Archives of
Disease in Childhood

# Ten-year survival of children with trisomy 13 or trisomy 18: a multi-registry European cohort study

| | |
|---|---|
| Journal: | *Archives of Disease in Childhood* |
| Manuscript ID | archdischild-2022-325068.R2 |
| Article Type: | Original research |
| Date Submitted by the Author: | 01-Feb-2023 |
| Complete List of Authors: | Glinianaia, Svetlana; Newcastle University Faculty of Medical Sciences, Population Health Sciences Institute<br>Rankin, Judith; Newcastle University Faculty of Medical Sciences, Population Health Sciences Institute<br>Tan, Joachim; St George's University of London, Population Health Research Institute<br>Loane, Maria; Ulster University Faculty of Life and Health Sciences, Centre for Maternal, Fetal and Infant Research<br>Garne, Ester; Lillebaelt Hospital - University Hospital of Southern Denmark, Department of Paediatrics and Adolescent Medicine<br>Cavero-Carbonell, Clara; FISABIO, Rare Diseases Research Unit, Foundation for the Promotion of Health and Biomedical Research in the Valencian Region<br>de Walle, Hermien; University of Groningen, University Medical Centre Groningen, Department of Genetics<br>Gatt, Miriam; Malta Congenital Anomalies Registry, Directorate for Health Information and Research<br>Gissler, Mika; Finnish Institute for Health and Welfare, Department of Knowledge Brokers; Academic Primary Health Care Centre<br>Klungsøyr, Kari; University of Bergen Department of Global Public Health and Primary Care; Norwegian Institute of Public Health, Division of Mental and Physical Health<br>Lelong, Natalie; INSERM, Université de Paris Cité, Obstetrical, Perinatal and Paediatric Epidemiology Research Team (EPOPé), CRESS<br>Neville, Amanda; University of Ferrara, IMER Registry (Emilia Romagna Registry of Birth Defects), Centre for Clinical and Epidemiological Research,<br>Pierini, Anna; Institute of Clinical Physiology National Research Council, Unit of Epidemiology of Rare Diseases and Congenital Anomalies; Fondazione Toscana Gabriele Monasterio per la Ricerca Medica e di Sanita Pubblica<br>Tucker, David; Public Health Wales,  Public Health Knowledge and Research<br>Urhoj, Stine; Lillebaelt Hospital - University Hospital of Southern Denmark, Department of Paediatrics and Adolescent Medicine; University of Copenhagen Department of Public Health, Section of Epidemiology<br>Wellesley, Diana; Princess Anne Hospital Wessex Clinical Genetics Service<br>Morris, Joan; St George's University of London, Population Health |

| | |
|---|---|
| | Research Institute |
| Keywords: | Child Health, Epidemiology, Genetics, Mortality, Syndrome |
| | |

*I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.*

*The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.*

*Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.*

# Ten-year survival of children with trisomy 13 or trisomy 18: a multi-registry European cohort study

Svetlana V Glinianaia[1]*, Judith Rankin[1], Joachim Tan[2], Maria Loane[3], Ester Garne[4], Clara Cavero-Carbonell[5], Hermien EK de Walle[6], Miriam Gatt[7], Mika Gissler[8,9,10,11], Kari Klungsøyr[12,13], Nathalie Lelong[14], Amanda J Neville[15], Anna Pierini[16,,17], David Tucker[18], Stine K Urhoj[4,19], Diana Wellesley[20], Joan K Morris[2]

**Affiliations:**
[1]Population Health Sciences Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom;
[2]Population Health Research Institute, St George's, University of London, London, United Kingdom;
[3]Faculty of Life & Health Sciences, Ulster University, Belfast, United Kingdom
[4]Department of Paediatrics and Adolescent Medicine, Lillebaelt Hospital, University Hospital of Southern Denmark, Kolding, Denmark
[5]Rare Diseases Research Unit, Foundation for the Promotion of Health and Biomedical Research in the Valencian Region, Valencia, Spain;
[6]University of Groningen, University Medical Centre Groningen, Department of Genetics, Groningen, The Netherlands;
[7]Malta Congenital Anomalies Registry, Directorate for Health Information and Research, Tal-Pietà, Malta;
[8]Department of Knowledge Brokers, THL Finnish Institute for Health and Welfare, Helsinki, Finland;
[9]Academic Primary Health Care Centre, Region Stockholm, Stockholm, Sweden;
[10]Department of Molecular Medicine and Surgery, Karolinska Institute, Stockholm, Sweden;
[11]University of Turku, Research Centre for Child Psychiatry and Invest Research Flagship, Turku, Finland;
[12]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway;
[13]Division of Mental and Physical Health, Norwegian Institute of Public Health, Bergen, Norway;
[14]Université de Paris Cité, Obstetrical, Perinatal and Paediatric Epidemiology Research Team (EPOPé), CRESS, INSERM, INRA, Paris, France;
[15]IMER Registry (Emilia Romagna Registry of Birth Defects), Centre for Clinical and Epidemiological Research, University of Ferrara, Ferrara, Italy;
[16]Unit of Epidemiology of Rare Diseases and Congenital Anomalies, Institute of Clinical Physiology, National Research Council, Pisa, Italy;
[17]Fondazione Toscana Gabriele Monasterio, Pisa, Italy;
[18]Public Health Wales, Public Health Knowledge and Research, Swansea, United Kingdom;
[19]Section of Epidemiology, Department of Public Health, University of Copenhagen, Copenhagen, Denmark;
[20]Wessex Clinical Genetics Service, Princess Anne Hospital, Southampton, United Kingdom.

***Address for correspondence to:** Svetlana Glinianaia, Newcastle University Population Health Sciences Institute, Faculty of Medical Sciences, Newcastle University, Baddiley-Clark

Building, Richardson Road, Newcastle upon Tyne, NE2 4AX, United Kingdom. Email: svetlana.glinianaia@newcastle.ac.uk

**Short title:** Survival of children with trisomy 13 or 18

**Abbreviations:** CA, congenital anomaly; CI, confidence interval; EUROCAT, European network of population-based registries for the epidemiological surveillance of congenital anomalies; ICD-9 and ICD-10, International Statistical Classification of Diseases and Related Health Problems, Ninth Revision and Tenth Revision; TOPFA, termination of pregnancy for fetal anomaly; T13, trisomy 13; T18, trisomy 18.

## What is already known on this topic?

- Children with trisomy 13 or trisomy 18 have extremely high neonatal and infant mortality.
- A recent Canadian population-based study reported that about 13% of children with trisomy 13 and 10% with trisomy 18 may survive to age 10 years.
- Long-term follow-up population-based studies of survival in children with trisomy 13 or trisomy 18 are lacking.

## What this study adds?

- The majority of children born alive with trisomy 13 or trisomy 18 between 1995 and 2014 in 13 Western European regions died during the first 28 days of life: 66% of children with trisomy 13 and 62% with trisomy 18.
- Survival at age 5 and 10 years was 16% (95% CI 10% to 26%) and 11% (95% CI 6% to 18%) respectively for children with trisomy 13, and 10% (95% CI 7% to 14%) and 8% (95% CI 5% to 13%) respectively for children with trisomy 18.
- Ten-year survival conditional on surviving the first 28 days of life was 32% (95% CI 23% to 41%) and 21% (95% CI 15% to 28%) for trisomy 13 and trisomy 18 respectively.

## How this study might affect research, practice or policy?

- This study demonstrates that reliable survival estimates can be obtained for children with rare anomalies by linking administrative mortality data to data on live births from European population-based congenital anomaly registries and combining results across registries. The results are important for counselling parents after prenatal diagnosis of these conditions.

**ABSTRACT**

**Objective** To investigate the survival to 10 years of age of children with trisomy 13 (T13) and children with trisomy 18 (T18), born 1995-2014.

**Design** Population-based cohort study that linked mortality data to data on children born with T13 or T18, including translocations and mosaicisms, from 13 member registries of EUROCAT, a European network for the surveillance of congenital anomalies.

