Range and frequency of congenital malformations among children with cleft lip and/or palate

Abstract

Objective: To assess the range and frequency of additional congenital malformations identified among children born alive with CL/P.
Design: Analysis of patient-level data from a national registry of cleft births linked to national administrative data of hospital admissions.
Setting: National Health Service, England.
Patients: Children born between 2000 and 2012 receiving cleft care in English NHS hospitals.
Outcome measures: The proportion of children with ICD-10 codes for additional congenital malformations, according to cleft type.
Results: The study included 9,403 children. Of these 2,114 (22.5%) had CL+/- A, 4,509 (48.0%) had CP, 1,896 (20.2%) had UCLP and 884 (9.4%) had BCLP. A total of 3,653 (38.8%) children had additional congenital malformations documented in their hospital admission records. The prevalence of additional congenital malformations was greatest among children with CP (53.0%), followed by those with BCLP (33.5%), UCLP (26.3%), and then CL+/- A (22.2%) ($p<0.001$). Among those with UCLP, children with right-sided clefts were more likely to have additional malformations than those with left-sided clefts (31.6% vs. 23.0%, $p <0.001$). Malformations of the skeletal system and circulatory system were most common, affecting 10.5% and 10.2% of the included children, respectively.16.8% of children had additional congenital malformations affecting two or more structural systems.
Conclusions: Congenital malformations are common among children born alive with a cleft, affecting over half of some cleft subgroups. Given the frequency of certain structural malformations, clinicians should consider standardized screening for these children. Establishing good links with pediatric and genetic services is recommended.

Key words: cleft, congenital, malformation, anomaly

INTRODUCTION

Orofacial clefts (OFCs) are among the most common major congenital malformations in humans, occurring in an estimated 1 in 700 live births worldwide (Mossey and Castilla, 2003). OFCs may affect only the lip +/- alveolus (CL+/- A), only the palate (CP) or both (CLP). Clefts affecting the lip can be further categorised as unilateral (UCL and UCLP) or bilateral (BCL and BCLP). Broadly, OFCs result from errors during the normal processes of craniofacial development that occur between five and 12 weeks of embryonic life. The embryological and genetic basis of CL+/- A, CLP and CP are understood to be distinct, which will have implications for the distribution of the associated conditions (Sivertsen et al., 2008; Sharp et al., 2017).

Although an OFC can occur in isolation, they may also occur alongside other congenital malformations. The reported frequency of these additional malformations vary between studies, ranging from 2.9% to 36.7% (Milerad et al., 1997; Stoll et al., 2000; Sárközi et al., 2005; Vallino-Napoli et al., 2006; Zhou et al., 2006; Calzolari et al., 2007; Beriaghi et al., 2009; Venkatesh, 2009; Sekhon et al., 2011; Abdollahi Fakhim et al., 2016; Nagalo et al., 2017; Pereira et al., 2018; Impellizzeri et al., 2019; Venkat Ramanan et al., 2019). In some cases, the pattern of malformations present may constitute a recognisable association or ‘syndrome’, and so give insight into the underlying aetiology of the cleft. Recognising the risk of additional malformations among babies presenting with an OFC is important for optimal medical management of the child, supporting accurate reproductive counselling for parents, prognostic and therapeutic evaluations, and for informing etiologic research.

In England, the prevalence of additional congenital malformations occurring among children born alive with a cleft is currently unknown, and routine screening for additional

malformations is not currently performed for children presenting with a cleft. Our group has previously reported cleft-related care and outcomes separately for those considered to have an isolated cleft and those with syndromes or associated anomalies (Fitzsimons et al., 2013; Fitzsimons et al., 2014; Fitzsimons et al., 2017). However, the list of diagnoses used to identify the latter group depends on the purpose of the study and outcomes of interest. The full range or frequency of structural malformations has not been explored in this population.

Using the national cleft registry linked to a national database of all National Health Service (NHS) hospital admissions in England, we sought to quantify the prevalence of additional congenital malformations occurring together with an OFC and to describe the range of these malformations, exploring whether differences exist between the main cleft type subgroups.

