Academic achievement at ages 11 and 16 years in children born with congenital anomalies in England: a multi-registry linked cohort study

**Running title**: Congenital anomalies and academic attainment

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Conflict of Interest

The authors declare no conflicts of interest.

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**SYNOPSIS**

Study question

What are the academic achievements at age 11 and 16 years in children born with specific structural congenital anomalies (CAs)?

**What is already known**

There is evidence that some non-syndromic CAs, such as **severe congenital heart defects, orofacial clefts and spina bifida, are associated with lower academic achievement, measured** using standardised or school tests, **in school-aged children.**

**What the study adds**

**Data on children from four population-based CA registries linked to national education records in England showed that >70% of children with isolated structural CAs achieved the expected attainment level at 11 years of age. They were 9% and 12% less likely to achieve expected attainment levels at ages 11 and 16 respectively compared with their peers, although this varied according to type of CA. We present subject-specific attainment levels at ages 11 and 16 years for children with over 50 different isolated structural CAs.**

**Abbreviations**: CA, congenital anomaly; CHD, congenital heart defect; CI, confidence interval; DfE, Department for Education; DS, Down syndrome; EUROCAT, European network of population-based registries for the surveillance of congenital anomalies; FSM, free school meals; GCSE, General Certificate of Secondary Education; ICD, International Statistical Classification of Diseases and Related Health Problems; KS2, Key Stage 2; KS4, Key Stage 4; NPD, National Pupil Database; OFC, orofacial clefts; ONS, Office for National Statistics; RR, risk ratio; SGUL, St George’s, University of London; SRS, Secure Research Service.

# ABSTRACT

**Background:** Children born with major congenital anomalies (CAs) have lower academic achievement compared with their peers, but the existing evidence is restricted to a number of specific CAs.

**Objectives:** To investigate academic outcomes at ages 11 and 16 years in children with major isolated structural CAs and children with Down or Turner syndromes.

**Methods:** This population-based cohort study linked data on approximately 11,000 school-aged children born with major CAs in 1994-2004 registered by four regional CA registries in England with education data from the National Pupil Database (NPD). The comparison group was a random sample of children without major CAs from the background population recorded in the NPD that were frequency matched (5:1) to children with CAs by birth year, sex and geographical area.

**Results:** Overall, 71.9%, 73.0% and 80.9% of children with isolated structural CAs achieved the expected attainment level **at age 11** co**mpared to 78.3%, 80.6% and 86.7% of the comparison group in English language, mathematics and science respectively.** Children with nervous system CAs as a whole had the lowest proportion who achieved the expected attainment at age 11. **At age 16, 46.9% of children with CAs** achieved the expected level compared to 52.5% of their peers. **Major CAs were associated with being up to 9% (95% CI 8%, 11%) and 12% (95% CI 9%, 14%) less likely to achieve expected levels at ages 11 and 16 respectively, after** adjustment for socioeconomic deprivation.

**Conclusions:** Although many children with isolated CAs achieved the expected academic level at age 11 and 16 years, they were at higher risk of underachievement compared to their peers. These stark yet cautiously encouraging results are important for counselling parents of children with specific CAs and also highlight the possible need for special education support to reduce potential academic difficulties.

# Keywords: school-age children; birth defects; academic performance; special education

Word count: 3,290

# 1 | BACKGROUND

Survival beyond infancy is improving for many children born with congenital anomalies (CAs)1-5 due to advances in neonatal care and surgical interventions, resulting in an increasing number of children reaching school age. While the association between some chromosomal/genetic syndromes (e.g. trisomy 21, Williams, Fragile X and Prader-Willi syndromes, sex chromosome aneuploidies) and learning difficulties is well described, there is relatively sparse population-based evidence for children born with non-syndromic structural CAs. A recent systematic review reported that children with some non-syndromic CAs were at a higher risk of lower academic achievement than their peers. Academic underperformance is not restricted to children with CAs associated with lower survival (e.g. congenital heart defects (CHDs) 6-8) but also occurs in children with anomalies with higher survival such as isolated orofacial clefts (OFCs).9-13 More evidence is needed **on the educational outcomes of children with other isolated structural CAs, not only to provide positive information to parents about their children’s achievements14 but also to make them aware of potential limitations and the necessity of special support that could assist with the development of their children’s academic performance.**

This study was undertaken as part of the European collaborative project EUROlinkCAT (<https://www.eurolinkcat.eu/>) that aimed to investigate the health and educational outcomes of children born with major CAs by linking live births to electronic administrative, health care, and education databases. The specific aim of this study was to investigate academic outcomes of children born with selected isolated structural CAs at age 11 and 16 years in state-funded schools using linked education data in the National Pupil Database (NPD).

# 2 | METHODS

2.1 | Study design, cohort and inclusion criteria

This study was a population-based retrospective linked cohort study. The cohort included all children with a major CA who were born to mothers resident in areas covered by four English EUROCAT (the European network for the surveillance of CAs)15-17 registries (East Midlands & South Yorkshire (EMSY), Northern England, Thames Valley and Wessex) and who were alive at the start of school age according to linked civil registrations data (henceforth referred to as EUROCAT children). Included birth years were 1994-2004 for all registries except for EMSY, which began data collection in 1998. A random sample of children from the background population in the NPD, frequency matched to EUROCAT children in a 5:1 ratio by birth year, sex and geographical area, were extracted to serve as a comparison group of peers (henceforth referred to as control children).

Major CAs were classified according to the EUROCAT anomaly subgroups. An isolated CA was defined as a major structural anomaly in one organ system only or as part of a known sequence (e.g. spina bifida with hydrocephalus). We included specific major isolated structural CAs and an overall group of children with any major isolated structural anomaly; in addition, results were presented for three chromosomal CAs (Down, Turner and Klinefelter syndromes) to check that our findings are consistent with existing evidence on the poorer achievements of children with syndromic CAs. In this study, we present results for selected subgroups that had sufficient data to yield interpretable estimates. The corresponding ICD codes and the list of subgroups included are presented in eTable1.

2.2 | Linkage process

The NPD contains detailed individual-level information about pupils in all state-funded schools (including special schools) in England, including test and exam results up to age 18, special education needs and sociodemographic data. The Department for Education (DfE) is the data controller for the NPD. Following approval by the DfE data sharing panel in February 2020, DfE staff performed the linkage between the four CA registries’ data and their NPD records using names, date of birth, sex and last known postcode. The extracts containing de-identified NPD data with a generated unique study ID were transferred into the Office for National Statistics (ONS) Secure Research Service (SRS). The same data items were provided for control children. Data on CAs for the EUROCAT children were separately merged with the NPD data using the study ID within the ONS SRS. The named researchers from St George’s, University of London (SGUL), i.e. JT, JB, HERE and JKM, were permitted remote access to the linked NPD data in the ONS SRS under an Assured Organisational Connectivity agreement between SGUL and the ONS. JR and SG were permitted access to pre-publication outputs exported from the ONS SRS.

2.3 | Educational outcomes

Key stage 2 (KS2) attainment data from national, externally marked tests were taken at the end of primary school, in year 6 (age 11 for most pupils). Pupils were expected to achieve level 4 by the end of KS2 therefore ‘Achieving level 4 and above’ by compulsory school subject (English, mathematics and science; the latter covers topics within the disciplines of biology, chemistry and physics) was selected as the educational outcome for KS2. The included academic years differed by subject, as only years when the assessments were based on national standardised tests were analysed. For English, included years were 2004/05-2011/12 because from 2012/13, English was calculated from reading test results and writing teacher assessment, making test results incomparable to previous years. For mathematics, we included years 2004/05-2014/15, as national curriculum levels were replaced by scaled Standard Assessment Tests scores in 2015/16. For science, we included 2004/05-2008/09 because from 2009/10, the KS2 national curriculum science test taken by all pupils was replaced by one taken by a sample of pupils only. The classification of subject results codes is given in eTable3.

