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ORIGINAL ARTICLE

European study showed that children with congenital anomalies often underwent multiple surgical procedures at different ages across Europe

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Abstract

Aim: Children with congenital anomalies often require surgery but data on the burden of surgery for these children are limited.

Methods: A population-based record-linkage study in Finland, Wales and regions of Denmark, England, Italy and Spain. A total of 91 504 children with congenital anomalies born in 1995–2014 were followed to their tenth birthday or the end of 2015. Electronic linkage to hospital databases provided data on inpatient surgical procedures and meta-analyses of surgical procedures were performed by age groups.

Abbreviations: EUROCAT, European network of population-based registries for the epidemiological surveillance of congenital anomalies; EUROlinkCAT, Establishing a linked European Cohort of Children with Congenital Anomalies; 95% CI, 95% confidence intervals.

Results: The percentage of children having surgery in the first year was 38% with some differences across regions and 14% also underwent surgery at age 1–4 years. Regional differences in age at the time of their first surgical procedure were observed for children with cleft palate, hydronephrosis, hypospadias, clubfoot and craniosynostosis. The children had a median of 2.0 (95% CI 1.98, 2.02) surgical procedures before age 5 years with children with oesophageal atresia having the highest median number of procedures (4.5; 95% CI 3.3, 5.8).

Conclusion: A third of children with congenital anomalies required surgery during infancy and often more than one procedure was needed before age 5 years. There was no European consensus on the preferred age for surgery for some anomalies.

KEYWORDS
congenital anomaly, median age, paediatric surgery, population-based record-linkage

1 | INTRODUCTION

Infants and children with congenital anomalies often require surgery but data on the burden of surgery for these children are limited.

Young children require general anaesthesia for surgery and there are concerns about the potential impact of this on long-term cognitive function.[1,2] Surgery in the neonatal period is considered a high-risk procedure despite recent major advances in managing anaesthesia.[3,4] Neonatal surgery also has an impact on family bonding and the initiation of breastfeeding.[5,6] A systematic review found an increased risk of traumatic psychological stress reactions following paediatric surgery, for both the children and the parents.[7]

The European network for surveillance of congenital anomalies (EUROCAT) comprises population-based congenital anomaly registries in 23 countries covering more than 1.7 million (29%) of European births per year.[8] To investigate the survival and morbidity of children with major congenital anomalies, members of the EUROCAT registries initiated the EUROlinkCAT project. The goal was to link data on children with congenital anomalies from EUROCAT registries to electronic health care databases.[9] The EUROlinkCAT study on length of stay in hospital showed that children with congenital anomalies were admitted to hospital more often, and for much longer, than children without congenital anomalies.[10]

The aim of this study was to use population-based data on surgery for children with congenital anomalies to estimate and compare across Europe the burden of disease during childhood. We measured this as a proportion of those undergoing surgery, their age at the time of their first surgical procedure and the number of surgical procedures.

Key Notes

- This European multicentre study explored the burden of surgical procedures for children born with congenital anomalies.
- One in three children born with congenital anomalies underwent surgery in infancy and one in seven also underwent surgery at age 1–4 years.
- There was no European consensus on the preferred age for surgery for some anomalies.

2 | METHOD

This study was a population-based data-linkage cohort study that included data from nine EUROCAT registries covering the whole of Finland and Wales and regions of Denmark, England, Italy and Spain (Table 1). We included the live born children with major congenital anomalies registered in the EUROCAT registries and born between 1995 and 2014. In some cases the start date was later, depending on when the registry started recording cases and the availability of the hospital data.[8,11]

Data on surgical procedures during hospitalisations for all children were obtained by electronic linkage to hospital databases. This data went up to the child's tenth birthday or 31 December 2015, whichever was earlier. This ensured that at least 1 year of follow-up after the birth was available for each child. Data on surgical procedures between 5–10 years of age were available for six of the nine registries, as only children born in 1995–2005 reached 10 years of age before the end of 2015. Details of the methods used in the EUROlinkCAT study including how they linked to the hospital databases and vital statistics have previously been published.[9,10] The aggregate tables and analytic results produced locally were then sent to a Central Results Repository at Ulster University for collation and re-distribution to the study team.