**Setting** 13 regions in nine Western European countries.

**Patients** 252 live births with T13 and 602 with T18.

**Main outcome measures** Survival at 1 week, 4 weeks and 1, 5 and 10 years of age estimated by random-effects meta-analyses of registry-specific Kaplan-Meier survival estimates.

**Results.** Survival estimates of children with T13 were 34% (95% CI 26% to 46%), 17% (95% CI 11% to 29%) and 11% (95% CI 6% to 18%) at 4 weeks, 1 and 10 years, respectively. The corresponding survival estimates were 38% (95% CI 31% to 45%), 13% (95% CI 10% to 17%), and 8% (95% CI 5% to 13%) for children with T18. The 10-year survival conditional on surviving to 4 weeks was 32% (95% CI 23% to 41%) and 21% (95% CI 15% to 28%) for children with T13 and T18 respectively.

**Conclusions**. This multi-registry European study found that despite extremely high neonatal mortality in children with T13 and T18, 32% and 21% respectively of those who survived to 4 weeks were likely to survive to age 10 years. These reliable survival estimates are useful to inform counselling of parents after prenatal diagnosis.

## INTRODUCTION

Congenital anomalies (CAs), including structural defects, chromosomal and genetic syndromes, affect about 2% to 3% of births in Europe[1] and in the USA,[2] and are a leading cause of infant mortality.[3,4] They are also a growing contributor to mortality of children under five years of age[5] and of older children.[6] Survival of children with major CAs beyond one year has substantially improved during the last few decades due to advances in neonatal care and surgical interventions.[7,8] As shown in our recent multi-centre European study, 10-year survival exceeded 90% for most major structural anomalies and the commonest chromosomal anomaly, Down syndrome (trisomy 21).[9] Trisomy 13 (T13) (Patau syndrome) and trisomy 18 (T18) (Edwards syndrome) are the most common autosomal trisomies after Down syndrome and are characterised by multiple structural anomalies and intellectual disability in survivors. The combined total prevalence including pregnancies resulting in a termination of pregnancy for fetal anomaly (TOPFA), stillbirths and live births varies from 5 to 10 per 10,000 births.[10-12] Children with T13 or T18 have a high mortality risk during the first weeks of life and the majority die during the first year.[11,13-17] Recent population-based US and Canadian studies reported median survival time of 5[14]-12.5[15] days for T13 and 8[14]-9[15] days for T18, while 5-year survival was 9.7% (95% CI 7.2% to 12.5%) for T13 and 12.3% (95% CI 10.1% to 14.8%) for T18 in the USA[14] and 15% (95% CI 10% to 21%) for T13 and 11% (95% CI 8% to 16%) for T18 in Canada.[15] In Canada, conditional 10-year survival for children who survived to 1 year, was 65% (95% CI 46% to 79%) for T13 and 77% (95% CI 56% to 89%) for T18.[15] Recent population-based information on longer-term survival of European children with T13 and T18 is lacking.[7]

The aim of this multi-registry European study was to investigate the survival up to 10 years of age of children born alive with T13 or T18 by linking data from 13 EUROCAT (European network for the surveillance of CAs) population-based registries in nine Western European countries to their local mortality data sources. This study was part of the wider EUROlinkCAT data linkage project that investigated the survival, health and educational outcomes to 10 years of age of European children born with a major CA.[18]

## METHODS

### Design, population and data linkage

We conducted a European, population-based linked cohort study. The full cohort included all live births with a major CA collected and validated by population-based CA registries which are members of EUROCAT (https://eu-rd-platform.jrc.ec.europa.eu/eurocat_en).

Each registry has ethics permissions and procedures for routine surveillance, data collection and transmission of anonymised individual-level data to a central database according to national guidelines. For the EUROlinkCAT study, local ethics approvals or other permissions to link registry data with local mortality data sources were obtained by 12 registries, one registry (Norway) obtained permission to use data that were already linked.

Data on all children with a major CA born alive between 1st January 1995 and 31st December 2014 recorded in the 13 registries in nine Western European countries were linked to administrative mortality data sources up to the child's 10th birthday or to 31st December 2015, whichever was earlier, so that all children have at least one year of follow-up information. Registries linked their CA data to either national/vital statistics (11 registries) or

to mortality records only (two registries) (Table 1). Linkage to national/vital statistics that included both birth and death registration data provided information on the vital status for all linked children (dead or alive) including those who moved to other country areas; in contrast, linkage to mortality records can identify deaths only and hence, children with no death record were assumed to be alive. A detailed description of the linkage process and accuracy of the linked data for each registry together with an analysis of the survival data validity is provided elsewhere.[19] The included birth year periods differed between registries due to different years of EUROCAT membership or due to inclusion of the years with high quality linked data only (Table 1 and Supplemental Table 1). There was no standard approach to neonatal treatment of children with T13/T18 across participating regions.

The inclusion criteria were all liveborn children with a diagnostic code (*International Statistical Classification of Diseases and Related Health Problems, Ninth Revision or Tenth Revision* [*ICD-9 or ICD-10*]) 758.1 (ICD-9) or Q914-Q917 (ICD-10) (karyotype 47,XX +13 or 47,XY +13 and translocations/mosaicism) for T13 and 758.2 (ICD-9) or Q910-Q913 (ICD-10) (karyotype 47,XX +18 or 47,XY +18 and translocations/mosaicism) for T18, meaning that children with less severe forms of T13 and T18 were also included. At a later stage, the registries reported the karyotype for infant deaths and for children who survived beyond one year where possible to confirm long-term survival results.

**Statistical analysis**

The study included the development of a common data model to standardise the local variables available in the national/vital statistics or mortality databases (https://www.eurolinkcat.eu/wp2-

buildingresultsrepository/eurolinkcatpubliccommondatamodels).[18] This formed the basis for the development of centrally written syntax scripts used for checking the data linkage quality and for the local analyses to be run by the participating registries.[18,19]

Each registry calculated the survival probability of children with T13 and T18 at pre-specified ages by running Kaplan-Meier survival analysis on the individual case data to account for censoring, as not all children reached their 10th birthday during the study period. The registry specific Kaplan-Meier survival estimates with 95% confidence intervals (CIs) (all 13 registries), the number at risk (alive at the beginning of each age point), and the number of deaths at each age (all registries, except Netherlands: Northern) were then uploaded to the Central Results Repository at Ulster University (UK) using a secure web platform. The Netherlands: Northern registry rounded the number of deaths to the nearest 0 or 5 after age 4 weeks due to the national small number restrictions, therefore their data could not be included in the meta-analysis.

No individual case data were shared.

The registry-based Kaplan-Meier survival estimates were combined centrally in random-effects meta-analyses of the survival at five ages (1 week, 4 weeks and 1, 5 and 10 years) to estimate the overall survival of children with T13 and T18. The meta-analytic approach applied to these data involved modifying a method proposed by Combescure et al.[20] and is described in detail elsewhere[9] and in Supplemental Box 1.

Kaplan-Meier survival analyses were performed using Stata v16 (College Station, TX: StataCorp LLC, 2019). Meta-analyses were performed using R software.

**RESULTS**

Table 1 shows the data from 13 EUROCAT population-based contributing registries covering a population of 6,159,520 births in 1995-2014. The live birth prevalence of T13 and T18 was much lower than the total prevalence, as total prevalence also includes TOPFAs and stillbirths. Overall, the live birth/total prevalence ratio decreased by about 40% between 1995-2004 and 2005-2014 (from 0.26 to 0.15 for T13 and from 0.22 to 0.13 for T18), which may have resulted from improvement in prenatal diagnosis and higher TOPFA rates.