Key Stage 4 (KS4) attainment data were based on national General Certificate of Secondary Education (GCSE) exams and equivalent qualifications at age 16. Results for academic years 2009/10-2015/16 were included as changes in grading were introduced in 2016/17. Level 2 is reached when the pupil has achieved 5 or more GCSEs and equivalents at grades A\*-C; we therefore selected Level 2 including GCSE in English and mathematics as the KS4 educational outcome, since it was used as a secondary schools’ performance measure and also deemed to be the foundation for further education or beginning employment.18

The requested NPD data also contained an individual-based free school meals eligibility (FSME) based on Spring Census data (collected annually in January). FSME is based on parents receiving certain means-tested benefits and we used FSME as a single measure of socioeconomic deprivation, a potential confounder of the association between CAs and educational attainment.

2.4 | Statistical analysis

Educational outcomes expressed as KS2 and KS4 attainment were analysed for EUROCAT children from the four English registries combined versus control children. As control children were frequency matched to EUROCAT children by birth year, sex and geographical area, these characteristics, including area-derived socioeconomic deprivation scores (income deprivation affecting children index), were comparable between the two groups. The initially planned 5:1 ratio of control to EUROCAT children was not achieved because of logistical reasons (e.g. no exact matches found, excluded due to data issues/duplicates), resulting in a final overall 4.5:1 ratio.

Generalised linear models with a Poisson distribution, log link and robust standard errors were used to estimate risk ratios (RRs) with 95% confidence intervals (CIs) for achieving expected levels of attainment for EUROCAT children versus control children, without and with adjustment for FSME. To control for differences in academic achievements by sex, the results for boys with hypospadias and Klinefelter syndrome were compared with those for control boys, and the results for girls with Turner syndrome were compared with those for control girls. The ONS SRS statistical disclosure policy does not permit reporting of small counts (<10), including derived quantities which would enable back-calculation of small counts (percentages, RRs), and hence suppression had been applied where necessary. Statistical analysis was performed using Stata (version 16.0, StataCorp LP, College Station, TX, USA).

2.5 | Missing data

Approximately 82% (11,142/13,599) and 80% (5,741/7,190) of EUROCAT children were linked to KS2 mathematics (comprising the full 1994-2004 cohort) and KS4 datasets in the NPD respectively. The primary reason for non-linkage was inadequate matching identifiers collected by registries. A further 3.6% and 5.9% of EUROCAT children had not reached the requisite year group to sit for KS2 mathematics and KS4 assessments respectively in the last year of available data (see eTable2). Overall, 4.9%, 3.1% and 0.1% of children who sat KS2 assessments had a missing result for English, mathematics and science tests respectively; for KS4 exam results, there were no missing data. For KS2 there were no missing data for child’s sex and the percentage of missing data was low for FSME (0.5% EUROCAT; 0.9% and control children). As there were higher percentages of missing data for FSME at KS4 (4.6% EUROCAT; 5.0% control children), we performed sensitivity analysis by sequentially imputing all missing values of FSME as eligible and then ineligible in the adjusted models.

2.6 | Ethics approval

The study had Health Research Authority ethics approval for the linkage between the CA registries’ and the NPD records to take place and did not require individual consent (NHS REC reference: 16/EM/0440).

# 3 | RESULTS

The analysis included up to 10,363 EUROCAT children and 59,090 control children who sat KS2 mathematics (the maximum cohort). Table 1 shows the number and the percentage of children achieving the expected level (level 4 and above) at KS2 for EUROCAT children and for control children. At age 11, 71.9% (95% CI 70.7%, 73.1%) of EUROCAT children achieved the expected level of achievement **in English language** co**mpared with 78.3% (95% CI** 77.9%, 78.7%**)** **of** control **children. For both EUROCAT and controls, p**roportionally more children achieved expected levels in science, followed by mathematics then English. C**ompared with control children, EUROCAT children were less likely to achieve expected attainment levels in English, mathematics and science (RR** 0.92 (95% CI 0.90, 0.93), **RR** 0.91 (95% CI 0.89, 0.92) **and RR** 0.93 (95% CI 0.91, 0.95) respectively); adjusting for FSME did not materially alter the results (Table 2). There were variations between isolated CA subgroups: children with congenital hydrocephalus, spina bifida, severe microcephaly, hypoplastic left heart and craniosynostosis were least likely to achieve expected levels in all or some subjects, whilst no differences were evident for children with anomalies of the digestive system (excepting children with ano-rectal atresia/stenosis in English language), multicystic renal dysplasia, limb reduction defects and boys with hypospadias. Only 1.6% of children with Down syndrome (DS) achieved the expected level in mathematics (adjusted RR 0.02, 95% CI 0.01, 0.03), ≤2.0% in English and ≤4.5% in science (percentages calculated assuming the maximum suppressed value). Girls with Turner syndrome were similarly likely to achieve expected levels in English and science as control girls, but did worse in mathematics (adjusted RR 0.70, 95% CI 0.59, 0.83); boys with Klinefelter syndrome performed less well across all subjects compared with control boys.

Table 3 shows the number (%) of children and the RRs (95% CIs) of achieving level 2 at KS4 (5+ GCSEs and equivalents at grades A\*-C, including GCSE English and mathematics), for EUROCAT children compared with control children. After adjusting for FSME, the RR of achieving level 2 was 0.88 (95% CI 0.86, 0.91) for children with isolated structural CAs overall compared to control children. Among children with isolated CAs there was substantial variation in achievement between specific CAs, ranging from expected low achievement for children with hydrocephalus and severe microcephaly to comparable achievement for other subgroups, although many are small samples with wide CIs. Children with atrial septal defect, tetralogy of fallot, cleft lip with/without cleft palate and ano-rectal atresia/stenosis were more likely to underperform at age 16 compared to control children, as were children with chromosomal anomalies (DS, Turner and Klinefelter syndromes). The sensitivity analysis of the effect of missing FSME data on the KS4 results showed that they would not have materially changed the adjusted ORs.

# 4 | COMMENT

4.1 | Principal findings

This study found that over 70% of children born with isolated CAs in England achieved the expected academic level at age 11 years and about 47% at age 16 years compared with approximately 78-87% and 53% for control children respectively. There was substantial variation in attainment between specific isolated CAs, with no differences evident for children with anomalies of the digestive system, multicystic renal dysplasia, limb reduction defects and boys with hypospadias. However, as expected, academic achievement was significantly lower for children with brain CAs (e.g. hydrocephalus and severe microcephaly) and for a heterogeneous group of children with severe CHDs. Where there was an attainment gap between children with specific isolated CAs and control children, it remained after adjustment for FSME, a proxy of socioeconomic deprivation, a well-established factor associated with lower academic achievement.

4.2 | Strengths of the study

This multi-registry linked cohort study is population-based and includes all children with CAs in four English EUROCAT registries’ catchment areas and a random sample of frequency-matched children from the background population recorded in the NPD. The EUROCAT registries are characterised by high levels of case ascertainment and a standardised approach to the classification and coding of CAs. **Given the well-recognised association between academic underachievement and socioeconomic deprivation, we selected the comparison group based on geographical area in addition to age and sex and adjusted for individual-level deprivation (FSME) in our analyses.** The use of age-matched control children for comparison allows for adjustment of time trends and for systemic changes in the education system introduced over the study period. To our knowledge, this is the first European study of school achievement of children with a wide range of isolated structural CAs in different organ systems at ages 11 and 16 years compared to control children originating from the same school population.