Five regional EUROCAT registries were linked to hospital databases covering the whole country: Funen (Denmark), Tuscany

(Italy), Thames Valley (England), Wessex (England) and the East Midlands and South Yorkshire (England). The hospital databases in the Valencian Region (Spain) and Emilia Romagna (Italy) covered the same region as the EUROCAT registry.

Analyses were performed on all children with major congenital anomalies. We also analysed specific groups of congenital anomalies, where surgery was relevant, with a livebirth prevalence above 1 per 10 000 births. The meta-analyses of specific congenital anomalies included children with isolated major anomalies, which meant that children with associated major anomalies in other organ systems and/or a diagnosis of a genetic condition were excluded.[12] Specific subgroups of congenital heart defects (CHD) will be published separately due to the large amount of data.

The types of surgeries followed the coding systems used in the national health record systems. Italy and Spain used the International Classification of Diseases—Ninth Revision—Clinical Modification for the study period, Wales and England used the Fourth Revision of the Office for Population Censuses and Surveys Classification of Interventions and Procedures. Finland and Denmark used national adaptations of the Nordic Medico-Statistical Committee Classification of Surgical Procedures. As these systems included codes for examinations and procedures such as ultrasound scans and lumbar punctures, a set of rules to determine which codes denoted surgery was developed (Table S1). The six European countries provided lists of how frequently different kinds of surgery were carried out and the procedure codes used in their hospital databases. These were independently reviewed by three paediatricians (AR, MD, EG) from two European countries and a consensus was reached on which codes denoted surgical procedures (Table S2). The coding system in Finland had local adaptations that included more than 9000 codes. Therefore, we decided to review the three-digit codes and compare those with the results from Denmark. There was an 88% agreement between the Finnish and Danish codes.

All EUROCAT registries obtained ethical and other relevant permissions for the data linkage according to their national legislations. Ulster University obtained ethics permission for the Central Results Repository on 15. September 2017.

2.1 | Statistics

Only two groups were included in the meta-analysis, under 1 year and 1–4 years, because some registries had very few children who reached age 10 years during the study period. The term children is used for all age groups. The percentage of children who had surgery were estimated using the Kaplan Meier analysis to account for children not reaching the end of follow-up (censoring) either due to the study end (31 December 2015), death or emigration from the study region or country. The proportion of children who had surgery was out of all children who was still alive at the end of each follow-up period. An alternative method of analysing the data would have been to count all the deaths that occurred before surgery as not having a surgery. Both methods were performed, but only the results from the first method are reported as the results were extremely similar. The pooled estimates of the percentages of children having surgery were obtained by transforming the proportions in each registry having surgery using the double log transformation on the natural log scale and then performing a random effects inverse-variance meta-analyses on the transformed proportions. The timing of first surgery during the first year of life was analysed according to the age categories <7 days, 7–27 days, 28–182 days and 183–364 days (6–12 months). A multilevel model was fitted with registry as the random effect using the gsem command with the mlogit option in STATA version 16 (StataCorp LLC, Texas, USA).

Quantile estimation methods were used to obtain pooled estimates of the median number of surgical procedures and the age at the time of the first surgery.[13,14] The reported medians and quartiles

TABLE 1 Proportion of children with congenital anomalies who underwent surgery, by age group and EUROCAT registry.