METHODS

Data source

The study cohort was identified in the Cleft Registry and Audit NEtwork (CRANE) database (www.crane-database.org.uk). CRANE collects information on all live-born children with a CL/P in England, Wales and Northern Ireland. There is no time limit on when the cleft must be diagnosed in order to be included in the registry, though typically it occurs antenatally or at/soon after birth, which was the case for 84.2% of those with diagnosis time reported. Children whose parents had given consent for their child's records to be included in CRANE (verified consent rate ~98%) were eligible to be linked to the Hospital Episode Statistics (HES) database. The HES database (www.digital.nhs.uk) contains records on all diagnoses and treatments made and given during admissions to NHS hospitals in England. The linked dataset contained records on births up to 31 December 2012 and hospital admissions up to 31

March 2015 (Hospital Episode Statistics, 2010). The NHS is a state-funded healthcare system which provides organised multi-disciplinary care for all children born with a cleft in England.

HES data are collected by professional health coders based in each NHS provider in England primarily for the purpose of reimbursement. Records from each hospital episode are reviewed by coders and the International Classification of Diseases 10th revision (ICD-10) is used to capture diagnoses. Full information on the HES data processing cycle and quality is publically available (NHS Digital, 2016).

Patients

10,483 children who were born alive between 1 January 2000 and 31 December 2012 and registered in CRANE were successfully linked to HES records. Of these, 1,080 were excluded because either cleft type information was missing (n=239) or there was no agreement on cleft type between the two data sources (n=841). In total, 9,403 children were included in the analyses.

Cleft type

Clefts were grouped as cleft lip +/- alveolus involvement (CL+/- A), cleft palate only (CP), unilateral cleft lip and palate (UCLP) or bilateral cleft lip and palate (BCLP) according to data held on the CRANE database and the diagnosis codes using the ICD-10 system in any of the available HES records.

Diagnoses of additional congenital malformations

ICD-10 codes were used to identify congenital malformations in the study cohort. HES records for any single admission contain at least 14 diagnosis code fields. The ICD-10

diagnostic codes representing congenital malformations and chromosomal abnormalities (Q00-Q99; see Appendix 1), in any diagnosis field of a HES record, were used to identify a child as having a congenital malformation in addition to their cleft. These malformations were categorised according to the body or organ system they affected.

Analyses

The proportion of children with ICD-10 codes for congenital malformations (listed in Appendix 1) was examined. These rates were determined for the four cleft-type subgroups and separately for right- and left-sided unilateral clefts. Since the cleft type distribution varies between males and females, the rates were also reported according to sex. The ethnic background of children included in the study was obtained from HES and the corresponding rates for additional congenital malformations were calculated.

The number of different body or organ systems with malformations was summed for each child and also reported by cleft type. 'Chromosomal abnormalities not elsewhere specified' (Q90-Q99) were not included in these particular analyses, as the aim was to sum the specific body systems affected by physical malformations, rather than the underlying cause. While certain chromosomal diagnoses may be associated with high likelihood of particular malformations, these were not assumed to be present unless otherwise recorded.

The Chi-squared test was used to assess variations in proportions across non-ordered groups, such as cleft type classification. A p value <0.05 was considered statistically significant. All statistical calculations were performed in Stata V.15 (Statacorp, College Station, TX, USA).

Ethical considerations

The study is exempt from NHS Health Research Authority ethics approval as it involves the analysis of an existing anonymised dataset that is collected for the purpose of service evaluation (Health Research Authority, 2021).

RESULTS

Patient characteristics

Table 1 shows the characteristics of the 9,403 children included in the analyses. 2,114 (22.5%) had CL+/- A, 4,509 (48.0%) had CP, 1,896 (20.2%) had UCLP and 884 (9.4%) had BCLP. Among those with a unilateral cleft affecting the lip, left-sided clefts were more common, presenting in 1,227 (64.5%) out of 1,904 with CL+/- A, and in 1,179 (62.7%) out of 1,881 children with UCLP who had cleft laterality reported. There were more males than females, which is typical for a cleft population (CRANE Project team on behalf of the Cleft Development Group, 2020), and the majority of children were classified as being of White ethnicity, which is typical of the English general population.

Prevalence of additional malformations

Overall, 3,653 (38.8%) children had diagnoses of additional congenital malformations in their HES records. These rates varied significantly according to cleft type, and were highest among those with CP (53.0%), followed by those with BCLP (33.5%), UCLP (26.3%), and then CL+/- A (22.2%) ($p<0.001$).

