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

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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.

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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.