Figure 1 shows the Kaplan-Meier survival estimates with 95% CIs at age 1 week, 4 weeks and 1 year for infants with T13 and T18 by contributing registries and the pooled survival provided by the meta-analysis. The heterogeneity between registries was high at 1 week (T13: $I^2$=54%; T18: $I^2$=63%) and lowest at 1 year (T13: $I^2$=24%; T18: $I^2$=23%). The variation of the survival estimates and the width of the 95% CIs were relatively high as a result of the different sizes of the population covered by each registry and the rarity of T13.

Table 2 reports pooled survival estimates with 95% CI at age 1 week, 4 weeks, 1, 5 and 10 years for the 252 children born with T13 (total deaths = 226) and the 602 with T18 (total deaths = 535). Forty-five percent of children with T13 and 41% with T18 died within the first week of life, 66% of children with T13 and 62% with T18 died within the first 4 weeks. Although the majority of these children died in infancy, 10.8% (95% CI 5.7% to 17.8%) of children with T13 and 8.0% (95% CI 5.0% to 12.8%) of children with T18 survived to age 10 years.

Pooled survival estimates produced by the sensitivity analysis that included 11 registries with more reliable linkage results (linked to vital/national statistics) were very similar to the survival estimates based on 13 registries (less than one percentage point difference).

Nine of the eleven registries with survivors beyond one year of age provided additional karyotype information for some children which suggest that the percentage of children with less severe trisomy forms was relatively higher among survivors than among infant deaths. We do not report the exact figures as karyotype information was missing in up to 22% of survivors, with substantial variation across registries.

The overall survival at 10 years conditional on surviving to 4 weeks (a third of children with either trisomy survived 28 days) was 32% (95% CI 23% to 41%) for children with T13 and 21% (95% CI 15% to 28%) for children with T18 (Table 2).

**DISCUSSION**

This multi-registry population-based European linked cohort study of liveborn infants delivered in 1995-2014 with T13 and T18 reported that over 60% of these infants died during the first 28 days of life and over 80% did not survive to their first birthday. Despite such high infant mortality, 16% and 10% of children with T13 and T18 respectively survived to 5 years and 11% (T13) and 8% (T18) survived to 10 years. The 10-year survival conditional on surviving to 28 days was 32% for children with T13 and 21% for children with T18. The survival estimates were relatively consistent between the contributing registries at 1 year, but there was a substantially higher heterogeneity at 1 week.

Due to very high infant mortality of live births with T13 and T18, earlier studies reported survival during infancy only. However, more recent population-based studies have demonstrated that approximately 6% to 20% of these children survived the first year[11,13-17,21,22] and around 10% survived up to 10 years[15,22] (Table 3). Our study's survival estimates at 1 month, 1 year and 5 years for European children with trisomy 18 are mostly in agreement with large recent international studies that included any trisomy variants[11,14,15] (Table 3). Ten-year survival is also comparable with that in a Canadian study covering a similar birth year period.[15] For children with T13, there is slightly more inconsistency in survival estimates between the published studies, in particular for longer-term survival. For example, 5-year survival of children with T13 is similar in our European study and the mentioned Canadian study,[15] while it is higher than in other large recent studies[11,14] (Table 3). As expected, the 1-, 5- and 10-year survival in our study that included children with any cytogenetic variants was higher than in studies reported for children with full trisomies[13,17,21] (Table 3), as partial and mosaic variants are associated with a higher survival. In addition, improved survival in more recent years may be associated with a wider use of neonatal intensive care in infants with T13 and T18 than previously, and surgical interventions[15,23-25] in some infants who survived the first week/month. For example, a recent single-centre Japanese study reported improvement in 3-year survival of children with T18 from 13.8% in 2008-2012 to 44.4% in 2013-2017, likely resulting from increased surgical interventions in the later period in infants with T18 admitted to a paediatric tertiary centre within the first 7 days of life.[25] Our study confirmed that children who survived the first 28 days of life had a higher likelihood of survival to age 10 years: 32% for children with T13 and 21% for children

with T18 compared to 30% (95% CI 20% to 41%) for T13 and 28% (95% CI 19% to 38%) for T18 in a Canadian study conditional on surviving to 30 days.[15]

Despite accumulating evidence of improvement in survival as a result of neonatal intensive treatment and surgical interventions in children with T13 and T18,[15,24-28] there is still some controversy regarding treatment strategies including cardiac surgery for patients with T13 and T18 due to poor prognosis for more vulnerable patients, significant neurodevelopmental disability in survivors, sparse information on quality of life of the children and families, high individual and societal costs, and a number of ethical issues involved.[29-35] Although the approaches to care of live births with T13 and T18 may differ between countries, with reports on neonatal intensive care and surgical interventions mostly from North America and Japan,[15,23,25,26,28,30,33] current medical expert's view is developing towards evidence-based individualised medical care of these children[24,28,30] with careful consideration of condition severity and co-morbidities, and discussions with parents taking into account their wishes and values and respecting their informed decisions.[29,31,32,36,37]

The main study strength was the follow-up of children with T13 and T18 to 10 years of age to determine the pooled survival estimates of these children using linked data between high-quality population-based specialised CA registries from 13 regions across nine Western European countries and their mortality data sources, including high quality linked data from national/vital statistics for 11 of 13 registries. This resulted in the creation of a large European cohort of children with T13 and T18 with 10-year survival data, which increased the study's statistical power and the reliability of its survival estimates. A further strength was a combination of standardised approaches to data collection, coding and classification in

EUROCAT registries and standardising the linked mortality data to a EUROlinkCAT common data model, development of standardised syntax scripts and production of standardised analytic results.

This study was limited to survival data only for children with T13 or T18 and therefore, no information on morbidity, hospitalisation or surgical interventions was available to explore their association with survival. Although the EUROCAT registries collect information on cytogenetic variants of these chromosomal syndromes and associated structural anomalies in live births, for this study we did not request that level of detail for practical reasons (expecting very small numbers by cytogenetic variant per registry), which prevented reporting pooled survival by trisomy variant and co-morbidities. However, an examination of trisomy variants among long-term survivors suggested a relatively higher percentage of children with mosaicism/translocation among survivors compared to infant deaths, as expected. The survival results for the Netherlands: Northern registry were included for the first four weeks of life only as after this age the number of survivors was too small and could not be included in the meta-analysis due to the national small number restrictions. Although the survival data were combined from 13 registries, the relatively low number of survivors beyond 1 year did not allow analysing the association with demographic/infant risk factors.

In conclusion, we confirmed that 1-year survival of children born with T13 or T18 remains low. However, we found that 16% and 10% of children born in 1995-2014 with T13 and T18 respectively survived to 5 years and 11% and 8% respectively survived to 10 years. Reliable information on longer-term survival of live births with T13 and T18 in Western Europe is important for health professionals when counselling parents following prenatal diagnosis of

these conditions and would help parents to make informed decisions in relation to termination of pregnancy. It is also valuable for parents of liveborn children with T13 and T18 to choose the treatment approach optimal for their child in consultation with health professionals.

**ACKNOWLEDGEMENTS**

We are very grateful to the whole EUROlinkCAT Working Group for their contribution to the project (data linkage and standardisation, running syntax scripts): Dr Joanne Given (Ulster University, Belfast, United Kingdom); Drs L. Renée Lutke and Nicole Siemensma-Mühlenberg (University Medical Center Groningen, Groningen, The Netherlands); Dr Oscar Zurriaga, Sandra Moreno Marro, Laia Barrachina Bonet and Laura García Villodre (Foundation for the Promotion of Health and Biomedical Research in the Valencian Region, Valencia, Spain); Dr Sonja Kiuru-Kuhlefelt, Anna Heino and Tuuli Puroharju (THL Finnish Institute for Health and Welfare. Helsinki, Finland); Drs Alessio Coi and Michele Santoro (Institute of Clinical Physiology, National Research Council, Pisa, Italy); ;Drs Gianni Astolfi, Aurora Puccini, Annarita Armaroli (Center for Clinical and Epidemiological Research, University of Ferrara, Ferrara, Italy); Nathalie Bertille and Dr Babak Khoshnood (INSERM, Paris, France); Professor Sue Jordan (Swansea University, Swansea, Wales, United Kingdom); Professor Elizabeth Draper (University of Leicester, Leicester, United Kingdom) and Professor Jenny Kurinczuk (University of Oxford, Oxford, United Kingdom). We also thank Mr Hugh Claridge (Population Health Research Institute, St George's, University of London, London, United Kingdom) for project management.