Rates of additional malformations were associated with laterality of the cleft among children with UCLP but not CL+/- A (Table 2). Compared to left-sided UCLPs, additional malformations were more prevalent among right-sided UCLPs (23.0% vs. 31.6%, $p<0.001$). Sex was also found to be associated with risk of additional malformations among those with

CP (50.4% among girls and 56.0% among boys, p<0.001) (Table 3), but not among those with other cleft types. The prevalence of additional malformations were found to vary according to ethnic group. Among those from a White background, 38.6% had additional malformations. Although the corresponding rates were higher among those from Mixed and Asian backgrounds (53.4% and 47.0%, respectively), these differences should be interpreted with caution due to low representation from minority ethnic groups and a relatively high proportion of missing data.

Body systems affected by additional malformations

Table 4 shows the prevalence of malformations affecting each body system, as identified by different ICD-10 codes. Over 10% of the study cohort had at least one malformation of the circulatory system. The predominant malformations were those affecting the cardiac septa and those of the great arteries (identified in 7.6% and 5.2% of the cohort, respectively – see Appendix 1 for a further breakdown of ICD-10 codes and the number of children with these diagnoses). Musculoskeletal malformations were also identified in over 10% of the cohort. Deformities of the feet were most prevalent, affecting 3.5% of children, followed by malformations of the skull and face bones, which were identified in 2.8% of children. Whilst 8.3% of the cohort were identified as having malformations of the digestive system, these were primarily attributed to malformations of the tongue, mouth and pharynx (6.1% of children).

The most common system affected by malformations varied according to cleft type. Among those with CL+/- A and BCLP, malformations and deformations of the musculoskeletal system were most common, affecting 6.0% and 11.2% of the subgroups, respectively. Among those with UCLP, malformations of the circulatory system were most common, affecting 7.3%. While malformations affecting these two systems were even more prevalent among children with CP (>14%), ‘other congenital malformations’ were identified in 1,482 out of

4,509 children (32.9%) with CP. 1,338 (29.7% of those with CP) of these had ICD-10 code Q87 'Other specified congenital malformation syndromes affecting multiple systems'. A further breakdown of this code revealed that 1,230 (27.3%) had 'Congenital malformation syndromes predominantly affecting facial appearance' (ICD-10 Q87.0). This diagnosis was much less common among those with CL+/- A (0.7%), UCLP (0.9%) and BCLP (1.5%). The only body system whereby the rate of additional malformations did not vary according to cleft type was the respiratory system. These malformations were present in approximately 5% of each cleft type subgroup.

Number of systems affected by additional malformations

Table 5 shows the number and percentage of children who had multiple (≥2) body systems (e.g. nervous, eye/ear/face/neck, circulatory, respiratory, digestive, genital/reproductive, urinary and musculoskeletal systems) affected by additional malformations. Overall, 16.7% of the study cohort had malformations across multiple body systems, in addition to the cleft lip and/or palate. This rate varied considerably between cleft types, and was highest among those with CP (38.5%) and lowest among those with CL+/- A (5.1%) ($p<0.001$).

DISCUSSION

Key findings

The current study describes the frequency and range of additional congenital malformations in a cohort of children born alive with a cleft in England, based on routinely collected administrative hospital data. It found that congenital malformations occurring in addition to an OFC are common and vary by cleft type, affecting approximately 1 in every 2 children with CP, 1 in every 3 with BCLP, 1 in every 4 with UCLP and 1 in every 4.5 with CL+/- A.

Malformations affecting two or more body systems, in addition to the cleft, were also common among those with CP, affecting 38.5% of the entire subgroup. Congenital malformations affecting multiple systems were less common among the other cleft subgroups but they were not rare. Malformations of the musculoskeletal system and circulatory system were frequently occurring. Among children with CP, over one quarter had diagnosis codes representing malformation syndromes predominantly affecting facial appearance. This category would include, for example, diagnoses such as acrocephalosyndactyly syndromes, Goldenhar syndrome, oro-facial-digital syndromes, and Pierre Robin sequence.