4.3 | Limitations of the data

Since the four regional CA registries do not cover all of England, our results may not be fully representative of the outcomes in other regions. Nonetheless, as comparisons have been made with geographically-matched children from the background population, we can be reasonably confident in the general validity of the estimated differences between children with and without CAs. Due to names not being routinely collected in the earlier years by the CA registries and addresses not being updated, about one-fifth of EUROCAT children could not be linked to the NPD, which have resulted in a smaller cohort available for analysis and some potential for bias. This is mitigated by the fact that non-linkage due to poor identifiers is unlikely to be associated with educational outcomes.

Around 5% of children attend private schools in England and would be missing from our data, but as attendance at a private school is highly dependent on their parents' choices and finances rather than the child’s CA, we do not believe this to be a source of bias. Related work by our group showed that only 5% of children with severe CHD in Finland did not plan to attend mainstream education beyond 16 years19; this suggests that a relatively small proportion of children with isolated structural CAs do not attend mainstream schools (the corresponding figure for children with Down syndrome was 87% not planning to attend mainstream education in Finland).

Residual confounding by gestational age (not available for control children), co-morbidities, exposure to general anaesthetic during corrective surgery in early childhood and severity of CA are additional limitations. Moreover, medical protocols for the management of children with CAs have evolved over time and may have also differed by hospital, and our findings only report average outcomes. Lastly, we relied on the secondary use of the education database which have been affected by policy changes and are collected primarily for administrative rather than research purposes, and hence the quality of core attainment variables may not have been consistent over the years. For example, the changes and discontinuities in assessment standards over time have restricted the number of years with data available for analysis.

4.4 | Interpretation

**The findings of our study are consistent with previous research on children with specific isolated/non-syndromic CAs.20** Published studies in Europe, the USA and Australia using school assessment of academic achievements of children with CAs such as OFCs10-12, 21, 22 and severe CHDs6, 8, 23 showed a higher risk of academic underperformance at different ages compared to their peers without CAs. According to a longitudinal cohort study, lower performance in children with OFCs persists from elementary to high school (7-17 years).13 Evidence on children with other CAs, such as gastrointestinal and abdominal wall anomalies, is more limited. Small studies using linked data from Arkansas, USA showed that complex gastroschisis and congenital diaphragmatic hernia were associated with poorer literacy during primary school24, 25; parent surveys in the USA and Netherlands also indicated that children with these conditions could be at greater risk of learning difficulties.26, 27 A meta-analysis of children with oesophageal atresia reported neurodevelopmental impairment during school age (6-18 years).28 Our study corroborates these findings and provides additional information on school achievement of children with a wider range of isolated CAs.

A previous English study found an independent association between school absence and lower attainment in children with OFCs aged 7 years.10 A EUROlinkCAT study showed that children with CAs aged <1 year and 1-4 years in 11 European regions were hospitalised more often and stayed longer than control children.29 If such trends persist in later childhood, then we expect school absence due to ill-health to adversely impact academic achievement. We could not explore the association of childhood morbidity with academic achievement as we did not manage to obtain permissions to link the data but hope to address this in future work.

**Following parental request for positive information about their children’s potential and achievement highlighted in focus groups across Europe with parents of children with a CA, our study’s encouraging finding is that many children with major isolated structural CAs (excepting brain anomalies) achieve expected levels of attainment at both 11 and 16 years. Nonetheless, in both age groups, children with isolated CAs were on average more likely than their peers to underperform academically, indicating the need for special education support in these children and specific counselling for parents.**

**Traditionally, children with DS, which is associated with intellectual disability of varying degrees, were placed in special schools. Since the 1981 and 1993 Education Acts in the UK, proportions of children with DS aged 5 to 16 in mainstream schools increased from 4% to 38% between 1983 and 1996, with wide variations between different Local Education Authorities. The proportion of children with DS attending mainstream schools was 58% (n=88) in a recent UK survey of parental views on special education needs provision30 and 65% in a survey of 569 parents on the educational experiences in pupils with DS in the UK. We found that** around 2% of children with DS achieved the expected attainment levels at age 11 **and age 16 respectively. These indicate that it is important for parents to be counselled on the likely achievements for their child. Growing evidence suggests that regular/mainstream schooling positively affects development of academic and communication skills in pupils with DS, compared to special schools, even when controlling for selective placement.31-34 In addition to the need for high-level help and support in mainstream schools, secondary school pupils with DS need an individualised approach in developing academic, social and life skills, and good communication within school and with parents is a key to success.35**

4.5 | Conclusions

Many children with isolated CAs achieved the expected academic level at age 11 and 16 years but there was a higher risk of underachievement for children with specific CAs compared to their peers. Results on educational outcomes for children born with specific CAs can be used for counselling parents regarding their child’s potential to achieve expected academic levels at school and also for informing them on anticipated difficulties. Timely interventions to access special education services and identification of type of support needed, are recommended to help children in reaching their full potential and improve their life chances.

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This work uses data from the Northern England Registry that has been provided by patients, the National Health Service (NHS) and other health care organisations as part of patient care and support. The data are collated, maintained and quality assured by the National Congenital Anomaly and Rare Disease Registration Service, which was part of Public Health England (PHE) at the time of data download. Access to the data was facilitated by the Office for Data Release.

The education data analysed for this publication have been extracted from the National Pupil Database (NPD) which is compiled and owned by the Department for Education (DfE). DfE does not accept responsibility for any inferences or conclusions derived from the DfE Data Extracts by third parties.

This work contains statistical data from ONS which is Crown Copyright. The use of the ONS statistical data in this work does not imply the endorsement of the ONS in relation to the interpretation or analysis of the statistical data. This work uses research datasets which may not exactly reproduce National Statistics aggregates. The analysis was carried out in the Secure Research Service, part of the Office for National Statistics.

Authors' contributions

Glinianaia and Tan share co-first authorship, i.e. they contributed equally to the publication.

Tan and Morris had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Glinianaia, Morris, Rankin, Tan.

Development of study methods, including standardisation of congenital anomalies, development of statistical analysis plan, writing analysis programs and statistical analysis: Brigden, Evans, Glinianaia, Loane, Morris, Rankin, Tan.

Data acquisition and interpretation of the results: All authors.

Drafting of the manuscript: Glinianaia, Tan.

Critical revision of the manuscript for important intellectual content: All authors.

Obtained funding: Morris, Rankin.

Supervision: Morris, Rankin.

All authors approved the final manuscript as submitted and agree to be accountable for major aspects of the work.