Region and birth years	Number of children	Percentage of children having any surgery (95% CI)			
		Age < 1 year	Age 1–4 years	Age 5–9 years	Surgeries at both <1 year and 1–4 years
Denmark, Funen 1995–2014	2423	36 (34–38)	40 (38–42)	31 (29–33)	17 (15–19)
Finland 1997–2014	38 324	28 (27–28)	32 (31–32)	22 (22–23)	11 (11–12)
Italy, Tuscany 2005–2014	4225	31 (30–33)	29 (28–31)	20 (18–23)	10 (8–11)
Italy, Emilia Romagna 2008–2014	5381	38 (36–39)	27 (25–28)	–	10 (9–12)
Spain, Valencian Region 2010–2014	4260	33 (31–34)	25 (24–27)	–	11 (10–13)
Wales 1998–2014	17 448	30 (29–31)	35 (35–36)	27 (26–28)	11 (11–12)
England, Thames Valley 2005–2013	3845	48 (47–50)	40 (39–42)	30 (27–34)	20 (19–22)
England, Wessex 2004–2014	4320	52 (50–53)	43 (41–44)	34 (32–37)	23 (21–25)
England, East Midlands and South Yorkshire 2003–2012	11 278	45 (44–46)	40 (39–41)	29 (28–31)	20 (19–21)
All registries	91 504	38 (32–43)	35 (31–38)		14 (11–18)

for each registry were used to select the best-fitting underlying parametric distribution: normal, log-normal, gamma or Weibull. This enabled us to calculate the asymptotic variance of the medians and subsequent random effects meta-analysis.[13] The analysis was conducted using R statistical software, version 4.0.3 (R Foundation, Vienna Austria) using the R package metamedian v.0.1.6 (McGill University, Quebec Canada).

3 | RESULTS

There were 93 879 children with congenital anomalies registered in the nine EUROCAT registries. Linkage success was very high with 91 504 children (97%) being linked to hospital databases and/or vital statistics and eligible for analysis (Table S3).

Overall, 38% of the children underwent surgery in the first year and 35% at age 1–4 years (Table 1). The proportion of children who underwent a surgical procedure in the first year ranged from 28% in Finland to 52% in the Wessex region (England). The proportion of children who had a surgical procedure decreased across the three age groups: <1 year, 1–4 years and 5–9 years. In Finland, Wales, Emilia Romagna (Italy), Tuscany (Italy) and Valencian Region (Spain) around 10% of children had surgery both in the first year and at 1–4 years of age. In Funen, Denmark and the three English registries around 20% had surgical procedures in both age groups (Table 1). Table 2 describes the age distribution at first surgery within the first year over three different time periods. 1995–2004, 2005–2009, 2010–2014. Compared with earlier years, children born from 2010 were more likely to have their first surgery within the first week of life than between 6–11 months.

The results from the meta-analyses of the proportion of children with specific isolated congenital anomalies that had any surgery before age 5 years are presented in Table 3. These excluded those with associated major anomalies and/or genetic anomalies. The majority of the affected children with facial clefts, gastro-intestinal anomalies or abdominal wall defects had a recorded surgical procedure before age 5 years. Fewer children with renal anomalies had surgical procedures: 35% before the age of 5 years for children with multicystic renal dysplasia and 42% for children with hydronephrosis. In most of the anomaly subgroups the percentage that had a surgical procedure was higher in the first year than at 1–4 years of age. The exceptions were children with hypospadias, multicystic renal dysplasia, limb reduction defects and syndactyly. Only a third of the children with hip dislocation or limb reduction defects had a surgical procedure performed in the first 5 years. Less than 2% of the children died before surgery in all subgroups, except for diaphragmatic hernia where 13% of the children died before surgery.

The median age at the time of their first surgical procedure was <1 week for children with spina bifida, gastro-intestinal anomalies and abdominal wall defects (Table 3). Figure 1 shows the data, by region, for the median age at the time of their first surgical procedure for children with anomalies that usually undergo surgery after the neonatal period. When it came to children with cleft lip, the median age at the time of their first surgical procedure was consistent across regions and there were very small interquartile ranges in all the regions. There were more variation in the median age at the time of their first surgical procedure for children with cleft palate. The median age at the time of their first surgical procedure for children with cleft palate was within the first year (26–50 weeks) for seven of the nine regions. Two had a median age of 60 and 64 weeks, namely Valencian Region (Spain) and Funen (Denmark), respectively. For children with congenital hydronephrosis, the median age at the time of their first surgical procedure was in the first year (15–44 weeks) in seven regions but it was 56 and 59 weeks in the East Midlands and South Yorkshire (England) and Wales, respectively. For children with hypospadias the median age at the time of their first surgical procedure was 1–2 years in seven regions and 2–3 years in Emilia Romagna (Italy) and Valencian Region (Spain). Most children with craniosynostosis underwent the first surgery in the first year with some variation in interquartile ranges in the regions. In the East Midlands and South Yorkshire (England) and the Thames Valley (England) the median age at the time of their first surgical procedure was after 1 year (60 and 64 weeks, respectively). For children with clubfoot the median age at the time of their first surgical procedure ranged from 7 weeks in Wessex (England) to 30 weeks in the East Midlands and South Yorkshire (England) and was 10–20 weeks for five regions. There were very narrow interquartile ranges for most regions, which indicated a general agreement on the age at surgery for clubfoot within each geographical area.