Comparisons with other studies

The present study found 38.8% of all children born alive with a cleft had at least one additional malformation. To our knowledge, this is the highest rate reported in the last 30 years, even when compared to studies based on data from congenital anomaly registers that include pregnancies that were terminated and stillbirths (Stoll et al., 2000; Sárközi et al., 2005; Vallino-Napoli et al., 2006; Calzolari et al., 2007; Impellizzeri et al., 2019). These studies have reported overall rates of additional malformations affecting between 21.0% and 36.7% of babies with an OFC. Of the previous studies including only live births, only two reported that additional malformations occurred in more than 30% of children with a cleft. Beriaghi et al. (2009) found that out of 1,127 children born between 1980 and 2000 with a cleft in the USA, 32.2% had additional malformations. Similarly, Pereira et al. (2018) reported that out of 701 children born with a cleft and treated in a tertiary cleft centre in Southern Portugal between 1981 and 2012, 31.2% had additional malformations.

Previous studies using CRANE-HES linked English data that report cleft-related care or outcomes have, on average, identified approximately 22% of all children with a cleft as

having additional anomalies or syndromes (Fitzsimons et al., 2013; Fitzsimons et al., 2014; Fitzsimons et al., 2017). In those previous studies, the list of congenital malformations and chromosomal abnormalities used to identify these children was primarily restricted to those of the nervous system, circulatory system, and some syndromes frequently occurring among children with a cleft that were thought to influence the care or outcomes being reported. The current study has expanded this definition to determine the range and frequency of all congenital malformations occurring among the cleft population, which accounts for the difference in reported rates. This highlights that reported rates of additional malformations or syndromes will depend on the definition used and the purpose for which the malformations were detected.

In the present study, the prevalence of additional malformations was not evenly distributed across the cleft type subgroups. Children with CP had the highest rate of additional malformations, whilst those with CL+/- A had the lowest rate. These relative differences are consistent with other European studies comparing prevalence of congenital malformations between cleft types (Stoll et al., 2000; Pereira et al., 2018; Impellizzeri et al., 2019). Our finding that 53.0% of children with CP had an additional malformation is higher than the previously reported highest rate of 46.7% by Stoll et al. (2000), which, contrary to this study, included pregnancies that were terminated and stillbirths. Our finding that 22.2% of children with CL+/- A had additional malformations is similar to rates reported by others, including those using congenital anomaly registers and others reporting rates for live births only (Pereira et al., 2018; Venkat Ramanan et al., 2019).

A valuable aspect of our study is reporting additional congenital anomaly rates separately for those with UCLP and BCLP. The majority of previous studies have reported rates for these

children combined. This study provides evidence that children with BCLP are more likely to have additional malformations than those with UCLP, which is consistent with the findings of the few small studies that have reported rates separately in the past (Milerad et al., 1997; Hagberg et al., 1998; Sekhon et al., 2011).

A novel finding from the present study is that right-sided UCLPs carry a significantly higher chance of additional malformations compared with left-sided UCLPs. The laterality of cleft phenotypes should therefore be taken into account when counselling parents and when considering additional screening.

In agreement with our study, malformations of the musculoskeletal and circulatory systems are often the most frequently cited in the literature, particularly for children with a cleft affecting the palate (Milerad et al., 1997; Beriaghi et al., 2009; Pereira et al., 2018). However, there are varying reports regarding the exact prevalence of these additional malformations and their specific nature, which are likely influenced by methodological factors. As the present study included over 9,000 children identified in a national cleft registry linked to national hospital admission records, it is felt that the rates of additional malformations affecting each body system reported here are reliable for children born alive with a cleft in England.

Comparison with studies reporting the prevalence and range of additional malformations among children with a cleft is challenging due to the different methods employed to identify malformations and the different inclusion criteria used. For example, differences between studies may relate to what constitutes a congenital malformation and to the source of information. Also, the length of time that children are followed up for is another factor to

consider and whether the study also includes termination of pregnancies and stillbirths or only children born alive. Several studies are based on patients attending just one cleft clinic, which may not be representative of the wider cleft population, and the location of the study may be important, given the possibility of varying rates of additional malformations across different ethnic groups, as indicated in the current study.

Implications

The distinction between true isolated OFC, and OFC with additional malformations has important implications for reproductive counselling of affected families. Most cases of isolated OFC are understood to have a multifactorial cause, likely arising from a complex interaction between inherited susceptibility and environmental risk factors (Leslie and Marazita, 2013). In such cases, the likelihood of identifying a single, causative genetic variation even by exhaustive genetic investigation is relatively low (Basha et al., 2018), and so counselling of families is typically based on empirical recurrence risk figures from large population studies. In the absence of a strong family history, these figures generally quote a risk that is elevated compared to the general population, but still relatively low in absolute terms (Grosen et al., 2010).