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**TABLE 1 Key stage 2 (KS2) level of attainment in national curriculum tests: number and percentage of children achieving level 4 and above (expected level) for EUROCAT children (children born with congenital anomalies: All anomalies, selected isolated anomalies and chromosomal syndromes) and the comparison group (controls) by school subject**

|  |  |  |  |
| --- | --- | --- | --- |
|  | ENGLISH LANGUAGE(2004/05-2011/12)a | MATHEMATICS(2004/05-2014/15)a | SCIENCE(2004/05-2008/09)a |
| Group | N of valid results | Achieved level 4 or above | N of valid results | Achieved level 4 or above | N of valid results | Achieved level 4 or above |
| n | % (95% CI)b or [% range]d | n | % (95% CI) bor [% range]d | n | % (95% CI) bor [% range]d |
| Controls | 36533 | 28604 | 78.3 (77.9, 78.7) | 59090 | 47597 | 80.6 (80.2, 80.9) | 18850 | 16349 | 86.7 (86.2, 87.2) |
| **All isolated structural anomalies** | 5614 | 4037 | 71.9 (70.7, 73.1) | 9450 | 6895 | 73.0 (72.1, 73.9) | 2785 | 2252 | 80.9 (79.4, 82.3) |
| **Nervous System** |  |  |  |  |  |  |  |  |  |
| Encephalocele | d | d | [26-50] | d | d | [26-50] | d | d | [76-100] |
| Spina Bifida | 40 | 25 | 62.5 (45.8, 77.3) | 73 | 36 | 49.3 (37.4, 61.3) | 27 | e | [76-100] |
| Hydrocephalus | 51 | 16 | 31.4 (19.1, 45.9) | 93 | 34 | 36.6 (26.8, 47.2) | 23 | 10 | 43.5 (23.2, 65.5) |
| Severe microcephaly | 39 | d | [0-25] | 56 | d | [0-25] | 20 | d | [0-25] |
| Arhinencephaly / holoprosencephaly | d | d | [0-25] | d | d | [0-25] | d | d | [0-25] |
| **Eye** |  |  |  |  |  |  |  |  |  |
| Anophthalmos / microphthalmos | 12 | e | [76-100] | 21 | e | [51-75] | d | d | [51-75] |
| Anophthalmos | d | d | [51-75] | d | e | [26-50] | d | d | [51-75] |
| Congenital cataract | 39 | 29 | 74.4 (57.9, 87.0) | 59 | 37 | 62.7 (49.1, 75.0) | 18 | e | [51-75] |
| Congenital glaucoma | d | d | [51-75] | d | d | [51-75] | d | d | [76-100] |
| **Ear, Face and Neck** |  |  |  |  |  |  |  |  |  |
| Anotia | d | d | [51-75] | d | d | [76-100] | d | d | [76-100] |
| **Congenital Heart Defects (CHD)** |  |  |  |  |  |  |  |  |  |
| ALL CHD | 2115 | 1557 | 73.6 (71.7, 75.5) | 3395 | 2466 | 72.6 (71.1, 74.1) | 1204 | 983 | 81.6 (79.3, 83.8) |
| Severe CHD | 645 | 446 | 69.1 (65.4, 72.7) | 1011 | 708 | 70.0 (67.1, 72.8) | 346 | 273 | 78.9 (74.2, 83.1) |
| Common arterial truncus | 10 | e | [51-75] | 11 | e | [26-50] | d | d | [76-100] |
| Double outlet right ventricle | 24 | e | [51-75] | 42 | 28 | 66.7 (50.5, 80.4) | 15 | e | [76-100] |
| Transposition of great vessels | 148 | 104 | 70.3 (62.2, 77.5) | 234 | 175 | 74.8 (68.7, 80.2) | 73 | e | [76-100] |
| Single ventricle | 12 | e | [51-75] | 17 | e | [51-75] | d | d | [76-100] |
| Ventricular septal defect | 1087 | 830 | 76.4 (73.7, 78.9) | 1664 | 1246 | 74.9 (72.7, 76.9) | 637 | 531 | 83.4 (80.2, 86.2) |
| Atrial septal defect | 291 | 202 | 69.4 (63.8, 74.7) | 532 | 374 | 70.3 (66.2, 74.2) | 151 | 122 | 80.8 (73.6, 86.7) |
| Atrioventricular septal defect | 51 | 38 | 74.5 (60.4, 85.7) | 84 | 61 | 72.6 (61.8, 81.8) | 27 | e | [76-100] |
| Tetralogy of Fallot | 103 | 64 | 62.1 (52.0, 71.5) | 164 | 106 | 64.6 (56.8, 71.9) | 60 | 41 | 68.3 (55.0, 79.7) |
| Triscuspid atresia and stenosis | 14 | e | [76-100] | 25 | e | [76-100] | d | d | [76-100] |
| Ebstein’s anomaly | 14 | e | [26-50] | 24 | e | [51-75] | d | d | [51-75] |
| Pulmonary valve stenosis | 249 | 182 | 73.1 (67.1, 78.5) | 380 | 274 | 72.1 (67.3, 76.6) | 161 | 126 | 78.3 (71.1, 84.4) |
| Pulmonary valve atresia | 10 | e | [51-75] | 26 | 15 | 57.7 (36.9, 76.6) | d | d | [76-100] |
| Aortic valve atresia/stenosis | 81 | 61 | 75.3 (64.5, 84.2) | 114 | 87 | 76.3 (67.4, 83.8) | 49 | 39 | 79.6 (65.7, 89.8) |
| Mitral valve anomalies | 34 | 22 | 64.7 (46.5, 80.3) | 54 | 33 | 61.1 (46.9, 74.1) | 18 | e | [76-100] |