The median number of surgical procedures for children with any congenital anomaly that had surgery before the age of 5 years was 2.0 (95% CI 1.98–2.02), which was consistent for all regions.

The median number of surgical procedures for children with specific isolated congenital anomalies are given in Table 3. This shows that the median number of procedures within the first 5 years was less than three for most of the anomalies presented. For children with congenital cataract the median number of surgical procedures was 3.6 (95% CI 3.1–4.2) and children with oesophageal atresia had

TABLE 2 Timing of surgery during the first year of life (95% CI) in children with congenital anomalies, based on birth years and adjusted for registry.

Birth year	Number of children with surgery in first year	Percentage of children who had any surgery (95% CI)			
		<7 days	7–27 days	28–182 days	6–11 months
1995–2004	8345	19 (15–23)	13 (12–14)	41 (39–43)	27 (26–29)
2005–2009	10 682	22 (17–27)	13 (12–14)	41 (39–44)	24 (22–26)
2010–2014	12 901	25 (19–32)	13 (11–14)	41 (38–44)	22 (19–23)

TABLE 3 The percentage of children with specific isolated congenital anomalies that had any surgery, by age groups.

Isolated congenital anomalies	Number of children born	Percentage who had any surgery (95% CI)			Median number of surgical procedures in the first 5 years (95% CI)	Median age in weeks at first surgery in the first 5 years (95% CI)
		<1 year	1–4 years	<5 years		
Spina bifida	353	72 (55–83)	50 (38–62)	85 (69–93)	2.7 (1.8–3.6)	<1 (<1–<1)
Hydrocephaly	586	48 (37–58)	38 (30–46)	60 (49–69)	2.2 (1.9–2.5)	9.0 (6.0–11.9)
Congenital cataract	628	61 (49–71)	43 (37–48)	70 (62–77)	3.6 (3.1–4.2)	10.0 (6.9–13.1)
CHD	26 442	35 (25–46)	24 (18–29)	50 (40–59)	2.3 (2.0–2.6)	17.6 (9.1–26.0)
Cleft lip with/without cleft palate	2443	95 (92–96)	43 (37–49)	96 (95–98)	2.7 (2.4–3.0)	17.8 (14.7–20.9)
Cleft palate	1915	66 (48–79)	54 (41–65)	91 (89–93)	1.3 (1.0–1.6)	44.7 (36.8–52.6)
Oesophageal atresia	407	90 (86–92)	47 (37–57)	92 (87–95)	4.5 (3.3–5.8)	<1 (<1–<1)
Duodenal atresia	284	85 (73–92)	16 (9–25)	87 (78–92)	1.8 (1.2–2.3)	<1 (<1–<1)
Atresia of small intestine	240	93 (88–95)	24 (18–30)	95 (91–97)	2.2 (1.9–2.4)	<1 (<1–<1)
Anorectal atresia and stenosis	429	83 (73–89)	29 (25–34)	86 (79–91)	2.5 (1.8–3.1)	<1 (<1–<1)
Diaphragmatic hernia	481	85 (81–89)	29 (24–35)	91 (84–95)	1.6 (1.1–2.1)	<1 (<1–<1)
Gastroschisis	931	82 (78–86)	24 (19–29)	86 (82–89)	2.0 (1.9–2.1)	<1 (<1–<1)
Omphalocele	219	84 (76–89)	29 (22–37)	90 (81–95)	1.9 (1.4–2.4)	<1 (<1–<1)
Multicystic renal dysplasia	1087	14 (10–19)	23 (14–33)	35 (24–47)	1.5 (1.1–1.8)	55.4 (37.4–73.4)
Hydronephrosis	4676	27 (21–33)	24 (21–27)	42 (37–47)	1.9 (1.6–2.1)	32.1 (21.3–42.8)
Hypospadias	4450	11 (7–16)	74 (66–80)	79 (74–84)	1.5 (1.2–1.9)	84.6 (68.5–100.6)
Limb reduction defects	833	12 (9–15)	28 (23–34)	33 (27–38)	2.2 (1.5–2.8)	70.3 (61.5–79.1)
Clubfoot	3530	53 (42–62)	26 (23–30)	62 (54–70)	1.3 (1.0–1.7)	15.5 (12.0–19.1)
Hip dislocation	1479	18 (14–23)	19 (13–26)	31 (22–40)	1.4 (1.0–1.8)	57.7 (15.3–100.1)
Polydactyly	3286	37 (24–50)	36 (31–42)	73 (58–83)	1.0 (1.0–1.0)	46.6 (36.8–56.5)
Syndactyly	1536	15 (11–19)	43 (33–53)	49 (39–58)	1.8 (1.4–2.1)	65.3 (58.0–72.6)
Craniosynostosis	982	53 (31–71)	42 (30–54)	85 (66–94)	1.0 (1.0–1.0)	40.3 (28.4–52.2)