**Contributors** SVG, JR and JKM 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. SVG, JKM and JR contributed to the study concept and design, development of statistical analysis plan and statistical analysis. JT contributed to the development of statistical analysis plan, wrote analysis programs under supervision by JKM and contributed to statistical analysis. SVG drafted the manuscript and modified it after critical revision for important intellectual content and comments by JR, JKM, JT, ML, EG, CCC, HEKW, MGa, MGi, KK, NL, AJN, AP, DT, SKU and DW. JR, ML, EG, CCC, HEKW, MGa, MGi, KK, NL, AJN, AP, DT, SKU and DW contributed to data acquisition or data standardisation and interpretation of the results. All authors approved the final manuscript as submitted and agree to be accountable for major aspects of the work.

**Funding** The European Union's Horizon 2020 research and innovation programme under grant agreement No. 733001 (Jan 2017 – May 2022) https://ec.europa.eu/programmes/horizon2020/en).

**Competing interests** None declared.

**Ethics approval** Ethical approval has been granted by registries for the collection of the congenital anomaly data and local ethics approvals or other permissions to link registry data with local mortality data sources were obtained for this study.

**Provenance and peer review** Not commissioned; externally peer reviewed.

## REFERENCES


1 European Platform on Rare Disease Registration: EUROCAT. Prevalence charts and tables 2013-2019. Available: https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence_en. [Accessed 25 May 2022].

2 Centers for Disease Control and Prevention. Morbidity and Mortality Weekly Report. Update on Overall Prevalence of Major Birth Defects - Atlanta, Georgia, 1978-2005. 2008. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5701a2.htm.

3 Euro-Peristat Project. European Perinatal Health Report. Core indicators of the health and care of pregnant women and babies in Europe in 2015. 2018. Available: https://europeristat.com/reports/8-our-publications.html. [Accessed 20 April 2021].

4 Heron M. Deaths: Leading Causes for 2017. *Natl Vital Stat Rep* 2019;68:1-77.

5 GBD 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;388:1725-74. doi: 10.1016/S0140-6736(16)31575-6.

6 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;384:894-903. doi: 10.1016/S0140-6736(13)61089-2.

7 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:e1003356. doi: 10.1371/journal.pmed.1003356.

8 Santoro M, Coi A, Morris JK*, 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. doi: 10.1111/ppe.12884.

9 Glinianaia SV, Rankin J, Pierini A*, et al.* Ten-Year Survival of Children With Congenital Anomalies: A European Cohort Study. *Pediatrics* 2022;149:e2021053793. doi: 10.1542/peds.2021-053793.

10 Irving C, Richmond S, Wren C, Longster C, Embleton ND. Changes in fetal prevalence and outcome for trisomies 13 and 18: a population-based study over 23 years. *J Matern Fetal Neonatal Med* 2011;24:137-41. doi: 10.3109/14767051003758879.

11 Goel N, Morris JK, Tucker D*, et al.* Trisomy 13 and 18-Prevalence and mortality-A multi-registry population based analysis. *Am J Med Genet A* 2019;179:2382-92. doi: 10.1002/ajmg.a.61365.

12 Public Health England. National Congenital Anomaly and Rare Disease Registration Service. Congenital anomaly statistics 2018. Dandy Booksellers Ltd: 2020. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1008030/NCARDRS_Congenital_anomaly_statistics_report_2018.pdf.

13 Rasmussen SA, Wong LY, Yang Q, May KM, Friedman JM. Population-based analyses of mortality in trisomy 13 and trisomy 18. *Pediatrics* 2003;111:777-84. doi: 10.1542/peds.111.4.777.

14 Meyer RE, Liu G, Gilboa SM*, et al.* Survival of children with trisomy 13 and trisomy 18: A multi-state population-based study. *Am J Med Genet A* 2016;170A:825-37. doi: 10.1002/ajmg.a.37495.

15 Nelson KE, Rosella LC, Mahant S, Guttmann A. Survival and Surgical Interventions for Children With Trisomy 13 and 18. *JAMA* 2016;316:420-8. doi: 10.1001/jama.2016.9819.

16 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;108:2008-18. doi: 10.1111/apa.14833.

17 Wu J, Springett A, Morris JK. Survival of trisomy 18 (Edwards syndrome) and trisomy 13 (Patau Syndrome) in England and Wales: 2004-2011. *Am J Med Genet A* 2013;161A:2512-8. doi: 10.1002/ajmg.a.36127.

18 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. doi: 10.1136/bmjopen-2020-047859.

19 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. doi: 10.1371/journal.pone.0256535.

20 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;33:2521-37. doi: 10.1002/sim.6111.

21 Niedrist D, Riegel M, Achermann J, Schinzel A. Survival with trisomy 18--data from Switzerland. *Am J Med Genet A* 2006;140:952-9. doi: 10.1002/ajmg.a.31172.

22 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 (Part A)* 2011;91:995-1003. doi: 10.1002/bdra.22858.

23 Nelson KE, Hexem KR, Feudtner C. Inpatient hospital care of children with trisomy 13 and trisomy 18 in the United States. *Pediatrics* 2012;129:869-76. doi: 10.1542/peds.2011-2139.

24 Carey JC. Emerging evidence that medical and surgical interventions improve the survival and outcome in the trisomy 13 and 18 syndromes. *Am J Med Genet A* 2020;182:13-4. doi: 10.1002/ajmg.a.61370.

25 Tamaki S, Iwatani S, Izumi A*, et al.* Improving survival in patients with trisomy 18. *Am J Med Genet A* 2022;188:1048-55. doi: 10.1002/ajmg.a.62605.

26 Kosho T, Nakamura T, Kawame H, Baba A, Tamura M, Fukushima Y. Neonatal management of trisomy 18: clinical details of 24 patients receiving intensive treatment. *Am J Med Genet A* 2006;140:937-44. doi: 10.1002/ajmg.a.31175.

27 Kosho T, Carey JC. Does medical intervention affect outcome in infants with trisomy 18 or trisomy 13? *Am J Med Genet A* 2016;170A:847-9. doi: 10.1002/ajmg.a.37610.

28 Carvajal HG, Callahan CP, Miller JR, Rensink BL, Eghtesady P. Cardiac Surgery in Trisomy 13 and 18: A Guide to Clinical Decision-Making. *Pediatr Cardiol* 2020;41:1319-33. doi: 10.1007/s00246-020-02444-6.

29 Kosho T, Kuniba H, Tanikawa Y, Hashimoto Y, Sakurai H. Natural history and parental experience of children with trisomy 18 based on a questionnaire given to a Japanese trisomy 18 parental support group. *Am J Med Genet A* 2013;161A:1531-42. doi: 10.1002/ajmg.a.35990.

30 Janvier A, Farlow B, Barrington K. Cardiac surgery for children with trisomies 13 and 18: Where are we now? *Semin Perinatol* 2016;40:254-60. doi: 10.1053/j.semperi.2015.12.015.

31 McCaffrey MJ. Trisomy 13 and 18: Selecting the road previously not taken. *Am J Med Genet C Semin Med Genet* 2016;172:251-6. doi: 10.1002/ajmg.c.31512.

32 Pallotto I, Lantos JD. Treatment Decisions for Babies with Trisomy 13 and 18. *HEC Forum* 2017;29:213-22. doi: 10.1007/s10730-017-9319-2.

33 Cooper DS, Riggs KW, Zafar F*, et al.* Cardiac Surgery in Patients With Trisomy 13 and 18: An Analysis of The Society of Thoracic Surgeons Congenital Heart Surgery Database. *J Am Heart Assoc* 2019;8:e012349. doi: 10.1161/JAHA.119.012349.

