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# COHORT PROFILE : THE NATIONAL CONGENITAL ANOMALY REGISTRATION DATASET IN ENGLAND



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# COHORT PROFILE : THE NATIONAL CONGENITAL ANOMALY REGISTRATION DATASET IN ENGLAND

Jennifer M Broughan, Ben Wreyford, Danielle Martin, Gabriella Melis, Kay Randall, Ewoma Obaro, John Broggio, Nicholas Aldridge , Sylvia Stoianova, Chloe Johnson, Donna Gibbard, Sarah Stevens & Kate Fleming

National Congenital Anomaly and Rare Disease Registration Service, National Disease Registration Service, Data and Analytics Directorate, NHS England, 7 Wellington Pl, Whitehall Rd, Leeds LS1 4EG, UK.

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Jennifer M Broughan,
Ben Wreyford, ben.wreyford@nhs.net
Danielle Martin, Danielle.Martin17@nhs.net
Gabriella Melis, Gabriella.Melis1@nhs.net
Kay Randall, kay.randall@nhs.net
Ewoma Obaro, ewoma.obaro@nhs.net
John Broggio, john.broggio@nhs.net
Nicholas Aldridge, nicholas.aldridge@nhs.net
Sylvia Stoianova, Sylvia.Stoianova@bristol.ac.uk
Chloe Johnson, Chloe.Johnson6@dhsc.gov.uk
Donna Gibbard, donna.gibbard@nhs.net
Sarah Stevens, sarah.stevens1@nhs.net
Kate M Fleming, kate.fleming5@nhs.net

Correspondence to:
Jennifer Broughan, PhD
National Disease Registration Service
NHS England
7 and 8 Wellington Pl,

Whitehall Rd,

Leeds

LS1 4EG,

UK.

Jennifer.Broughan@nhs.net

Tel +44 7769282928

ORCID 0000-0002-4450-2147

# ABSTRACT

## Purpose

The National Congenital Anomaly and Rare Disease Registration Service (NCARDRS), part of National Disease Registration Service (NDRS) in NHS England, collects, quality assures, curates and analyses individual data on the pregnancies, fetuses, babies, children and adults with congenital anomalies and rare diseases across England. The congenital anomaly (CA) register provides a resource for patients and their families, clinicians, researchers, and public health professionals in furthering the understanding of CAs.

## Participants

NCARDRS registers CAs that occur in babies born alive and stillborn, fetal losses and terminations in England. NCARDRS collects data from secondary and tertiary health care providers with maternal or paediatric departments, private providers and laboratories covering fetal medicine, maternity or paediatric services. Data describe the pregnancy, mother, baby, and anomaly. Established in 2015, NCARDRS expanded CA registration coverage from 22% of total births in England in 2015 until national coverage was achieved in 2018. Prior to 2015, data collection was performed independently by regional registers in England and this data is also held by NCARDRS.

## Findings to date:

With a coverage of approximately 600,000 total births per year, the NCARDRS CA register is the largest globally. Data on prevalence, risk factors and survival for children with CAs are available. Data has been used in several peer reviewed publications. Birth prevalence statistics, including public health indicators such as the association with maternal age, infant and perinatal mortality, are published annually. NCARDRS supports clinical audit for screening programmes and service evaluation.

## Future plans:

NCARDRS provides a valuable resource for the understanding of the epidemiology, surveillance, prevention and treatment of CAs. Currently, approximately 21,000 new registrations of babies or fetuses with suspected or confirmed CAs are added each year. Identifiers are collected, enabling linkage to routinely collected healthcare and population statistics, further enhancing the value of the data.

## Key words

Epidemiology, Public Health, Registries, neonatology, paediatrics

## Details of contributions:

JMB led the drafting of the manuscript with additional sections drafted by BW, DG, CJ, SS, NA. Data analysis was performed by JMB, DM, GM and EO. All authors reviewed and commented on the manuscript.

## Conflicts of interests statement

No conflicts of interest have been declared.

## Data availability statement

Permission to access congenital anomaly registration data can be granted to individuals who demonstrate that either there is a justified purpose for the data release, that there is an appropriate legal basis with safeguards in place to protect the data, or the data release is deemed to be anonymous (e.g. aggregate data). The access process for NDRS data is managed by Data Access Request Service (DARS) in NHS England. Full details, including data dictionaries, are available. Further details on the process of data access and associated costs are available on the DARS website [https://digital.nhs.uk/services/data-access-request-service-dars](1).