the highest median number of surgical procedures before 5 years of age, which was 4.5 (95% CI 3.3–5.8).

4 | DISCUSSION

Our study showed that one in three children born with congenital anomalies underwent surgery in infancy. Children with congenital anomalies continued to undergo surgical procedures in childhood, either for the anomaly or associated co-morbidities. However, the percentage of children who had surgery later in childhood decreased. The study was based on population-based data of all children born in the registry catchment areas with congenital anomalies rather than on case series from individual hospitals and specialised departments. Therefore, it provides a more accurate overview of the burden of congenital anomalies within whole populations. We are not aware of any previous study that presented results on surgery for children with congenital anomalies in a population-based setting.

The percentage of the children that had surgery was generally higher in Wales and the three English regions and lower in Finland. A possible explanation may be that the Finnish EUROCAT registry includes more children with less severe anomalies than the English EUROCAT registries.[15] Another possibility is that we may not have had the complete list of surgery codes for Finland as the surgical procedures were identified using three-digit codes rather than more specific codes.[15] It is well-known that there are differences in the prevalence of congenital anomalies requiring surgery across Europe with higher rates of gastroschisis and neural tube defects in England and Wales.[16,17] There may also have been regional differences in minor surgical procedures performed on outpatients or outside hospitals as these were not included in this study. However, some children with major congenital anomalies may also undergo minor surgery in hospitals as inpatients as associated cardiac and pulmonary problems increases their risk of the anaesthesia.

Our study showed that a relatively higher proportion of children born during 2010–14 had their first surgery within the first week after birth compared to children born in 1995–2005. An explanation may be that major advances in the management of anaesthesia and post-operative care in the neonatal period have led to lower risks for early surgery.[4] It may also be explained by the increased prenatal detection rate of congenital anomalies as these births may have taken