| Hypoplastic left heart | 13 | e | [26-50] | 25 | 11 | 44.0 (24.4, 65.1) | d | d | [51-75] |
| Hypoplastic right heart | d | d | [76-100] | d | d | [76-100] | d | d | [76-100] |
| Coarctation of aorta | 151 | 107 | 70.9 (62.9, 78.0) | 241 | 170 | 70.5 (64.3, 76.2) | 70 | 54 | 77.1 (65.6, 86.3) |
| Aortic atresia / interrupted aortic arch | d | d | [51-75] | 10 | e | [51-75] | d | d | [0-25] |
| Total anomalous pulmonary venous return | 29 | e | [51-75] | 47 | 33 | 70.2 (55.1, 82.7) | 16 | e | [76-100] |
| PDA as only CHD in term infants (>=37 weeks) | 31 | 20 | 64.5 (45.4, 80.8) | 108 | 72 | 66.7 (56.9, 75.4) | 0 | 0 |  |
| **Respiratory** |  |  |  |  |  |  |  |  |  |
| Choanal atresia | 11 | e | [51-75] | 17 | e | [76-100] | d | d | [76-100] |
| Cystic adenomatous malformation of lung | 29 | e | [51-75] | 46 | e | [76-100] | d | d | [76-100] |
| **Oro-facial clefts** |  |  |  |  |  |  |  |  |  |
| Cleft lip with or without cleft palate | 383 | 266 | 69.5 (64.6, 74.0) | 600 | 442 | 73.7 (69.9, 77.2) | 197 | 160 | 81.2 (75.1, 86.4) |
| Cleft palate | 249 | 178 | 71.5 (65.4, 77.0) | 367 | 249 | 67.8 (62.8, 72.6) | 117 | 88 | 75.2 (66.4, 82.7) |
| **Digestive System** |  |  |  |  |  |  |  |  |  |
| Oesophageal atresia with or without tracheo-oesophageal fistula | 65 | 51 | 78.5 (66.5, 87.7) | 85 | 67 | 78.8 (68.6, 86.9) | 29 | e | [76-100] |
| Duodenal atresia or stenosis | 36 | e | [76-100] | 59 | 47 | 79.7 (67.2, 89.0) | 13 | 13 | 100.0 (75.3, 100.0) |
| Atresia or stenosis of other parts of small intestine | 29 | e | [76-100] | 35 | e | [76-100] | d | d | [76-100] |
| Ano-rectal atresia and stenosis | 51 | 32 | 62.7 (48.1, 75.9) | 86 | 62 | 72.1 (61.4, 81.2) | 20 | e | [51-75] |
| Hirschsprung’s disease | 42 | 31 | 73.8 (58.0, 86.1) | 78 | 63 | 80.8 (70.3, 88.8) | 15 | e | [51-75] |
| Atresia of bile ducts | d | d | [76-100] | d | e | [76-100] | d | d | 100.0 (2.5, 100.0) |
| Diaphragmatic hernia | 62 | 43 | 69.4 (56.3, 80.4) | 96 | 70 | 72.9 (62.9, 81.5) | 36 | e | [76-100] |
| **Abdominal wall defects** |  |  |  |  |  |  |  |  |  |
| Gastroschisis | 127 | 90 | 70.9 (62.1, 78.6) | 231 | 166 | 71.9 (65.6, 77.6) | 73 | 61 | 83.6 (73.0, 91.2) |
| Omphalocele | 27 | e | [51-75] | 52 | e | [76-100] | 12 | e | [76-100] |
| **Urinary** |  |  |  |  |  |  |  |  |  |
| Multicystic renal dysplasia | 131 | 101 | 77.1 (68.9, 84.0) | 218 | 170 | 78.0 (71.9, 83.3) | 73 | 60 | 82.2 (71.5, 90.2) |
| Congenital hydronephrosis | 409 | 321 | 78.5 (74.2, 82.4) | 710 | 570 | 80.3 (77.2, 83.1) | 202 | 182 | 90.1 (85.1, 93.8) |
| **Genital** |  |  |  |  |  |  |  |  |  |
| Hypospadias | 248 | 185 | 74.6 (68.7, 79.9) | 592 | 488 | 82.4 (79.1, 85.4) | 59 | e | [76-100] |
| Indeterminate sex | 15 | e | [51-75] | 22 | e | [51-75] | 12 | e | [76-100] |
| **Limb** |  |  |  |  |  |  |  |  |  |
| Limb reduction defects  | 110 | 83 | 75.5 (66.3, 83.2) | 179 | 138 | 77.1 (70.2, 83.0) | 60 | e | [76-100] |
| Club foot – talipes equinovarus | 124 | 95 | 76.6 (68.2, 83.7) | 217 | 159 | 73.3 (66.9, 79.0) | 51 | e | [76-100] |
| Hip dislocation and/or dysplasia | 32 | e | [76-100] | 52 | e | [76-100] | d | d | [76-100] |
| Polydactyly | 127 | 98 | 77.2 (68.9, 84.1) | 313 | 252 | 80.5 (75.7, 84.8) | 28 | e | [76-100] |
| Syndactyly | 105 | 79 | 75.2 (65.9, 83.1) | 224 | 176 | 78.6 (72.6, 83.8) | 19 | e | [76-100] |
| **Other anomalies** |  |  |  |  |  |  |  |  |  |
| Craniosynostosis | 25 | d | [26-50] | 41 | 27 | 65.9 (49.4, 79.9) | 16 | e | [51-75] |
| Situs inversus | d | d | [26-50] | 11 | e | [51-75] | d | d | [76-100] |
| **Chromosomal** |  |  |  |  |  |  |  |  |  |
| Down syndrome | 450 | d | [0-25] | 751 | 12 | 1.6 (0.8, 2.8) | 203 | d | [0-25] |
| Turner syndrome  | 72 | 53 | 73.6 (61.9, 83.3) | 101 | 58 | 57.4 (47.2, 67.2) | 40 | 29 | 72.5 (56.1, 85.4) |
| Klinefelter syndrome  | 36 | 12 | 33.3 (18.6, 51.0) | 62 | 29 | 46.8 (34.0, 59.9) | 25 | 12 | 48.0 (27.8, 68.7) |