34 Weaver MS, Birge N, Hsu H*, et al.* Mixed method study of quality of life for children with trisomy 18 and 13 after cardiac surgery. *Cardiol Young* 2020;30:231-7. doi: 10.1017/S1047951120000013.

35 Neubauer K, Boss RD. Ethical considerations for cardiac surgical interventions in children with trisomy 13 and trisomy 18. *Am J Med Genet C Semin Med Genet* 2020;184:187-91. doi: 10.1002/ajmg.c.31767.

36 Pyle AK, Fleischman AR, Hardart G, Mercurio MR. Management options and parental voice in the treatment of trisomy 13 and 18. *J Perinatol* 2018;38:1135-43. doi: 10.1038/s41372-018-0151-6.

37 Cleary JP, Janvier A, Farlow B, Weaver M, Hammel J, Lantos J. Cardiac Interventions for Patients With Trisomy 13 and Trisomy 18: Experience, Ethical Issues, Communication, and the Case for Individualized Family-Centered Care. *World J Pediatr Congenit Heart Surg* 2022;13:72-6. doi: 10.1177/21501351211044132.

38 Higgins J, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557. doi: 10.1136/bmj.327.7414.557.

## Figure legends

**Figure 1** Registry-specific Kaplan-Meier survival estimates with 95% confidence intervals and the combined survival: a) at 1 week, b) 4 weeks and c) 1 year for children with trisomy 13 and trisomy 18

**Note:** DK, Funen = Denmark: Funen; FR, Paris = France: Paris; IT, E Romagna = Italy: Emilia Romagna; IT, Tuscany = Italy: Tuscany; North Neth = Netherlands: Northern; SP, Valencian R = Spain: Valencian Region; UK, CAROBB = UK: Thames Valley; UK, EMSYCAR = UK: East Midlands and South Yorkshire; UK, WANDA = UK: Wessex.
The numbers given in square brackets for each registry at 1 week (a)) are the numbers alive at birth (number at risk), the numbers at risk for age 4 weeks and 1 year are suspended due to small number of cases.

The registries are ordered in descending order of survival estimates. The number of presented registries differs depending on the data available at certain age, e.g. there were no live births with trisomy 13 in the Italy: Emilia Romagna registry; the 1-week and 4-week survival for children with trisomy 13 is not presented for the Denmark: Funen registry as there were ≤5 live births; the survival estimates after 4 weeks of age are not presented for the Netherlands: Northern registry due to the national small number restrictions.

**TABLE 1** Participating EUROCAT* registries, birth years, population covered, total and live birth (LB) prevalence of cases with trisomy 13 (T13) and trisomy 18 (T18) (per 10,000 births) by registry

| | | | Trisomy 13 | | Trisomy 18 | |
|---|---|---|---|---|---|---|
| **Participating registries** | **Included birth years** | **Birth population covered†** | **Total prevalence per 10,000 (95% CI)†** | **LB prevalence per 10,000 (95% CI)†** | **Total prevalence per 10,000 (95% CI)†** | **LB prevalence per 10,000 (95% CI)†** |
| ***Registries which linked to national/vital statistics‡*** | | | | | | |
| Denmark: Funen | 1995-2014 | 105,570 | 1.9 (1.2 to 2.9) | 0.1 (0.0 to 0.5) | 5.2 (3.9 to 6.8) | 1.0 (0.5 to 1.9) |
| Finland | 1995-2014 | 1,174,727 | 2.4 (2.1 to 2.7) | 0.7 (0.5 to 0.8) | 6.8 (6.4 to 7.3) | 1.4 (1.2 to 1.6) |
| France: Paris | 1995-2014 | 597,822 | 3.9 (3.4 to 4.4) | 0.3 (0.2 to 0.4) | 11.4 (10.6 to 12.3) | 0.7 (0.5 to 0.9) |
| Italy: Emilia Romagna | 2008-2014 | 282,094 | 1.0 (0.7 to 1.4) | 0 | 3.9 (3.2 to 4.7) | 0.4 (0.2 to 0.7) |
| Italy: Tuscany | 2005-2014 | 299,869 | 1.7 (1.3 to 2.2) | 0.2 (0.1 to 0.4) | 5.1 (4.4 to 6.0) | 0.4 (0.2 to 0.7) |
| Netherlands: Northern | 1995-2014 | 372,192 | 1.5 (1.1 to 2.0) | 0.5 (0.3 to 0.8) | 5.5 ( 4.8 to 6.3) | 1.2 (0.9 to 1.6) |
| Norway | 1999-2014 | 956,939 | 1.9 (1.6 to 2.2) | 0.5 (0.4 to 0.7) | 4.4 (4.0 to 4.9) | 1.2 (1.0 to 1.4) |
| UK: East Midlands and South Yorkshire | 2003-2012 | 717,264 | 2.3 (2.0 to 2.7) | 0.4 (0.3 to 0.6) | 5.4 (4.9 to 6.0) | 0.8 (0.6 to 1.0) |
| UK: Thames Valley | 2005-2013 | 270,327 | 3.4 (2.8 to 4.2) | 0.5 (0.3 to 0.8) | 8.0 (6.9 to 9.1) | 0.9 (0.6 to 1.3) |
| UK: Wales | 1998-2014 | 569,341 | 2.1 (1.8 to 2.6) | 0.4 (0.2 to 0.6) | 5.4 (4.9 to 6.1) | 1.0 (0.8 to 1.3) |
| UK: Wessex | 2004-2014 | 325,339 | 2.9 (2.4 to 3.6) | 0.3 (0.2 to 0.6) | 7.6 (6.7 to 8.6) | 0.9 (0.6 to 1.3) |
| ***Registries which linked to mortality records‡*** | | | | | | |
| Malta | 1995-2014 | 84,737 | 0.7 (0.3 to 1.5) | 0.7 (0.3 to 1.5) | 3.7 (2.5 to 5.2) | 3.1 (2.0 to 4.5) |
| Spain: Valencian Region | 2007-2014 | 403,099 | 1.5 (1.2 to 2.0) | 0.2 (0.1 to 0.4) | 4.1 (3.5 to 4.8) | 0.5 (0.3 to 0.7) |
| **Total** | | **6,159,520** | | | | |

*EUROCAT (European network of population-based registries for the epidemiological surveillance of congenital anomalies)
†Extracted from the EUROCAT website: https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence_en (accessed on 01/06/2022). Total prevalence includes terminations of pregnancy for fetal anomaly (TOPFA), fetal deaths/stillbirths from 20 week' gestation and live births per 10,000 registered live and stillbirths.

‡National/vital statistics include birth and death registration data and all live births will have a record; mortality records only include death registration and live births who remain alive will not have a record.
The registers in Finland, Norway, Wales and Malta are national, while other registries are regional.
In Malta, termination of pregnancy is illegal which explains similar total and live birth prevalence of T13 and T18 in Malta.
95% CI, 95% confidence interval.