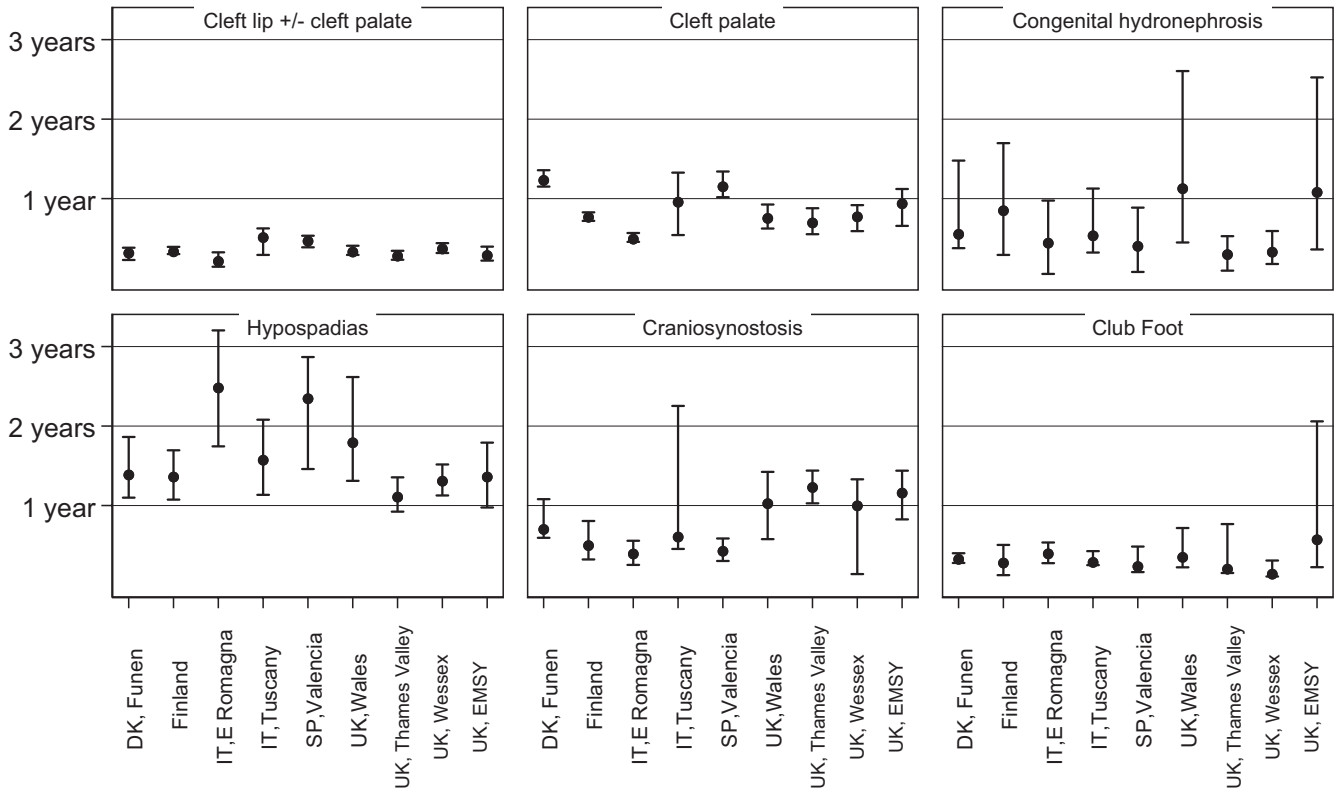

FIGURE 1 Median age (weeks) at first surgery for selected isolated congenital anomalies, by registry and with upper and lower quartiles.

place at a tertiary centre for surgery and the surgical team being aware of the date of the birth.

The median age at the time of their first surgical procedure was quite similar across the regions for children with a cleft lip or clubfoot. There was no consensus on the optimal age for surgery for some anomalies and for these there was more variation in the age at their first surgical procedure across regions and also when comparing regions in the same country. This study found large variations across registries in the age at their first surgical procedure for children with cleft palate as seven of the nine registries had a median age of 26–50 weeks, while two registries had a median age of 60 and 64 weeks. We do not know why these differences occurred. Early surgery for a cleft palate may have a negative impact on the growth of the maxilla and late surgery may have a negative impact on speech development.[18,19] The recommended age for surgery for hypospadias is 6–18 months or later in childhood.[19-21] Small anatomy may be a surgical challenge, but one study reported that adolescents who are not able to recall the surgery seemed to have a more positive body image.[20] This study found that the median age at the time of their first surgical procedure ranged from 61 weeks (14 months) to 131 weeks (30 months) and the 25th centile was above 12 months in all the registries. For craniosynostosis the median age at the time of their first surgical procedure was around 6 months in five registries and 1 year or higher in Wales and the three English registries. A systematic review from 2019 was not able to document the best timing of this surgery in relation to developmental outcomes, but there was inconclusive evidence that earlier surgery at less than 6–7 months was beneficial.[22] An American study showed lower rates of complications with earlier surgery.[23] Based on our results we may conclude that decisions about the age for surgery seemed to be taken at local level and that most children in each region had surgery at the same age. These regional and national differences in the median age at the time of their first surgical procedure could be a starting point for further studies to try to identify the optimal age for surgery for various congenital anomalies.