aThe years in which children were tested differed according to subject and hence the denominators differed for each subject.

b Exact binomial confidence intervals. Where counts have been suppressed the quartile that includes the estimated percentage is indicated by [ ].

c Subgroups included in Severe CHD are indicated in eTable2.

d Suppressed small count (<10) with [ ] indicating the quartile that includes the estimated percentage.

e Secondary suppression (<10 did not achieve level 4 or above)

CHD, congenital heart defect; CI: confidence interval; GA, gestational age; PDA, patent ductus arteriosus.

# **TABLE 2:** Key Stage 2 (KS2) level of attainment: unadjusted and adjusted risk ratios (95% CI) of achieving level 4 and above (expected level) for EUROCAT children versus control children by school subject, estimated by generalised linear models

|  |  |
| --- | --- |
|  | Achieved level 4 or above (expected level) |
|  | ENGLISH LANGUAGE a | MATHEMATICS a | SCIENCE a |
|  | Unadjusted RR (95% CI) | RR adjusted b(95% CI) | Unadjusted RR (95% CI) | RR adjusted b(95% CI) | Unadjusted RR (95% CI) | RR adjusted b(95% CI) |
|  |  |  |  |  |  |  |
| Controls | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| **All isolated structural anomalies** | 0.92 (0.90, 0.93) | 0.92 (0.90, 0.93) | 0.91 (0.89, 0.92) | 0.91 (0.89, 0.92) | 0.93 (0.91, 0.95) | 0.93 (0.91, 0.95) |
| **Nervous System** |  |  |  |  |  |  |
| Encephalocele | f | 0.34 (0.07, 1.75) | f | 0.48 (0.20, 1.13) | f | 0.91 (0.54, 1.53) |
| Spina Bifida | 0.80 (0.63, 1.01) | 0.81 (0.64, 1.03) | 0.61 (0.49, 0.77) | 0.62 (0.49, 0.79) | f | 0.90 (0.73, 1.10) |
| Hydrocephalus | 0.40 (0.27, 0.60) | 0.41 (0.27, 0.61) | 0.45 (0.35, 0.59) | 0.46 (0.35, 0.60) | 0.50 (0.31, 0.80) | 0.51 (0.32, 0.81) |
| Severe microcephaly | f | 0.07 (0.02, 0.25) | f | 0.13 (0.06, 0.29) | f | 0.06 (0.01, 0.39) |
| Arhinencephaly/holoprosencephaly | g | g | g | g | g | g |
| **Eye** |  |  |  |  |  |  |
| Anophthalmos / microphthalmos | f | 0.95 (0.69, 1.30) | f | 0.77 (0.55, 1.08) | f | 0.74 (0.42, 1.31) |
| Anophthalmos | f | 0.88 (0.37, 2.11) | f | 0.54 (0.19, 1.55) | f | 0.56 (0.14, 2.23) |
| Congenital cataract | 0.95 (0.79, 1.14) | 0.91 (0.76, 1.10) | 0.78 (0.64, 0.95) | 0.77 (0.63, 0.93) | f | 0.81 (0.61, 1.09) |
| Congenital glaucoma | f | 0.81 (0.36, 1.80) | f | 0.64 (0.28, 1.42) | f | 1.12 (1.11, 1.12) |
| **Ear, Face and Neck** |  |  |  |  |  |  |
| Anotia | f | 0.81 (0.36, 1.80) | f | 1.02 (0.76, 1.38) | f | 1.12 (1.11, 1.12) |
| **Congenital Heart Defects (CHD)** |  |  |  |  |  |  |
| ALL CHD | 0.94 (0.92, 0.97) | 0.94 (0.92, 0.97) | 0.90 (0.88, 0.92) | 0.90 (0.88, 0.92) | 0.94 (0.92, 0.97) | 0.94 (0.91, 0.97) |
| Severe CHD | 0.88 (0.84, 0.93) | 0.89 (0.85, 0.93) | 0.87 (0.83, 0.91) | 0.87 (0.84, 0.91) | 0.91 (0.86, 0.96) | 0.91 (0.86, 0.96) |
| Common arterial truncus | f | 0.77 (0.48, 1.23) | f | 0.57 (0.31, 1.06) | f | 0.87 (0.59, 1.28) |
| Double outlet right ventricle | f | 0.88 (0.66, 1.17) | 0.83 (0.67, 1.03) | 0.83 (0.67, 1.03) | f | 1.03 (0.84, 1.26) |
| Transposition of great vessels | 0.90 (0.81, 1.00) | 0.90 (0.82, 1.00) | 0.93 (0.86, 1.00) | 0.93 (0.86, 1.00) | f | 1.01 (0.92, 1.10) |
| Single ventricle | f | 0.88 (0.60, 1.30) | f | 0.81 (0.57, 1.14) | f | 0.90 (0.63, 1.29) |
| Ventricular septal defect | 0.98 (0.94, 1.01) | 0.98 (0.95, 1.01) | 0.93 (0.90, 0.96) | 0.93 (0.90, 0.95) | 0.96 (0.93, 1.00) | 0.96 (0.93, 0.99) |
| Atrial septal defect | 0.89 (0.82, 0.96) | 0.88 (0.82, 0.95) | 0.87 (0.83, 0.92) | 0.87 (0.83, 0.92) | 0.93 (0.86, 1.01) | 0.92 (0.85, 1.00) |
| Atrioventricular septal defect | 0.95 (0.81, 1.12) | 0.96 (0.82, 1.12) | 0.90 (0.79, 1.03) | 0.90 (0.80, 1.03) | f | 1.06 (0.95, 1.19) |
| Tetralogy of Fallot | 0.79 (0.68, 0.92) | 0.81 (0.70, 0.93) | 0.80 (0.72, 0.90) | 0.81 (0.73, 0.91) | 0.79 (0.66, 0.94) | 0.79 (0.67, 0.94) |
| Triscuspid atresia and stenosis | f | 1.08 (0.88, 1.32) | f | 0.98 (0.81, 1.18) | f | 1.02 (0.80, 1.28) |
| Ebstein’s anomaly | f | 0.55 (0.30, 1.00) | f | 0.79 (0.58, 1.07) | f | 0.59 (0.29, 1.20) |
| Pulmonary valve stenosis | 0.93 (0.87, 1.01) | 0.95 (0.88, 1.02) | 0.90 (0.84, 0.95) | 0.90 (0.84, 0.96) | 0.90 (0.83, 0.98) | 0.91 (0.83, 0.98) |
| Pulmonary valve atresia | f | 0.87 (0.59, 1.28) | 0.72 (0.52, 1.00) | 0.70 (0.51, 0.97) | f | 1.12 (1.11, 1.12) |
| Aortic valve atresia/stenosis | 0.96 (0.85, 1.09) | 0.95 (0.84, 1.08) | 0.95 (0.86, 1.05) | 0.94 (0.85, 1.04) | 0.92 (0.80, 1.06) | 0.91 (0.79, 1.05) |