By contrast, the yield from genetic investigations in cases where OFC is accompanied by additional structural malformations is incrementally increased (Cao et al., 2016). A specific genetic diagnosis can enable tailoring of medical care, since many examples have specific additional implications for health and/or development. This can also allow more specific prognostic information to be offered to families. Furthermore, some genetic diagnoses may be associated with a substantially elevated risk of recurrence in a future pregnancy, and so their recognition can enable the provision of reproductive options such as preimplantation

genetic diagnosis to couples at risk. With the increasing availability of powerful genomic technologies for the investigation of pediatric developmental disorders in the UK (Wright et al., 2015), early recognition of OFC with associated malformations is crucial to identify those patients within cleft cohorts who are most likely to benefit from a genetic assessment and investigation.

The relatively high frequency of particular additional congenital malformations identified in this study, including those affecting the circulatory system, raises the question as to whether systematic screening for malformations should be integrated into standard care for children with OFC. Where pre-natal malformation screening with ultrasonography is available, we believe that sonographers need to have detailed understanding of the nature and frequency of associated malformations to allow directed systematic scanning where an OFC is identified. Furthermore, we believe that recognising and understanding the implications of the associated malformations most frequently occurring among children with a cleft and the different cleft phenotypes is essential when counselling parents after diagnosis. This information is important for the delivery of support and care to the family and also useful in the design of cleft care resources.

Strengths and limitations

This is a national population-based study reporting additional congenital malformations in over 9,000 children born alive with OFCs during a relatively recent 13-year birth period. The study has an important strength: it is based on a national cleft registry database that aims to include all children born alive with a cleft in England from 2000 onwards. Records from the registry were linked to national administrative hospital data, which includes records of all children treated for a cleft in English National Health Service hospitals. HES captures a vast

range of information on each patient, including ICD-10 diagnosis codes. As the NHS is a publicly funded national healthcare system, providing care to at least 95% of the population, our sample is unlikely to be confounded by ascertainment bias based on socio-economic status, and hence can be assumed to be representative of the population studied.

Another strength is our ability to report malformation rates according to four main cleft subgroups and to further examine laterality of cleft lip involvement, as well as sex. The findings are not only important when counselling parents or when considering referral for screening, but they also have potential implications for future research investigating causality of clefting affecting the lip and palate, be it genetic or environmental.

This study was restricted to children born alive. Spontaneous abortions, elective terminations, and stillborn foetuses were not possible to include. Furthermore, as there is no standard protocol for evaluating other body systems for anomalies in children presenting with a cleft in England, there may well be subclinical and untreated anomalies that have been missed in the study population. The true prevalence of additional malformations is, therefore, likely to be underrepresented. From a clinical perspective, true prevalence would be ideal for antenatal counselling purposes. However, for future planning of health care services, the rates of additional malformations in live-born children is most relevant.

Whilst the use of ICD-10 codes allowed us to report many congenital malformations, HES restricts the entry of these codes to 4 characters (e.g. Q87.0). This meant that some codes were not sensitive enough to distinguish between certain diagnoses (for example, Pierre Robin Sequence and Goldenhar syndrome share the same 4 character ICD-10 code). Furthermore, ICD-10 codes utilised in HES tend to focus on a physical diagnosis or

phenotype, rather than the underlying genetic cause. This means the prevalence of specific genetic and/or syndromic diagnoses associated with orofacial clefts and other congenital malformations could not be reported.

Finally, subgroup analyses showing the proportion of children with additional malformations according to ethnic background was limited by missing data and relatively low representation by minority ethnic groups. Differences in the prevalence of additional malformations among those with OFCs from different ethnic backgrounds would benefit from further research.

Summary

Identifying the frequency and range of additional structural malformations occurring among children born with a cleft is important for counselling parents and for planning and commissioning cleft services. Implementing routine screening for certain cleft phenotypes is recommended based on the high prevalence of additional malformations identified in this study. Good links with local genetic and pediatric services (particularly cardiovascular, musculoskeletal, uro-genital, gastro-intestinal and respiratory) are also recommended as associated malformations of these nature occur individually in over 5% of live cleft presentations in England. Priorities for future work include investigating the etiological links between OFCs and additional malformations, exploring additional malformations according to the laterality of the cleft, establishing the prevalence of other diagnoses, such as neurodevelopmental disorders, and investigating potential delays in the identification of additional structural anomalies. These data would help to inform both a rational approach to screening and planning of care for children affected by congenital malformations.