**TABLE 2** Pooled survival estimates (with 95% confidence intervals, CI) for five age points up to 10 years of age and 10-year survival conditional on surviving to 4 weeks for children born with trisomy 13 or trisomy 18 in 13 EUROCAT registries in nine Western European countries, 1995-2014

| | | | Survival estimates % (95% CI) | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Trisomy type** | **No. of live births** | **No. of deaths up to 10 years** | **1 week** | **4 weeks** | **1 year** | **5 years** | **10 years** | **10 years conditional on surviving to 4 weeks** |
| Trisomy 13 | 252 | 226 | 55.1 (43.2 to 70.1) | 34.3 (25.7 to 45.7) | 17.4 (10.6 to 28.6) | 16.1 (10.0 to 25.8) | 10.8 (5.7 to 17.8) | 32 (23 to 41) |
| $I^2$ | | | 54% | 38% | 24% | 45% | 37% | |
| Trisomy 18 | 602 | 535 | 59.1 (51.4 to 67.9) | 37.6 (31.4 to 45.1) | 12.8 (9.5 to 17.3) | 10.0 (6.9 to 14.4) | 8.0 (5.0 to 12.8) | 21 (15 to 28) |
| $I^2$ | | | 63% | 41% | 23% | 46% | 0% | |

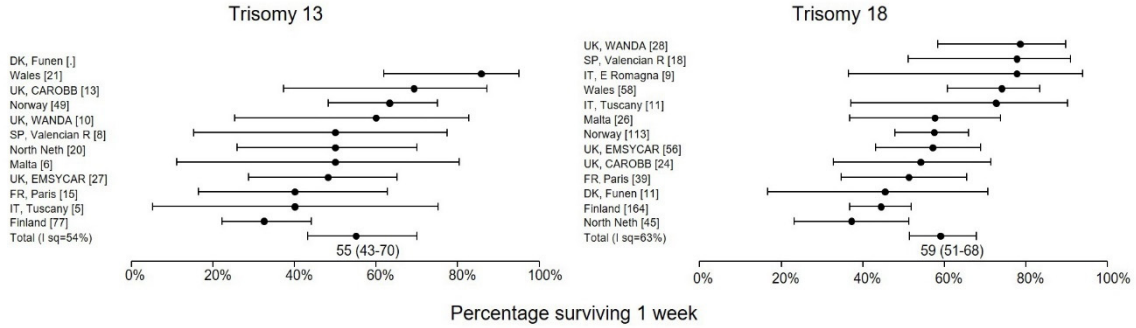
**Note:** There was no complete follow-up for all registries and all birth years to age 10 years, hence, 10-year survival cannot be calculated as deaths/births. Therefore, Kaplan-Meier survival analysis that accounts for censoring was used to estimate registry-specific survival.
The number of deaths from the Netherlands: Northern registry was rounded to the nearest 0 or 5 after age 4 weeks to follow the national restrictions in relation to small numbers and therefore could not be included in the meta-analysis.
$I^2$ statistic was used as a measure of the observed between-registry heterogeneity (with $I^2 > 50\%$ indicating significant heterogeneity[38]) calculated by a random effect meta-analysis.

**TABLE 3** Summary of long-term survival data from population-based studies in children born alive with trisomy 13 or trisomy 18

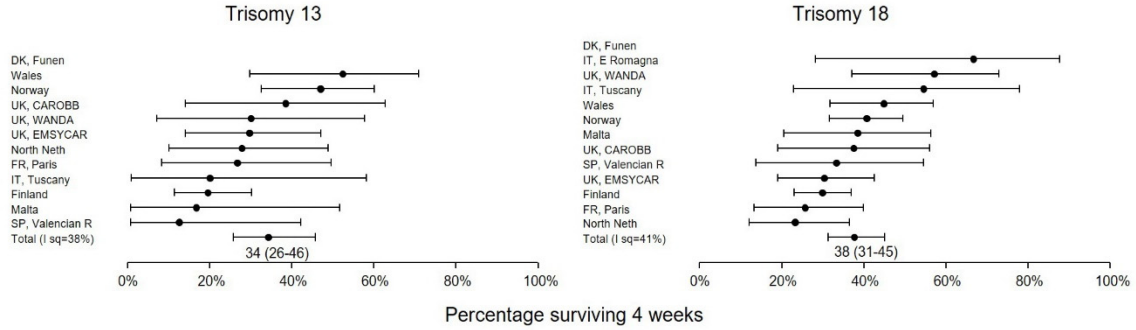
| Study | Rasmussen et al. (2003)[13] | Niedrist et al. (2006)[21] | Wang et al. (2011)[22] | Wu et al. (2013)[17] | Meyer et al. (2016)[14] | Nelson et al. (2016)[15] | Schneuer et al. (2019)[16] | Goel et al. (2019)[11] | Current study |
|---|---|---|---|---|---|---|---|---|---|
| **Trisomy 13** | | | | | | | | | |
| Study period | 1968-1999 | □ | 1983-2006 | 2004-2011 | 1999-2007 | 1991-2012 | 2004-2009 | 1974-2014 | 1995-2014 |
| Geographical region | Georgia, USA | □ | New York State, USA | England & Wales | USA, multi-state | Ontario, Canada | NSW, Australia | Multi-registry | Western Europe |
| Sample size | 70 | □ | 525 | 120 | 693 | 174 | 25 | 2,537 | 252 |
| Trisomy variant included | Mosaicism excluded | □ | Any | Full trisomy | Any | Any | Any | Any | Any |
| Age | **Proportion surviving (%)** | | | | | | | | |
| 1 month | 30.0 | | 38.1 | 29 | 25.5 | 42 | 40.0 | NR | 34.3 |
| 1 year | 8.6 | □ | 21.3 | 8.0 | 11.5 | 19.8 | LN | 13 | 17.4 |
| 5 years | 1 | □ | 18.4 | 3 | 9.7 | 15 | LN | 7 | 16.1 |
| 10 years | NR | □ | NR* | NR | NR | 12.9 | NR | NR | 10.8 |
| **Trisomy 18** | | | | | | | | | |
| Study period | 1968-1999 | 1964-2003 | 1983-2006 | 2004-2011 | 1999-2007 | 1991-2012 | 2004-2009 | 1974-2014 | 1995-2014 |
| Geographical region | Georgia, USA | Switzerland | New York State, USA | England & Wales | USA, multi-state | Ontario, Canada | NSW, Australia | Multi-registry | Western Europe |
| Sample size | 114 | 161 | 773 | 309 | 1,113 | 254 | 34 | 6,122 | 602 |
| Trisomy variant included | Mosaicism excluded | Mosaicism excluded | Any | Full trisomy | Any | Any | Any | Any | Any |
| Age | **Proportion surviving (%)** | | | | | | | | |
| 1 month | 38.6 | 22.4 | 46.8 | 39 | 37.2 | 35 | 35.3 | NR | 37.6 |
| 1 year | 8.4 | 6.2 | 18.8 | 8.0 | 13.4 | 12.6 | 20.6 | 12 | 12.8 |
| 5 years | NR | 2 | 15.2 | NR | 12.3 | 11 | 17.6 | 7.7 | 10.0 |
| 10 years | NR | 1.2 | NR* | NR | NR | 9.8 | NR | NR | 8.0 |

LN, low number (less than 5 cases at risk at that time interval); NR, not reported; NSW, New South Wales; □ the study was restricted to trisomy 18 only; 1 month can differ between 28 and 30 days in different studies, e.g. 28 days in Meyer et al., Wang et al. and in our study.
NR* Ten-year survival not reported, 15-year survival was 16.2% and 13.2% for children with trisomy 13 and 18 respectively.

