenital anomalies in Europe. In: de la Posada Paz M, Groft SC, eds. *Rare diseases epidemiology*. Springer; 2010:349-364.
- Centers for Disease Control and Prevention. *Update on Overall Prevalence of Major Birth Defects—Atlanta, Georgia, 1978–2005*. Centers for Disease Control and Prevention; 2008.
- Ely DM, Driscoll AK. Infant mortality in the United States, 2019: data from the period linked birth/infant death file. *Natl Vital Stat Rep*. 2021;70:1-18.
- Pitt MJ, Morris JK. European trends in mortality in children with congenital anomalies: 2000–2015. *Birth Defects Res*. 2021;113:958-967.
- Gimeno L, Brown K, Harron K, Peppia M, Gilbert R, Blackburn R. Trends in survival of children with severe congenital heart defects by gestational age at birth: a population-based study using administrative hospital data for England. *Paediatr Perinat Epidemiol*. 2023;37:390-400.
- Oster ME, Lee KA, Honein MA, Riehle-Colarusso T, Shin M, Correa A. Temporal trends in survival among infants with critical congenital heart defects. *Pediatrics*. 2013;131:e1502-e1508.
- Santoro M, Coi A, Pierini A, et al. Temporal and geographical variations in survival of children born with congenital anomalies in Europe: a multi-registry cohort study. *Paediatr Perinat Epidemiol*. 2022;36:792-803.
- D'Onofrio BM, Class QA, Rickert ME, Larsson H, Långström N, Lichtenstein P. Preterm birth and mortality and morbidity: a population-based quasi-experimental study. *JAMA Psychiatry*. 2013;70:1231-1240.
- Corbin T. Mortality in Children Aged Under 8: Office for National Statistics. 2004.
- Woodall AM, Driscoll AK. *Racial and Ethnic Differences in Mortality Rate of Infants Born to Teen Mothers: United States, 2017–2018*. National Center for Health Statistics; 2020.
- 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;91:995-1003.
- Wang Y, Liu G, Druschel CM, Kirby RS. Maternal race/ethnicity and survival experience of children with congenital heart disease. *J Pediatr*. 2013;163:1437-1442.
- Best KE, Tennant PWG, Rankin J. Survival, by birth weight and gestational age, in individuals with congenital heart disease: a population-based study. *J Am Heart Assoc*. 2017;6:6.
- Rankin J, Tennant PW, Bythell M, Pearce MS. Predictors of survival in children born with down syndrome: a registry-based study. *Pediatrics*. 2012;129:e1373-e1381.
- Tucker FD, Morris JK, Neville A, et al. EUROCAT: an update on its functions and activities. *J Community Genet*. 2018;9:1-4.
- EUROCAT. Guidelines for data registration v1.4. 2021 Available from [https://eu-rd-platform.jrc.ec.europa.eu/eurocat/data-collection/guidelines-for-data-registration\\_en](https://eu-rd-platform.jrc.ec.europa.eu/eurocat/data-collection/guidelines-for-data-registration_en)
- Morris JK, Garne E, Loane M, et al. 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:e047859.
- Glinianaia SV, Rankin J, Pierini A, et al. Ten-year survival of children with congenital anomalies: a European cohort study. *Pediatrics*. 2022;149:e2021053793.
- 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:e0256535.
- Garne E, Dolk H, Loane M, et al. 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(Suppl 1):S44-S50.
- Jackson D, Riley R, White IR. Multivariate meta-analysis: potential and promise. *Stat Med*. 2011;30:2481-2498.
- Riley RD, Jackson D, Salanti G, et al. Multivariate and network meta-analysis of multiple outcomes and multiple treatments: rationale, concepts, and examples. *BMJ*. 2017;358:j3932.
- Jackson D, White IR, Riley RD. Quantifying the impact of between-study heterogeneity in multivariate meta-analyses. *Stat Med*. 2012;31:3805-3820.
- Claridge H, Tan J, Loane M, et al. Ethics and legal requirements for data linkage in 14 European countries for children with congenital anomalies. *BMJ Open*. 2023;13:e071687.
- Tennant PW, Pearce MS, Bythell M, Rankin J. 20-year survival of children born with congenital anomalies: a population-based study. *Lancet*. 2010;375:649-656.
- Wang Y, Liu G, Canfield MA, et al. Racial/ethnic differences in survival of United States children with birth defects: a population-based study. *J Pediatr*. 2015;166:819-826.
- Crump C, Sundquist J, Winkleby MA, Sundquist K. Gestational age at birth and mortality from infancy into mid-adulthood: a national cohort study. *Lancet Child Adolesc Health*. 2019;3:408-417.
- Laas E, Lelong N, Ancel P-Y, et al. Impact of preterm birth on infant mortality for newborns with congenital heart defects: the EPICARD population-based cohort study. *BMC Pediatr*. 2017;17:124.
- Malcoe LH, Shaw GM, Lammer EJ, Herman AA. The effect of congenital anomalies on mortality risk in white and black infants. *Am J Public Health*. 1999;89:887-892.
- Aliasi M, Snoep MC, van Geloven N, Haak MC. Birthweight and isolated congenital heart defects—a systematic review and meta-analysis. *BJOG*. 2022;129:1805-1816.
- Honein MA, Kirby RS, Meyer RE, et al. The association between major birth defects and preterm birth. *Matern Child Health J*. 2009;13:164-175.



32. Sujan AC, O'Reilly LM, Rickert ME, et al. A nation-wide Swedish cohort study on early maternal age at first childbirth and risk for offspring deaths, accidents, and suicide attempts. *Behav Genet.* 2022;52:38-47.
33. Braudt DB, Lawrence EM, Tilstra AM, Rogers RG, Hummer RA. Family socioeconomic status and early life mortality risk in the United States. *Matern Child Health J.* 2019;23:1382-1391.
34. Knowles RL, Bull C, Wren C, et al. Modelling survival and mortality risk to 15 years of age for a National Cohort of children with serious congenital heart defects diagnosed in infancy. *PLoS ONE.* 2014;9:e106806.
35. Epstein D, Wong CF, Khemani RG, et al. Race/ethnicity is not associated with mortality in the PICU. *Pediatrics.* 2011;127:e588-e597.
36. Esteban E, Bujaldon E, Esparza M, Jordan I, Esteban ME. Sex differences in children with severe health conditions: causes of admission and mortality in a pediatric intensive care unit. *Am J Hum Biol.* 2015;27:613-619.
37. Johansson Frigyesi E, Andersson P, Frigyesi A. Boys have better short-term and long-term survival rates after intensive care admissions than girls. *Acta Paediatr.* 2017;106:1973-1978.
38. UNICEF. Infant and Child Mortality Rates, SDG Regions: Europe and Northern America. In: UN\_IGME, ed. UNICEF Data Warehouse 2005-2020.

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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