The results on the median number of surgical procedures and the median age at the time of their first surgical procedure were based on children with isolated congenital anomalies and not on all children born with the anomaly (Table 3). The timing of surgery for children with more than one anomaly may not have been the same as for the children with isolated anomalies and the number of surgical procedures are expected to be higher.

The median number of surgical procedures before the age of five was greater than one for 21 of the 23 specific anomalies presented in Table 3. We do not know whether the anomalies were corrected in steps or if subsequent surgical procedures were performed due to complications. Codes for dilatation of the oesophagus and the removal of foreign bodies were included in the study as surgery codes and it is likely that these procedures explain the high number of surgical procedures performed in children with oesophageal atresia. Children with congenital anomalies may also need the same surgical procedures as children in the background population such as an adenotomy, tonsillectomy or surgery following an injury. These surgical procedures were also included in the results in Table 3.

4.1 | Strengths and limitations

The main strength of this study was the population-based setting covering all children and not only those referred to tertiary hospitals for treatment, in comparison to many existing studies. The EUROCAT registries have high levels of case ascertainment and use standardised definitions and coding of congenital anomalies across the registries. This study has demonstrated that reliable estimates of surgical procedures in children with congenital anomalies can be obtained across a wide geographical area. This was achieved by linking groups of patients to hospital databases, standardising definitions of surgery and pooling results by performing meta-analyses. This was a valuable method for assessing geographical variation on the number of surgical procedures performed on children with congenital anomalies and the differences in age at the time of surgery across Europe. The main challenge was the different coding systems used for surgical procedures and the need to review all the codes obtained after linkage. Our method provides an example for studies on other types of patients using data across regions and countries.

There were some limitations. There may have been underreporting of surgery in some regions as some children might have been transferred outside the region for specialist surgery. There may also have been problems with registering the surgery in the first days after birth due to delays in having a personal identity number or name. This explains why the proportion of children that had surgery was less than 100% for anomalies where surgery is needed for survival. In addition some births following prenatal diagnoses of severe anomalies may have taken place outside the region in Emilia Romagna (Italy) and in Valencian Region (Spain). This meant that only the follow-up treatment after neonatal surgery were visible for some children in the hospital databases included in the study. Lastly, not including day surgery was a potential limitation for comparisons across regions. Some of the children with less severe anomalies may have received routine surgery in outpatient settings in some health care systems, but not in others. Our study focused on inpatient surgical procedures that represented a significant aspect of the burden of disease for children with major congenital anomalies.

5 | CONCLUSION

One in three children with congenital anomalies needed surgery during infancy and more than one surgical procedure was often needed before age of 5 years. The burden of disease for the children and their parents should be acknowledged by health care professionals and support should be given to the families. The age at the time of the first surgical procedure decreased from 1995 to 2014. There were major differences across countries and regions for congenital anomalies with no consensus on the optimal timing of the surgery. These differences encourage further studies to try to identify the optimal age for surgery for the children with these anomalies. More generally, the study has demonstrated that pooling data on surgery by linking groups of patients to hospital databases was feasible. It also provided a sound method of obtaining population-level evidence on congenital anomalies, many of which were also rare diseases.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The study data are available from the authors for scientifically valid requests and with the permission of the participating registries. https://www.eurolinkcat.eu/contactinformationanddatarequests.

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SUPPORTING INFORMATION

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

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