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Table 1. Characteristics of the children included in the analyses and the number and percentage of those with additional malformations, according to those characteristics

Characteristic	Full study cohort N	(%)	Children with additional malformations n	(%)
Full study cohort	9,403	(100.0)	3,653	(38.8)
Type of cleft				
Cleft lip	2,114	(22.5)	470	(22.2)
Cleft palate	4,509	(48.0)	2,388	(53.0)
Unilateral cleft lip and palate	1,896	(20.2)	499	(26.3)
Bilateral cleft lip and palate	884	(9.4)	296	(33.5)
Sex				
Female	4,149	(44.1)	1,672	(40.3)
Male	5,254	(55.9)	1,981	(37.7)
Ethnicity				
White	6,264	(84.9)	2,417	(38.6)
Mixed	189	(2.6)	101	(53.4)
Asian	621	(8.4)	292	(47.0)
Black	128	(1.7)	47	(36.7)
Other	176	(2.4)	65	(36.9)
Unknown	2,025	-	731	(36.1)

Table 2. Number and percentage of children born with a cleft who have additional congenital malformations, according to laterality of the cleft lip

	All children with unilateral cleft lip			Left-sided cleft			Right-sided cleft			
	Total	Congenital malformations present		Total	Congenital malformations present		Total	Congenital malformations present		
Cleft type	N	n	%	N	n	%	N	n	%	p value
CL+/- A	1,904	415	(21.8)	1,227	266	(21.7)	677	149	(22.0)	0.87
UCLP	1,881	493	(26.3)	1,179	271	(23.0)	702	222	(31.6)	<0.001

P value for difference in proportion of children with additional congenital malformations between left- and right-sided unilateral cleft lip. Note, 192/2114 children with CL+/-A had bilateral cleft lip. 18/2,114 children with CL+/-A and 15/1,896 children with UCLP were missing laterality information.

Table 3. Number and percentage of children born with a cleft who have additional congenital malformations, according to cleft type and sex

	All children			Males			Females			
	Total	Congenital malformations present		Total	Congenital malformations present		Total	Congenital malformations present		
Cleft type	N	n	%	N	n	%	N	n	%	p value
CL+/- A	2,114	470	(22.2)	1,328	304	(22.9)	786	166	(21.1)	0.344
CP	4,509	2,388	(53.0)	2,033	1,139	(56.0)	2,476	1,249	(50.4)	<0.001
UCLP	1,896	499	(26.3)	1,283	337	(26.3)	613	162	(26.4)	0.941
BCLP	884	296	(33.5)	610	201	(33.0)	274	95	(34.7)	0.616
Total	9,403	3,653	(38.8)	5,254	1,981	(37.7)	4,149	1,672	(40.3)	0.01

P value for difference in proportion of children with additional congenital malformations between the sexes.

Table 4. Number and percentage of children born with a cleft who have additional congenital malformations, according to the type of malformation and cleft type

ICD-10 codes	Description/system	CL+/- A N=2,114 n	(%)	CP N=4,509 n	(%)	UCLP N=1,896 n	(%)	BCLP N=884 n	(%)	Total N=9,403 n	(%)	p value
Q00-Q07	Congenital malformations of the nervous system	20	(0.9)	250	(5.5)	33	(1.7)	32	(3.6)	335	(3.6)	<0.001
Q10-Q18	Congenital malformations of eye, ear, face and neck	50	(2.4)	333	(7.4)	64	(3.4)	67	(7.6)	514	(5.5)	<0.001
Q20-Q28	Congenital malformations of the circulatory system	82	(3.9)	648	(14.4)	139	(7.3)	87	(9.8)	956	(10.2)	<0.001
Q30-Q34	Congenital malformations of the respiratory system	112	(5.3)	238	(5.3)	97	(5.1)	40	(4.5)	487	(5.2)	0.816
Q38-Q45	Other congenital malformations of the digestive system	92	(4.4)	496	(11.0)	120	(6.3)	68	(7.7)	776	(8.3)	<0.001
Q50-Q56	Congenital malformations of the genital organs	84	(4.0)	249	(5.5)	86	(4.5)	61	(6.9)	480	(5.1)	0.002
Q60-Q64	Congenital malformations of the urinary system	28	(1.3)	141	(3.1)	28	(1.5)	28	(3.2)	225	(2.4)	<0.001
Q65-Q79	Congenital malformations and deformations of the musculoskeletal system	126	(6.0)	653	(14.5)	112	(5.9)	99	(11.2)	990	(10.5)	<0.001
Q80-Q89	Other congenital malformations	61	(2.9)	1,482	(32.9)	74	(3.9)	74	(8.4)	1,691	(18.0)	<0.001
Q90-Q99	Chromosomal abnormalities, not elsewhere classified	25	(1.2)	294	(6.5)	33	(1.7)	32	(3.6)	384	(4.1)	<0.001
	At least one congenital malformation in addition to a cleft	470	(22.2)	2,388	(53.0)	499	(26.3)	296	(33.5)	3,653	(38.8)	<0.001