| Mitral valve anomalies | 0.83 (0.64, 1.06) | 0.90 (0.71, 1.14) | 0.76 (0.61, 0.94) | 0.77 (0.62, 0.96) | f | 0.98 (0.77, 1.24) |
| Hypoplastic left heart | f | 0.50 (0.26, 0.97) | 0.55 (0.35, 0.85) | 0.56 (0.36, 0.86) | f | 0.71 (0.37, 1.36) |
| Hypoplastic right heart | f | 0.97 (0.63, 1.51) | f | 0.93 (0.65, 1.32) | f | 1.12 (1.11, 1.12) |
| Coarctation of aorta | 0.91 (0.82, 1.00) | 0.90 (0.81, 0.99) | 0.88 (0.81, 0.95) | 0.87 (0.80, 0.94) | 0.89 (0.78, 1.01) | 0.89 (0.78, 1.01) |
| Aortic atresia / interrupted aortic arch | f | 0.61 (0.15, 2.43) | f | 0.74 (0.45, 1.23) | g | g |
| Total anomalous pulmonary venous return | f | 0.90 (0.73, 1.12) | 0.87 (0.72, 1.05) | 0.87 (0.72, 1.05) | f | 0.85 (0.64, 1.11) |
| PDA as only CHD in term infants (>=37 weeks) | 0.82 (0.63, 1.07) | 0.82 (0.63, 1.07) | 0.83 (0.72, 0.95) | 0.83 (0.73, 0.96) | g | g |
| **Respiratory** |  |  |  |  |  |  |
| Choanal atresia | f | 0.77 (0.49, 1.21) | f | 0.91 (0.70, 1.19) | f | 0.89 (0.58, 1.39) |
| Cystic adenomatous malformation of lung | f | 0.92 (0.73, 1.16) | f | 1.01 (0.89, 1.15) | f | 0.96 (0.66, 1.38) |
| **Oro-facial clefts** |  |  |  |  |  |  |
| Cleft lip with or without cleft palate | 0.89 (0.83, 0.95) | 0.88 (0.83, 0.94) | 0.91 (0.87, 0.96) | 0.91 (0.87, 0.96) | 0.94 (0.88, 1.00) | 0.92 (0.86, 0.99) |
| Cleft palate | 0.91 (0.84, 0.99) | 0.91 (0.84, 0.98) | 0.84 (0.78, 0.90) | 0.84 (0.78, 0.90) | 0.87 (0.78, 0.96) | 0.86 (0.78, 0.95) |
| **Digestive System** |  |  |  |  |  |  |
| Oesophageal atresia with or without tracheo-oesophageal fistula | 1.00 (0.88, 1.14) | 0.99 (0.87, 1.12) | 0.98 (0.88, 1.09) | 0.98 (0.88, 1.09) | f | 0.97 (0.84, 1.12) |
| Duodenal atresia or stenosis | f | 1.09 (0.97, 1.23) | 0.99 (0.87, 1.13) | 1.00 (0.88, 1.13) | 1.15 (1.15, 1.16) | 1.13 (1.10, 1.16) |
| Atresia or stenosis of other parts of small intestine | f | 0.95 (0.77, 1.18) | f | 0.95 (0.79, 1.13) | f | 1.03 (0.81, 1.31) |
| Ano-rectal atresia and stenosis | 0.80 (0.65, 0.99) | 0.82 (0.67, 0.99) | 0.90 (0.78, 1.02) | 0.90 (0.80, 1.02) | f | 0.83 (0.63, 1.09) |
| Hirschsprung’s disease | 0.94 (0.79, 1.13) | 0.95 (0.80, 1.14) | 1.00 (0.90, 1.12) | 1.00 (0.90, 1.12) | f | 0.86 (0.64, 1.16) |
| Atresia of bile ducts | f | 1.02 (0.64, 1.63) | f | 1.13 (0.88, 1.46) | f | 1.12 (1.11, 1.12) |
| Diaphragmatic hernia | 0.89 (0.75, 1.05) | 0.90 (0.77, 1.06) | 0.91 (0.80, 1.02) | 0.91 (0.81, 1.03) | f | 0.90 (0.75, 1.07) |
| **Abdominal wall defects** |  |  |  |  |  |  |
| Gastroschisis | 0.91 (0.81, 1.01) | 0.94 (0.84, 1.05) | 0.89 (0.82, 0.97) | 0.92 (0.85, 0.99) | 0.96 (0.87, 1.07) | 0.99 (0.90, 1.09) |
| Omphalocele | f | 0.84 (0.65, 1.09) | f | 1.02 (0.90, 1.15) | f | 0.97 (0.77, 1.21) |
| **Urinary** |  |  |  |  |  |  |
| Multicystic renal dysplasia | 0.98 (0.90, 1.08) | 0.99 (0.90, 1.08) | 0.97 (0.90, 1.04) | 0.97 (0.90, 1.04) | 0.95 (0.85, 1.05) | 0.94 (0.84, 1.05) |
| Congenital hydronephrosis | 1.00 (0.95, 1.05) | 0.99 (0.94, 1.04) | 1.00 (0.96, 1.03) | 0.99 (0.95, 1.03) | 1.04 (0.99, 1.09) | 1.02 (0.98, 1.07) |
| **Genital** |  |  |  |  |  |  |
| Hypospadiasd | 1.01 (0.94, 1.09) | 1.01 (0.94, 1.08) | 1.02 (0.99, 1.06) | 1.02 (0.99, 1.06) | f | 0.97 (0.88, 1.08) |
| Indeterminate sex | f | 0.79 (0.54, 1.16) | f | 0.74 (0.53, 1.02) | f | 0.89 (0.66, 1.20) |
| **Limb** |  |  |  |  |  |  |
| Limb reduction defects  | 0.96 (0.87, 1.07) | 0.95 (0.86, 1.06) | 0.96 (0.88, 1.04) | 0.95 (0.88, 1.03) | f | 0.99 (0.89, 1.10) |
| Club foot – talipes equinovarus | 0.98 (0.89, 1.08) | 0.95 (0.86, 1.06) | 0.91 (0.84, 0.99) | 0.90 (0.83, 0.98) | f | 1.05 (0.97, 1.14) |
| Hip dislocation and/or dysplasia | f | 1.09 (0.96, 1.24) | f | 1.02 (0.91, 1.15) | f | 1.14 (1.10, 1.17) |
| Polydactyly | 0.99 (0.90, 1.08) | 0.98 (0.89, 1.08) | 1.00 (0.95, 1.06) | 0.99 (0.94, 1.05) | f | 0.97 (0.83, 1.14) |
| Syndactyly | 0.96 (0.86, 1.07) | 0.95 (0.85, 1.06) | 0.98 (0.91, 1.04) | 0.97 (0.91, 1.04) | f | 0.97 (0.80, 1.18) |
| **Other anomalies** |  |  |  |  |  |  |
| Craniosynostosis | f | 0.46 (0.28, 0.78) | 0.82 (0.66, 1.02) | 0.82 (0.66, 1.01) | f | 0.71 (0.49, 1.04) |
| Situs inversus | f | 0.44 (0.08, 2.50) | f | 0.90 (0.62, 1.31) | f | 1.21 (1.08, 1.35) |
| **Chromosomal** |  |  |  |  |  |  |
| Down syndrome | f | 0.02 (0.01, 0.05) | 0.02 (0.01, 0.03) | 0.02 (0.01, 0.03) | f | 0.03 (0.01, 0.07) |
| Turner syndromee  | 0.94 (0.82, 1.08) | 0.95 (0.83, 1.09) | 0.71 (0.60, 0.84) | 0.70 (0.59, 0.83) | 0.84 (0.69, 1.01) | 0.84 (0.70, 1.02) |
| Klinefelter syndromed  | 0.45 (0.28, 0.72) | 0.44 (0.28, 0.69) | 0.58 (0.45, 0.76) | 0.57 (0.44, 0.74) | 0.56 (0.37, 0.84) | 0.55 (0.36, 0.82) |