## Collaboration statement

NDRS supports collaborations with academic and other institutions to use the data for a justified purpose. Enquiries, requests for statistical code used and anonymised data should be directed to ndrs.enquiries@nhs.net.

## Strengths and limitations

- NCARDRS is one of the largest congenital anomaly registers in the world. Since 2018, coverage of congenital anomalies has been national across England (approximately 600,000 total births per year). This enables the calculation of accurate estimates of prevalence even for rare congenital anomalies. Legacy congenital anomaly registration data is held for some regions for births since 1985.
- NCARDRS collects personal identifiers and data are linked to other routinely collected administrative and health care data, allowing assessment of long-term outcome and survival over the life course of the baby, as well as associations with health inequalities and other risk factors.
- Information in NCARDRS can be linked to other national data sources, allowing the exploration of societal factors such as equity of access to treatment and clinical outcomes.
- NCARDRS provides data on all birth outcomes, including live births, stillbirths, fetal losses and terminations.
- Case-ascertainment is high for severe conditions, or those that are more frequently diagnosed antenatally or in the neonatal period. Registration and case ascertainment

in NCARDRS regions that initiated congenital anomaly registration from 2018 continues to develop and is progressing well.

## INTRODUCTION

Congenital anomalies are a significant source of morbidity, mortality and long-term care needs in children. Approximately 2-3% of children born in Europe have a congenital anomaly (2) which are defined as conditions present at birth and include structural, chromosomal, genetic and biochemical conditions. Some congenital anomalies are detected during pregnancy, some are found at birth, while others are diagnosed only as a baby grows older. In England and Wales, congenital anomalies were the most common cause of death in the post neonatal period in 2020, accounting for 36.3% of deaths (3). Globally it is estimated that 240,000 new-borns die within the neonatal period as a result of congenital anomalies (4).

Registration of congenital anomalies became established in many countries from the 1960s and 70s as a consequence of the thalidomide tragedy and serves multiple purposes supporting epidemiology and public health (5). The National Congenital Anomaly and Rare Disease Registration Service (NCARDRS) is part of the National Disease Registration Service (NDRS) of NHS England which collects, quality assures and analyses data on all people living in England with cancer (6), congenital anomalies and rare diseases. NCARDRS curates a population-based congenital anomaly registry, collecting data on the pregnancies, fetuses, babies, children and adults with congenital anomalies across the whole of England. Data is collected to further the understanding of the causes of congenital anomalies, to inform the commission of public services, to audit health and social care and to provide information for patients, their carers and clinicians on their condition.

Established in 2015 in response to the UK Rare Disease Strategy (7, 8), NCARDRS assumed responsibility for congenital anomaly registration in regions with an existing register and

expanded geographically to provide congenital anomaly registration across the whole country(9) (Figure 1). Prior to 2015, data collection was performed independently by regional registers operating across some areas of England, covering up to 32% of births. NCARDRS continues to host the regional registers' legacy registration data. National coverage for registration and reporting has been in place for babies born since 2018 (10).

# COHORT DESCRIPTION

## Study population

NCARDRS registers congenital anomalies that occur in babies that are live born and stillborn, fetal losses and terminations at any gestation delivered in England. NCARDRS does not have a minimum gestation for fetal loss and registers all fetal losses reported, although in line with international standards (11) only anomalies that occur in live births, stillbirths, terminations at any gestation and fetal losses between 20-24 completed weeks of gestation are included in prevalence reporting(12, 13). There are approximately 600,000 live births and stillbirths in England every year. There is no upper age limit and information can be added for children as they grow older Information on survival and vital status is updated at least annually.

Inclusion and exclusion criteria for registration of congenital anomalies in NCARDRS follow internationally recognised formats (11) and all registrations are coded to international standards. Anomalies are clinically coded to international standards using the World Health Organisation's International Classification of Diseases 10$^{th}$ revision (ICD-10)(14) with the British Paediatric Association (BPA) Adaptation, which gives supplementary one-digit extensions to ICD-10 codes to allow greater specificity of coding (11). Inclusion criteria are

based on international guidance (11) predominantly covering the Q chapter in ICD-10. A detailed summary of the current inclusion and exclusion criteria is presented in Table S1 in the supplementary materials. NCARDRS excludes cases with an isolated minor anomaly as specified by the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT) (11). However, if minor anomalies occur in association with other anomalies, then these are registered.