ICD-10, International Classification of Diseases – 10th Edition; P value for difference in proportion of children with additional congenital malformations between cleft types.

Table 5. Number of body systems affected by additional congenital malformations, according to cleft type

Number of systems affected by additional malformations	CL+/- A N=2,114 n	(%)	CP N=4,509 n	(%)	UCLP N=1,896 n	(%)	BCLP N=884 n	(%)	Total N=9,403 n	(%)
0	1,650	(78.1)	2,159	(47.9)	1,402	(73.9)	593	(67.1)	5,804	(61.7)
1	356	(16.8)	614	(13.6)	344	(18.1)	161	(18.2)	1,475	(15.7)
≥2	108	(5.1)	1,736	(38.5)	150	(7.9)	130	(14.7)	2,124	(22.6)

Appendix 1: Diagnostic codes used to identify congenital malformations, and the number (%) of children in the cleft cohort with these codes in their Hospital Episode Statistics history

ICD-10 code	Description	N=9,403 n (%)
	Congenital malformations of the nervous system	***335 (3.6)***
Q00	Anencephaly and similar malformations	2 (0.0)
Q01	Encephalocele	5 (0.1)
Q02	Microcephaly	142 (1.5)
Q03	Congenital hydrocephalus	54 (0.6)
Q04	Other congenital malformations of brain	152 (1.6)
Q05	Spina bifida	15 (0.2)
Q06	Other congenital malformations of spinal cord	17 (0.2)
Q07	Other congenital malformations of nervous system	30 (0.3)
	Congenital malformations of eye, ear, face and neck	***514 (5.5)***
Q10	Congenital ptosis	96 (1.0)
Q11	Anophthalmos, microphthalmos and macrophthalmos	44 (0.5)
Q12	Congenital lens malformations	30 (0.3)
Q13	Congenital malformations of anterior segment of eye	71 (0.8)
Q14	Congenital malformations of posterior segment of eye	71 (0.8)
Q15	Other congenital malformations of eye	29 (0.3)
Q16	Congenital malformations of ear causing impairment of hearing	43 (0.5)
Q17	Other congenital malformations of ear	161 (1.7)
Q18	Other congenital malformations of face and neck	156 (1.7)
	Congenital malformations of the circulatory system	***956 (10.2)***
Q20	Congenital malformations of cardiac chambers and connections	67 (0.7)
Q21	Congenital malformations of cardiac septa	714 (7.6)
Q22	Congenital malformations of pulmonary and tricuspid valves	93 (1.0)
Q23	Congenital malformations of aortic and mitral valves	78 (0.8)
Q24	Other congenital malformations of heart	143 (1.5)
Q25	Congenital malformations of great arteries	491 (5.2)
Q26	Congenital malformations of great veins	35 (0.4)
Q27	Other congenital malformations of peripheral vascular system	33 (0.4)
Q28	Other congenital malformations of circulatory system	5 (0.1)
	Congenital malformations of the respiratory system	***487 (5.2)***
Q30	Congenital malformations of nose	239 (2.5)
Q31	Congenital malformations of larynx	182 (1.9)
Q32	Congenital malformations of trachea and bronchus	87 (0.9)
Q33	Congenital malformations of lung	33 (0.4)
Q34	Other congenital malformations of respiratory system	22 (0.2)
	Other congenital malformations of the digestive system	***776 (8.3)***
Q38	Other congenital malformations of tongue, mouth and pharynx	575 (6.1)
Q39	Congenital malformations of oesophagus	48 (0.5)
Q40	Other congenital malformations of upper alimentary tract	40 (0.4)
Q41	Congenital absence, atresia and stenosis of small intestine	20 (0.2)
Q42	Congenital absence, atresia and stenosis of large intestine	27 (0.3)
Q43	Other congenital malformations of intestine	102 (1.1)
Q44	Congenital malformations of gallbladder, bile ducts and liver	10 (0.1)
Q45	Other congenital malformations of digestive system	1 (0.0)
	Congenital malformations of the genital organs	***480 (5.1)***
Q50	Congenital malformations of ovaries, fallopian tubes and broad ligaments	0 (0.0)
Q51	Congenital malformations of uterus and cervix	4 (0.0)
Q52	Other congenital malformations of female genitalia	20 (0.2)
Q53	Undescended testicle	289 (3.1)
Q54	Hypospadias	126 (1.3)
Q55	Other congenital malformations of male genital organs	120 (1.3)
Q56	Indeterminate sex and pseudohermaphroditism	14 (0.1)