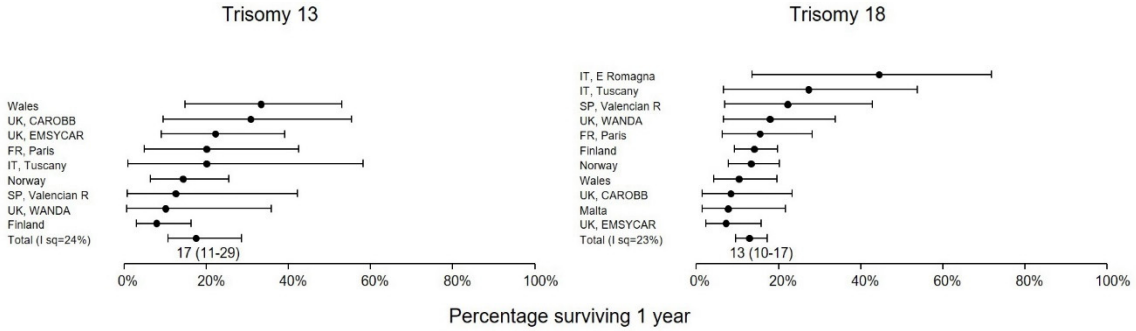
a)




b)




c)



**Supplemental Table 1** Characteristics of the participating population-based EUROCAT* registries and linkage quality

| Registries | Earliest EUROCAT birth year | Population coverage | Linkage method† | Linkage and follow up (FU) performance for registries linking to VS | | Birth years included‡ |
|---|---|---|---|---|---|---|
| | | | | % live births linked | Incomplete FU (% all births) | |
| Denmark: Funen | 1995 | Regional | VS | 100 | 2.6 | 1995-2014 |
| Finland | 1995 | National | VS | 99.9 | 0.5 | 1995-2014 |
| France: Paris | 1995 | Regional | VS | 99.1 | 0.3 | 1995-2014 |
| Italy: Emilia Romagna | 1995 | Regional | VS | 91.4§ | NA | 2008-2014 |
| Italy: Tuscany | 1995 | Regional | VS | 87.2§ | 1.4 | 2005-2014 |
| Malta | 1995 | National | MR | NA** | NA | 1995-2014 |
| Netherlands: Northern | 1995 | Regional | VS | 96.7 | 1.2 | 1995-2014 |
| Norway | 1999 | National | VS | 100 | 1.6 | 1999-2014 |
| Spain: Valencian Region | 2007 | Regional | MR | NA** | NA | 2007-2014 |
| UK: East Midlands and South Yorkshire | 1998 | Regional | VS | 89.5§ | 4.9 | 2003-2012 |
| UK: Thames Valley | 1995 | Regional | VS | 87.8§ | 6.7 | 2005-2013 |
| UK: Wales | 1998 | National | VS | 99.7 | 9.8 | 1998-2014 |
| UK: Wessex | 1995 | Regional | VS | 86.4§ | 3.6 | 2004-2014 |

* EUROCAT (European network of population-based registries for the epidemiological surveillance of congenital anomalies).

† National/vital statistics include birth and death registration data and all live births will have a record, including those who moved to other areas of the country, so deaths occurring in areas of the country not covered by the registry will also be known; mortality records only include death registration data and live births who remain alive will not have a record.

$ Incomplete follow up (for the full 10 years of life or to 31st December 2015): children who were lost to follow up/linkage due to adoption or emigration; the Emilia Romagna registry did not have loss to follow-up information.

‡ Included birth years differed due to different years of EUROCAT membership (Norway, Valencian Region, East Midlands & South Yorkshire and Wales) or due to inclusion of the years with high quality linked data only (Tuscany, Emilia Romagna, Thames Valley, Wessex and East Midlands & South Yorkshire).

§ Because of the lower linkage success in the earlier years (see Loane et al, 2022[1]), only birth years with linkage success over 85% for all years were included (i.e. over 95% from 2003 for East Midlands and South Yorkshire, from 2006 for Thames Valley and from 2009 for Emilia Romagna, over 90% from 2006 for Wessex – see Loane et al, 2022[1]).

** The success of registries linking to mortality records only cannot be estimated in a similar way as to vital statistics (see further information in Loane et al, 2022[1]).

MR - registry linked to mortality record database; VS - registry linked to national/vital statistics data; NA - not applicable as linkage was performed with the mortality database only.

**References**

1 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. doi: 10.1371/journal.pone.0256535.

**Supplemental Box 1.** Detailed description of the meta-analytic approach used to combine the registry-specific survival data produced by Kaplan-Meier survival analysis run by registries participating in the EUROlinkCAT study (adopted from Glinianaia et al, 2022[1])

Combescure proposed the random-effects meta-analysis of survival curves by using the DerSimonian and Laird multivariate procedure[2] on arc-sine transformations of the conditional survival probabilities with a continuity correction of 0.25. However, when analyzed by individual CA subgroups, low numbers of cases in each registry and relatively low death rates for certain CA subgroups resulted in 100% survival for all registries for certain age years. By applying the method above, the model estimated a decrease in survival at these ages despite no deaths occurring, resulting in an underestimation of the overall survival. We therefore applied three adaptations. Firstly, instead of using the fixed continuity correction of 0.25 within the arc-sine transformation, a variable continuity correction equal to 1/n (the number of children alive at the start of the period) was used. This allowed the continuity correction to shrink with increasing sample sizes, while simultaneously reducing the overweighting of high survivals when sample sizes are small, which occurs due to the multivariate meta-analytic technique. This reduced the bias introduced into the country-level estimates when their samples sizes were six children and above. Secondly, data were excluded from the analysis if there were less than six children alive with the specified anomaly in a registry at a certain age. This was required as even the variable 1/n continuity correction still introduced bias for sample sizes below six. Thirdly, if no deaths occurred in any of the registries after a certain age, the overall survival for the remaining ages was imputed as the survival rate for the previous time period. This is a logical assumption as no deaths had been observed. In scenarios where there were no deaths in any registry during specific ages (for example ages 3 and 4), but deaths did occur in later time periods, the meta-analyses were run on a reduced number of time points to limit the prevalence of the “no death” time periods. In these scenarios, instead of the nine yearly time points (2-10) average survival was calculated between ages 1-5 and 6-10. This preserved the use of all the data but reduced the number of time points in which continuity corrections would introduce significant bias. All meta-analyses were performed using R software.

## References

1 Glinianaia SV, Rankin J, Pierini A*, et al.* Ten-Year Survival of Children With Congenital Anomalies: A European Cohort Study. *Pediatrics* 2022;149:e2021053793. doi: 10.1542/peds.2021-053793.

2 Jackson D, White IR, Thompson SG. Extending DerSimonian and Laird's methodology to perform multivariate random effects meta-analyses. *Stat Med* 2010;29:1282-97. doi: 10.1002/sim.3602.

**Re: archdischild-2022-325068.R1** - "Ten-year survival of children with trisomy 13 or trisomy 18: a multi-registry European cohort study".

Dear Editors,

Thank you for your invitation to submit a minor revision of our manuscript. Please find our responses to the Editor's comments below. We enclose a revised manuscript (both the clean version and the version with marked up changes) together with additional supplementary material in response to these comments. Changes in the text of the revised marked up version are highlighted in yellow.

*Editor's comments:*
*Thank you for your detailed responses to the reviewers comments. Within those responses, I believe you have addressed most of their concerns. However, it is not clear that these responses have been fully incorporated into the manuscript submission itself so that, ultimately, the reader (who may have the same/similar questions) understands what you have done and why you have done it that way.*

*Given the tight word count, I would like to see supplementary information (table/figure) that can be included with this publication that more fully explains the registries/countries included/death and survival data validity (including any references to any data validation or quality assessment for death data).*

We thank the Editor for additional comments and suggestions. We have highlighted below what changes have been made in the previously revised manuscript in response to the reviewers' comments and also what supplementary material has been included in this new revision:

**Reviewer 1:**
We have added to the Methods section (page 6):
"There was no standard approach to neonatal treatment of children with T13/T18 across participating regions."

**Reviewer 2:**
1) Given the reviewer's comment, we have modified the first paragraph of the Results (page 8) and included the highlighted sentence below.

"Overall, the live birth/total prevalence ratio decreased by about 40% between 1995-2004 and 2005-2014 (from 0.26 to 0.15 for T13 and from 0.22 to 0.13 for T18), which may have resulted from improvement in prenatal diagnosis and higher TOPFA rates."

2) We have added the following clarification to the Methods section (highlighted) to emphasise that information on vitals status of children who moved to other areas of the

country was available to 11 out of 13 registries who linked their registry data to national/vital statistics:

"Linkage to national/vital statistics that included both birth and death registration data provided information on the vital status for all linked children (dead or alive) including those who moved to other country areas;…"

3) We have also highlighted that the additional examination that we requested the registries to do was to check the karyotype for infant deaths and for children who survived beyond one year and survival status for long-term survivors.