## Registration model and source data

NCARDRS employs a multisource, event-based registration model. Over the life course of a patient, NCARDRS can be notified antenatally, at birth or in the neonatal period and beyond as the child is treated by various paediatric specialist services. Registration data are processed, held on a custom-built live application, and regularly cloned to a separate PostgreSQL database which creates regular snapshots of data for analysis, reporting and data release (Figure 2).

The data collected by NCARDRS come from a range of sources including maternity units, multidisciplinary team meetings, postmortem reports, molecular testing results, treatment records, hospital patient administration systems, clinical data systems, national data sets describing hospital activity, clinical biochemistry and genetics laboratories. Hospital trusts, including all trusts with a maternity or paediatric service, submit data which are processed and combined by trained registration officers into a comprehensive clinical record of each baby and anomaly.

Data can be submitted at the individual case-level or in large data extracts from clinical management data systems. Custom-built extracts from neonatal clinical data management systems (BadgerNet), including remote access to the record itself, are available for 94% of the trusts with a neonatal unit in England. Extracts of relevant data from fetal medicine software systems including fetal medicine (Viewpoint; Astraia) and specific services

(HeartSuite) have been developed in conjunction with software suppliers; these extracts are produced and submitted to NCARDRS by the provider.

Information from providers is combined with routinely collected national data utilised for both data quality and case-ascertainment purposes. Linkage is conducted through NHS number or through date of birth, full name and address. Cases with defined ICD-10 codes that have been validated for accuracy are identified from Hospital Episode Statistics (HES) for ascertainment purposes. Death certificate data from the Office for National Statistics (ONS) is provided to NCARDRS monthly for children born alive after 1st January 2018 and where a relevant ICD-10 coded condition (within a specified range) is listed as a cause of death. Information about babies that were born alive or stillborn after 24 weeks gestation (civilly registrable in England) is supplemented using birth registration information supplied by the ONS.

## Data processing

Once received, data are processed by trained registration officers. Processing involves manual extraction of clinical information from clinical reports and letters or free text comments in clinical software systems. Registration officers require detailed knowledge of congenital anomalies, clinical coding and clinical pathways for the range of different conditions collected. Further information is requested from the relevant clinician or obtained by direct interrogation of patient records via secure remote access to clinical software systems or clinical documents where this is available.

Data are input onto the data management system in two ways: 1) data on individual patients submitted by providers are assessed by trained registration officers and manually entered or 2) data from electronic sources are loaded via a semi-automatic process known as the data waterfall (Figure 2). Most cases consist of information processed by both methods.

## Data structure

Registration is framed at the level of the anomaly, baby, pregnancy and birth mother. The data are organised into 5 main tables: mother, pregnancy, baby, anomaly and test, with one-to-many relationships across all. Each table contains a primary key that uniquely identifies records within that table and allows joins between tables. A baby and a mother are each assigned a unique identifier. The data items in the base tables are organised into a series of custom-built analytical views. Registration records are never closed and new events can be added if new information is submitted.

## Key data fields

Detailed clinical and demographic information on the mother, baby, anomaly and pregnancy is recorded (Table 2). Multiple anomalies can be registered against a baby, each with different evidence and confirmation status.

NCARDRS works closely with the NHS Fetal Anomaly Screening Programme (FASP) to audit the detection of the 15 conditions included. To facilitate this audit, more extensive information on antenatal screening and the nature and timing of diagnostic testing is collected for these conditions and other closely related or similar conditions. The conditions that are covered by this enhanced registration include severe cardiac anomalies and trisomy 13, trisomy 18 and trisomy 21, along with neural tube defects, lethal skeletal dysplasia, cleft lip+/palate, bilateral renal agenesis, exomphalos, gastroschisis and congenital diaphragmatic hernia (see Table S1 in the supplementary materials).

## Data Quality

Automatic and manual quality checks are embedded into the registration process at points of entry, at the level of the individual record and on the birth cohort as a whole prior to finalisation of the data for reporting. As well as internal data quality indicators (DQIs), the data are evaluated against DQIs for international bodies against known targets(15). For example, the prevalence of anencephaly is reported as an indicator of ascertainment of conditions detected at earlier gestations. Other DQIs focus on the accuracy of diagnosis, for example the number of babies with more than one anomaly, or the prevalence of selected codes that have used the BPA extension code in addition to the ICD-10 code.

## Patient and public involvement

Patients groups and third sector organisations representing patients were involved in the design of this register-based cohort and were members of an expert committee of stake holders made up of academics, clinicians, third sector organisation and patient interest groups that oversaw the formation of NCARDRS.