a The number of pupils with valid results for each school subject is reported in Table 1.

bAdjusted for Free School Meals eligibility (proxy of socioeconomic deprivation).

c Subgroups included in Severe CHD are indicated in eTable2.

d Compared with control boys only.

e Compared with control girls only.

f Unadjusted RRs suppressed to prevent derivation of small counts. Adjusted RRs do not disclose small counts as the number of children in adjusted models have not been provided.

g Insufficient data for estimation

CHD, congenital heart defect; CI, confidence interval; EUROCAT, European network of population-based registries for the surveillance of congenital anomalies; GA, gestational age; PDA, patent ductus arteriosus; RR, risk ratio.

# **TABLE 3** Key stage 4 (KS4) level of attainment: number, percentage of children and unadjusted and adjusted risk ratios (RR) of achieving 5 or more General Certificate of Secondary Education (GCSE) and equivalents at grades A\*-C (Level 2), including GCSE English and mathematics, for EUROCAT children versus the comparison group (controls)

|  |  |  |
| --- | --- | --- |
|  | N pupils with a valid result | Achieved 5 or more GCSE and equivalents at grades A\*-C (Level 2)including GCSE English and mathematics (2009/10-2015/16) |
|  | n | % (95% CI)a or [% range] | Unadjusted RR (95% CI) | RR adjusted b (95% CI) |
| Controls | 32770 | 17196 | 52.5 (51.9, 53.0) | 1.00 (Reference) | 1.00 (Reference) |
| **All isolated structural anomalies** | 4824 | 2262 | 46.9 (45.5, 48.3) | 0.89 (0.87, 0.92) | 0.88 (0.86, 0.91) |
| **Nervous System** |  |  |  |  |  |
| Encephalocele | f | f | [0-25] | g | 0.38 (0.07, 2.14) |
| Spina Bifida | 39 | 15 | 38.5 (23.4, 55.4) | 0.74 (0.50, 1.11) | 0.81 (0.56, 1.17) |
| Hydrocephalus | 42 | f | [0-25] | g | 0.33 (0.17, 0.65) |
| Severe microcephaly | 36 | f | [0-25] | g | 0.11 (0.03, 0.42) |
| Arhinencephaly/holoprosencephaly | f | 0 | [0-25] | i | i |
| **Eye** |  |  |  |  |  |
| Anophthalmos / microphthalmos | f | f | [26-50] | g | 0.80 (0.35, 1.81) |
| Anophthalmos | f | 0 | [0-25] | i | i |
| Congenital cataract | 32 | 19 | 59.4 (40.6, 76.3) | 1.15 (0.86, 1.53) | 1.22 (0.93, 1.60) |
| Congenital glaucoma | f | f | 100.0 (29.2, 100.0) | g | 1.73 (1.72, 1.75) |
| **Ear, Face and Neck** |  |  |  |  |  |
| Anotia | f | f | 100.0 (15.8, 100.0) | g | 1.73 (1.72, 1.75) |
| **Congenital Heart Defects (CHD)** |  |  |  |  |  |
| ALL CHD | 1865 | 879 | 47.1 (44.8, 49.4) | 0.91 (0.86, 0.95) | 0.90 (0.85, 0.94) |
| Severe CHD | 563 | 247 | 43.9 (39.7, 48.1) | 0.85 (0.77, 0.93) | 0.84 (0.76, 0.92) |
| Common arterial truncus | 10 | h | [51-75] | g | 0.91 (0.50, 1.65) |
| Double outlet right ventricle | 22 | f | [26-50] | g | 0.91 (0.58, 1.44) |
| Transposition of great vessels | 128 | 57 | 44.5 (35.7, 53.6) | 0.86 (0.71, 1.04) | 0.86 (0.71, 1.05) |
| Single ventricle | 10 | h | [26-50] | g | 0.77 (0.38, 1.57) |
| Ventricular septal defect | 977 | 487 | 49.8 (46.7, 53.0) | 0.96 (0.90, 1.03) | 0.95 (0.89, 1.01) |
| Atrial septal defect | 247 | 102 | 41.3 (35.1, 47.7) | 0.80 (0.69, 0.92) | 0.82 (0.71, 0.94) |
| Atrioventricular septal defect | 46 | 17 | 37.0 (23.2, 52.5) | 0.71 (0.49, 1.04) | 0.72 (0.50, 1.04) |
| Tetralogy of Fallot | 96 | 33 | 34.4 (25.0, 44.8) | 0.66 (0.50, 0.87) | 0.64 (0.49, 0.85) |
| Triscuspid atresia and stenosis | 14 | h | [51-75] | g | 1.06 (0.65, 1.75) |
| Ebstein’s anomaly | 12 | h | [26-50] | g | 0.72 (0.31, 1.67) |
| Pulmonary valve stenosis | 232 | 103 | 44.4 (37.9, 51.0) | 0.86 (0.74, 0.99) | 0.88 (0.77, 1.01) |
| Pulmonary valve atresia | f | f | [26-50] | g | 0.77 (0.37, 1.60) |
| Aortic valve atresia/stenosis | 75 | 40 | 53.3 (41.4, 64.9) | 1.03 (0.83, 1.27) | 0.98 (0.79, 1.22) |
| Mitral valve anomalies | 26 | f | [26-50] | g | 0.71 (0.42, 1.20) |
| Hypoplastic left heart | 10 | h | [26-50] | g | 0.61 (0.25, 1.48) |
| Hypoplastic right heart | f | f | [76-100] | g | 1.48 (0.75, 2.92) |
| Coarctation of aorta | 126 | 61 | 48.4 (39.4, 57.5) | 0.94 (0.78, 1.12) | 0.94 (0.79, 1.12) |
| Aortic atresia / interrupted aortic arch | f | 0 | [0-25] | i | i |
| Total anomalous pulmonary venous return | 22 | f | [26-50] | g | 0.76 (0.47, 1.23) |
| PDA as only CHD in term infants (>=37 weeks) | 10 | h | [26-50] | g | 0.55 (0.22, 1.39) |
| **Respiratory** |  |  |  |  |  |
| Choanal atresia | f | f | [76-100] | g | 1.35 (0.95, 1.91) |
| Cystic adenomatous malformation of lung | 22 | f | [26-50] | g | 0.91 (0.60, 1.40) |
| **Oro-facial clefts** |  |  |  |  |  |
| Cleft lip with or without cleft palate | 336 | 140 | 41.7 (36.3, 47.1) | 0.80 (0.71, 0.91) | 0.79 (0.70, 0.89) |
| Cleft palate | 206 | 96 | 46.6 (39.6, 53.7) | 0.90 (0.78, 1.04) | 0.91 (0.78, 1.05) |
| **Digestive System** |  |  |  |  |  |
| Oesophageal atresia with or without tracheo-oesophageal fistula | 57 | 31 | 54.4 (40.7, 67.6) | 1.05 (0.83, 1.33) | 1.00 (0.79, 1.27) |
| Duodenal atresia or stenosis | 30 | 18 | 60.0 (40.6, 77.3) | 1.16 (0.87, 1.55) | 1.05 (0.77, 1.43) |
| Atresia or stenosis of other parts of small intestine | 15 | h | [51-75] | g | 1.20 (0.82, 1.74) |
| Ano-rectal atresia and stenosis | 42 | 13 | 31.0 (17.6, 47.1) | 0.60 (0.38, 0.94) | 0.64 (0.42, 0.99) |
| Hirschsprung’s disease | 36 | 16 | 44.4 (27.9, 61.9) | 0.86 (0.60, 1.24) | 0.88 (0.61, 1.25) |
| Atresia of bile ducts | f | f | [51-75] | g | 1.16 (0.52, 2.57) |
| Diaphragmatic hernia | 49 | 21 | 42.9 (28.8, 57.8) | 0.83 (0.60, 1.14) | 0.85 (0.62, 1.17) |
| **Abdominal wall defects** |  |  |  |  |  |
| Gastroschisis | 106 | 43 | 40.6 (31.1, 50.5) | 0.78 (0.62, 0.99) | 0.83 (0.66, 1.04) |
| Omphalocele | 23 | h | [51-75] | g | 1.15 (0.83, 1.60) |
| **Urinary** |  |  |  |  |  |
| Multicystic renal dysplasia | 120 | 64 | 53.3 (44.0, 62.5) | 1.03 (0.87, 1.22) | 0.98 (0.84, 1.16) |
| Congenital hydronephrosis | 358 | 181 | 50.6 (45.3, 55.9) | 0.98 (0.88, 1.08) | 0.94 (0.85, 1.04) |
| **Genital** |  |  |  |  |  |
| Hypospadiasd | 195 | 95 | 48.7 (41.5, 56.0) | 0.94 (0.81, 1.09) | 0.93 (0.81, 1.07) |
| Indeterminate sex | 18 | f | [26-50] | g | 0.74 (0.40, 1.36) |
| **Limb** |  |  |  |  |  |
| Limb reduction defects  | 99 | 47 | 47.5 (37.3, 57.8) | 0.92 (0.75, 1.13) | 0.93 (0.75, 1.14) |
| Club foot – talipes equinovarus | 111 | 60 | 54.1 (44.3, 63.6) | 1.04 (0.88, 1.24) | 0.98 (0.81, 1.17) |
| Hip dislocation and/or dysplasia | 25 | h | [51-75] | g | 1.39 (1.11, 1.74) |
| Polydactyly | 108 | 54 | 50.0 (40.2, 59.8) | 0.97 (0.80, 1.17) | 0.96 (0.79, 1.16) |
| Syndactyly | 82 | 42 | 51.2 (39.9, 62.4) | 0.99 (0.80, 1.22) | 0.95 (0.77, 1.17) |
| **Other anomalies** |  |  |  |  |  |
| Craniosynostosis | 24 | f | [26-50] | g | 0.71 (0.43, 1.16) |
| Situs inversus | f | f | [51-75] | g | 1.16 (0.52, 2.57) |
| **Chromosomal** |  |  |  |  |  |
| Down syndrome | 389 | f | [0-25] | g | 0.01 (0.00, 0.05) |
| Turner syndromee  | 67 | 26 | 38.8 (27.1, 51.5) | 0.74 (0.55, 1.00) | 0.66 (0.48, 0.92) |
| Klinefelter syndromed  | 39 | f | [0-25] | g | 0.20 (0.08, 0.51) |

a Exact binomial confidence intervals. Where counts have been suppressed the quartile that includes the estimated percentage is indicated by [ ].

b Adjusted for Free School Meals (FSM) Eligibility. Overall proportion of children missing FSM: 5.0% (controls); 4.6% (all anomalies).

c Subgroups included in Severe CHD are indicated in eTable2.

d Compared with control boys only.

e Compared with control girls only.

f Denotes suppressed small count (<10).

g Unadjusted RRs suppressed to prevent derivation of small counts. Adjusted RRs do not disclose small counts as the number of children in adjusted models have not been provided.

h Secondary suppression (<10 did not achieve)

i Estimation not possible

CHD, congenital heart defect; CI, confidence interval; EUROCAT, European network of population-based registries for the surveillance of congenital anomalies; GA, gestational age; PDA, patent ductus arteriosus; RR, risk ratio.

1. current affiliation [↑](#footnote-ref-2)