"At a later stage, the registries reported the karyotype for infant deaths and for children who survived beyond one year where possible to confirm long-term survival results."

4) As suggested by the reviewer, we performed a sensitivity analysis by including in the meta-analysis only those 11 registries that linked their registry data to vital statistics and added the following sentence to the Results section (page 9, para 1) to report the results of the sensitivity analysis.

"Pooled survival estimates produced by the sensitivity analysis that included 11 registries with more reliable linkage results (linked to vital/national statistics) were very similar to the survival estimates based on 13 registries (less than one percentage point difference)."

5) As per reviewer's suggestion, we have reworded the corresponding text of the results to the following:

"The variation of the survival estimates and the width of the 95% CIs were relatively high as a result of the different sizes of the population covered by each registry and the rarity of T13."

6*) Discussion, pg 9 lines 59* - We have added the citations to the text of the Discussion (page 10, sentence 2).

"However, more recent population-based studies have demonstrated that approximately 6% to 20% of these children survived the first year[11,13-17,21,22] and around 10% survived up to 10 years[15,22] (Table 3)."

7) Additionally, in response to the Editor's suggestion, we have included the Supplementary Box 1 with the detailed description of the method used in our meta-analysis (enclosed in the end of this letter).

Page 7: "The meta-analytic approach applied to these data involved modifying a method proposed by Combescure et al.[20] and is described in detail elsewhere[9] and in Supplemental Box 1."

8) As per Editor's suggestion, we have also created a Supplementary table on registries contributing their data to this study (enclosed in the end of this letter).

We have modified the text in the Methods section accordingly and removed the names of the corresponding registries given in parenthesis in the previous revision, because they are listed now in the footnote of the Supplementary Table 1.

"The included birth year periods differed between registries due to different years of EUROCAT membership or due to inclusion of the years with high quality linked data only (Table 1 and Supplemental Table 1)."

We have also modified the following sentence referring to the EUROlinkCAT paper that was specifically devoted to a detailed description of the quality and accuracy of linkage to national vital statistics or mortality records (Loane et al, 2022):

"A detailed description of the linkage process and accuracy of the linked data for each registry together with an analysis of the survival data validity is provided elsewhere.[19]"

We thank you for your time and attention to our manuscript and look forward to hearing from you in due course regarding the final editorial decision.

Yours sincerely,

Svetlana V Glinianaia on behalf of the co-authors

**Supplemental Box 1.** Detailed description of the meta-analytic approach used to combine the registry-specific survival data produced by Kaplan-Meier survival analysis run by registries participating in the EUROlinkCAT study (adopted from Glinianaia et al, 2022[1])

Combescure proposed the random-effects meta-analysis of survival curves by using the DerSimonian and Laird multivariate procedure[2] on arc-sine transformations of the conditional survival probabilities with a continuity correction of 0.25. However, when analyzed by individual CA subgroups, low numbers of cases in each registry and relatively low death rates for certain CA subgroups resulted in 100% survival for all registries for certain age years. By applying the method above, the model estimated a decrease in survival at these ages despite no deaths occurring, resulting in an underestimation of the overall survival. We therefore applied three adaptations. Firstly, instead of using the fixed continuity correction of 0.25 within the arc-sine transformation, a variable continuity correction equal to 1/n (the number of children alive at the start of the period) was used. This allowed the continuity correction to shrink with increasing sample sizes, while simultaneously reducing the overweighting of high survivals when sample sizes are small, which occurs due to the multivariate meta-analytic technique. This reduced the bias introduced into the country-level estimates when their samples sizes were six children and above. Secondly, data were excluded from the analysis if there were less than six children alive with the specified anomaly in a registry at a certain age. This was required as even the variable 1/n continuity correction still introduced bias for sample sizes below six. Thirdly, if no deaths occurred in any of the registries after a certain age, the overall survival for the remaining ages was imputed as the survival rate for the previous time period. This is a logical assumption as no deaths had been observed. In scenarios where there were no deaths in any registry during specific ages (for example ages 3 and 4), but deaths did occur in later time periods, the meta-analyses were run on a reduced number of time points to limit the prevalence of the "no death" time periods. In these scenarios, instead of the nine yearly time points (2-10) average survival was calculated between ages 1-5 and 6-10. This preserved the use of all the data but reduced the number of time points in which continuity corrections would introduce significant bias. All meta-analyses were performed using R software.

## References

1 Glinianaia SV, Rankin J, Pierini A*, et al.* Ten-Year Survival of Children With Congenital Anomalies: A European Cohort Study. *Pediatrics* 2022;149:e2021053793. doi: 10.1542/peds.2021-053793.

2 Jackson D, White IR, Thompson SG. Extending DerSimonian and Laird's methodology to perform multivariate random effects meta-analyses. *Stat Med* 2010;29:1282-97. doi: 10.1002/sim.3602.

**Supplemental Table 1** Characteristics of the participating population-based EUROCAT* registries and linkage quality

| Registries | Earliest EUROCAT birth year | Population coverage | Linkage method† | Linkage and follow up (FU) performance for registries linking to VS | | Birth years included‡ |
|---|---|---|---|---|---|---|
| | | | | % live births linked | Incomplete FU (% all births) | |
| Denmark: Funen | 1995 | Regional | VS | 100 | 2.6 | 1995-2014 |
| Finland | 1995 | National | VS | 99.9 | 0.5 | 1995-2014 |
| France: Paris | 1995 | Regional | VS | 99.1 | 0.3 | 1995-2014 |
| Italy: Emilia Romagna | 1995 | Regional | VS | 91.4§ | NA | 2008-2014 |
| Italy: Tuscany | 1995 | Regional | VS | 87.2§ | 1.4 | 2005-2014 |
| Malta | 1995 | National | MR | NA** | NA | 1995-2014 |
| Netherlands: Northern | 1995 | Regional | VS | 96.7 | 1.2 | 1995-2014 |
| Norway | 1999 | National | VS | 100 | 1.6 | 1999-2014 |
| Spain: Valencian Region | 2007 | Regional | MR | NA** | NA | 2007-2014 |
| UK: East Midlands and South Yorkshire | 1998 | Regional | VS | 89.5§ | 4.9 | 2003-2012 |
| UK: Thames Valley | 1995 | Regional | VS | 87.8§ | 6.7 | 2005-2013 |
| UK: Wales | 1998 | National | VS | 99.7 | 9.8 | 1998-2014 |
| UK: Wessex | 1995 | Regional | VS | 86.4§ | 3.6 | 2004-2014 |

* EUROCAT (European network of population-based registries for the epidemiological surveillance of congenital anomalies).

† National/vital statistics include birth and death registration data and all live births will have a record, including those who moved to other areas of the country, so deaths occurring in areas of the country not covered by the registry will also be known; mortality records only include death registration data and live births who remain alive will not have a record.

$ Incomplete follow up (for the full 10 years of life or to 31st December 2015): children who were lost to follow up/linkage due to adoption or emigration; the Emilia Romagna registry did not have loss to follow-up information.

‡ Included birth years differed due to different years of EUROCAT membership (Norway, Valencian Region, East Midlands & South Yorkshire and Wales) or due to inclusion of the years with high quality linked data only (Tuscany, Emilia Romagna, Thames Valley, Wessex and East Midlands & South Yorkshire).

§ Because of the lower linkage success in the earlier years (see Loane et al, 2022[1]), only birth years with linkage success over 85% for all years were included (i.e. over 95% from 2003 for East Midlands and South Yorkshire, from 2006 for Thames Valley and from 2009 for Emilia Romagna, over 90% from 2006 for Wessex – see Loane et al, 2022[1]).

** The success of registries linking to mortality records only cannot be estimated in a similar way as to vital statistics (see further information in Loane et al, 2022[1]).

MR - registry linked to mortality record database; VS - registry linked to national/vital statistics data; NA - not applicable as linkage was performed with the mortality database only.

**References**

1 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. doi: 10.1371/journal.pone.0256535.