## Ethical approval and governance arrangements

NCARDRS has legal permission to collect patient-level data on those with a confirmed or suspected congenital anomaly or rare disease for specified purposes, without consent, to use it to protect the health of the population. Data are collected under legal instructions known as Directions, from the Secretary of State for Health and Social Care, under section 254 of the Health and Social Care Act 2012 (2012 Act) (16). Strict technical and contractual controls are put in place to prevent unauthorized access and use of the data, with staff undergoing regular training on data protection and information governance.

## FINDINGS TO DATE

As of June 2023, NCARDRS held information on 117,682 mothers and 121,184 babies born in England since 2015. Table 1 shows the number of babies and other characteristics registered in regions with full congenital anomaly registration coverage by year of birth.

NCARDRS currently collects data on more than 1,000 different congenital anomalies, many of which are rare diseases, and provides expert analysis and interpretation of the data across a wide range of national and international functions. The data are available as a source of intelligence for clinicians, public health, health-care performance, basic and applied research, patient groups, academics and commissioning and industry partners. A summary of the data is published each year describing congenital anomalies in England in the context of prevalence reported by anomaly group, timing of diagnosis and important public health indicators such as maternal age and infant mortality (10, 17-19). In 2020, NCARDRS reported a total of 13,065 babies with one or more confirmed or probable congenital anomalies in 589,454 total births (live births and stillbirths), giving an overall birth prevalence of 221.7 per 10,000 total births (95% confidence intervals (CI) 217.9 - 225.5). or 1 for every 45 births (20). The rate of perinatal mortality associated with a congenital anomaly was highest for genetic disorders (3.1 per 10,000 total births, 95% CI 2.7-3.6), followed by congenital heart anomalies (2.8 per 10,000 total births, 95% CI 2.4-3.2). Infant mortality rate was highest for congenital heart anomalies (4.9 per 10,000 live births, 95% CI 4.4-5.5), followed by genetic conditions (3.0 per 10,000 live births, 95% CI 2.6-3.5). The rate of genetic conditions in babies born to women over 40 years old was almost 7 times higher relative to babies born to mothers under 20 years old (risk ratio equal to 6.9, 95% CI 5.2-9.2).

Congenital anomaly registration data for England is submitted to international bodies to allowing pooling of data across a wider geographical area to support analysis into causes of these rare conditions and how to prevent them. Data is submitted annually to EUROCAT and

to the International Clearinghouse for Birth Defects Surveillance and Research (ICHBDSR). Surveillance is performed annually using internationally recognised tools to identify potential clusters of anomalies and changes in trends (21).

NCARDRS works closely with NHS Screening Programmes delivering service evaluation for antenatal and new-born screening services. NCARDRS audits the detection of the conditions included in the Fetal Anomaly Screening Programme (FASP) (see Table S1 in the supplementary materials) and, to enable this, these conditions are subject to enhanced registration and active ascertainment. By linking information at patient level, NCARDRS creates a longitudinal record of the screening and diagnostic pathway for each mother, fetus, or baby, enabling analysis of the efficacy of the tests, the behavioural choices on the pathway, and the operational standards of the service. NCARDRS have recently published the first national study of fetal anomaly ultrasound scan detection rates in England (22). The data is used to provide reliable information about the quality of screening services at local, regional and national level and contributes towards the safety and effectiveness of screening services. Each screening provider receives a report detailing hospital-level detection rates and also individual case-level detection status to allow further clinical audit and identify training requirements. NCARDRS is supporting the NHS evaluative roll-out of non-invasive prenatal testing (NIPT) for Edwards' syndrome, Patau's syndrome, and Down's syndrome in England (23). Routine laboratory surveillance is conducted on a monthly, quarterly and annual level, and test performance will be evaluated by linking laboratory and registration data.

At the start of the COVID-19 pandemic, NCARDRS informed the production of the Shielded Patient List (SPL) (24) by identifying individuals living with congenital anomalies and selected rare diseases that may have been at increased risk from COVID-19 infection and NCARDRS will support the continued evaluation of vaccines against COVID-19 in pregnancy (25).

Many publications use datasets that predate NCARDRS including the legacy regional registers. NCARDRS data has been used to examine the epidemiology of congenital anomalies across Europe including Dandy-Walker syndrome (26), VACTERL association (27,

28), neural tube defects(29), aplasia cutis (30) achondroplasia (31) and vascular disruption anomalies (32). Studies aim to improve outcomes of babies with a congenital anomaly and to inform policy so that some may be prevented, for example to justify the fortification of flour with folic acid (29). Recently, the UK government announced plans for the fortification of flour with folic acid to reduce neural tube defects (33). NCARDRS will support the evaluation and monitoring of the impact of implementation of this policy (34).