	Congenital malformations of the urinary system	***225***	***(2.4)***
Q60	Renal agenesis and other reduction defects of kidney	37	(0.4)
Q61	Cystic kidney disease	42	(0.4)
Q62	Congenital obstructive defects of renal pelvis and congenital malformations of ureter	100	(1.1)
Q63	Other congenital malformations of kidney	81	(0.9)
Q64	Other congenital malformations of urinary system	18	(0.2)
	Congenital malformations and deformations of the musculoskeletal system	***990***	***(10.5)***
Q65	Congenital deformities of hip	86	(0.9)
Q66	Congenital deformities of feet	330	(3.5)
Q67	Congenital musculoskeletal deformities of head, face, spine and chest	164	(1.7)
Q68	Other congenital musculoskeletal deformities	100	(1.1)
Q69	Polydactyly	65	(0.7)
Q70	Syndactyly	84	(0.9)
Q71	Reduction defects of upper limb	54	(0.6)
Q72	Reduction defects of lower limb	34	(0.4)
Q73	Reduction defects of unspecified limb	6	(0.1)
Q74	Other congenital malformations of limb(s)	113	(1.2)
Q75	Other congenital malformations of skull and face bones	267	(2.8)
Q76	Congenital malformations of spine and bony thorax	106	(1.1)
Q77	Osteochondrodysplasia with defects of growth of tubular bones and spine	27	(0.3)
Q78	Other osteochondrodysplasias	43	(0.5)
Q79	Congenital malformations of the musculoskeletal system, not elsewhere classified	67	(0.7)
	Other congenital malformations	***1691***	***(18.0)***
Q80	Congenital ichthyosis	1	(0.0)
Q81	Epidermolysis bullosa	1	(0.0)
Q82	Other congenital malformations of skin	180	(1.9)
Q83	Congenital malformations of breast	7	(0.1)
Q84	Other congenital malformations of integument	20	(0.2)
Q85	Phakomatoses, not elsewhere classified	10	(0.1)
Q86	Congenital malformation syndromes due to known exogenous causes, not elsewhere classified	80	(0.9)
Q87	Other specified congenital malformation syndromes affecting multiple systems	1438	(15.3)
Q89	Other congenital malformations, not elsewhere classified	117	(1.2)
	Chromosomal abnormalities, not elsewhere classified	***384***	***(4.1)***
Q90	Down syndrome	42	(0.4)
Q91	Edwards syndrome and Patau syndrome	32	(0.3)
Q92	Other trisomies and partial trisomies of the autosomes, not elsewhere classified	59	(0.6)
Q93	Monosomies and deletions from the autosomes, not elsewhere classified	177	(1.9)
Q95	Balanced rearrangements and structural markers, not elsewhere classified	23	(0.2)
Q96	Turner syndrome	15	(0.2)
Q97	Other sex chromosome abnormalities, female phenotype, not elsewhere classified	6	(0.1)
Q98	Other sex chromosome abnormalities, male phenotype, not elsewhere classified	26	(0.3)
Q99	Other chromosome abnormalities, not elsewhere classified	150	(1.6)

ICD-10, International Classification of Diseases – 10th Edition;