## STRENGTHS AND LIMITATIONS:

### National Coverage

The key strength of the NCARDRS data set is its national coverage across a large birth population. NCARDRS is the largest register in Europe (35) in both size of population and representativeness. With complete population coverage of pregnancies from 2018 onwards, the data are representative and comprehensive, capitalising on the centralised nature of English health care. Registration records are never closed, and data can continue to passively accumulate, enriching each record and facilitating the potential identification of future syndromes or providing more information on the phenotypic manifestations of genetic differences identified later in life.

### Standardised disease coding and data entry

The development of NCARDRS has demonstrated that it is possible to conduct national registration on a large population using standardised approaches to data collection and management, disease coding, data classification, analysis and reporting. Data are coded consistently across the country and regions can be compared, allowing the identification of clusters and geographical disparities which may be a result of population demographics, social determinants of health or local exposure.

## Ascertainment

National prevalence in England for 2018-2020 is consistent with European surveillance data for the same time period (excluding data for England) across most major congenital anomaly groups (Figure 3). The prevalence of severe anomalies, such as severe congenital heart, abdominal wall, oro-facial cleft, respiratory and genetic conditions was higher than the European average. These anomaly subgroups include FASP-conditions and so are subject to enhanced registration. Their higher prevalence reflects the integration of clinical audit in NCARDRS and demonstrates the impact of clinical engagement on data quality and ascertainment. The England national prevalence estimates for all cardiac conditions, limb anomalies and congenital anomalies of the kidney and urinary tract (CAKUT) conditions are lower than the average for other European registers. This likely reflects some under-ascertainment of anomalies that are predominantly confirmed postnatally in regions of NCARDRS new to reporting(13).

Across England, there is some variation in the prevalence of different anomaly groups depending on the length of time registration has been established, reflecting developing ascertainment in regions new to congenital anomaly registration particularly for anomalies that are more frequently identified postnatally (13). As registration becomes embedded and ascertainment increases, differences in prevalence because of data collection should dissipate, revealing true regional differences, if they exist.

## Timeliness of data collection

Babies with a congenital anomaly are first registered by NCARDRS approximately 12 months after their expected date of delivery. This time lag allows for the notification of outcome of the pregnancy and a confirmatory diagnosis after delivery along with the notification of other relevant postnatal information and follow-up if required. Finalised delivery year cohorts are available approximately 14 to 18 months following the end of a delivery year e.g., babies

delivered in 2021 would be reported on in 2023. Recent advances in the automated processing of defined data feeds (e.g. fetal medicine software system extracts) aim to improve the timeliness of data by reducing the time lag.

### Risk factor information

Information on the demographics of the mother is collected for each pregnancy and include ethnicity, Body Mass Index, illnesses or medications, folic acid intake and other lifestyle factors such as smoking. This information can be supplemented using data linkage to examine other factors, including social deprivation measured at the area-level through deprivation scores for mother's residential address at delivery,

## FUTURE WORK

Planned improvements to the timeliness of data reporting and continued improvement to developing ascertainment for new regions and completeness of fields will further improve data quality. As the service matures, new data sources will be added to improve data quality or ascertainment. Proximity to the more established cancer registration service allows the register to build on synergies in data management, analytical infrastructure and data liaison. Transition to NHS England has situated NCARDRS closer to clinical providers and commissioning services which should improve data access and facilitate linkage to a wider network of data e.g. Maternity Services Dataset in NHS England. The inclusion of primary care data would be an obvious improvement to the ascertainment of postnatally diagnosed conditions.

Linkage to other datasets provides vital information on survival and health outcomes for these children throughout their life course. Cancer registration data collected by NDRS has been linked to the community prescriptions dataset (36) and linkage with the congenital anomaly registration data is in progress. This could provide information on possible drug interactions

and potential teratogens. Further linkage is being pursued with the Maternity Services Dataset, with the aim to facilitate registration of cases and enhance data completeness for key analytical fields. Linkage to other disease registers, subject to adequate consenting materials and approvals, is possible and could provide valuable information on health outcomes for children with congenital anomalies.

## CONCLUSIONS

If the thalidomide scandal of the 1960s prompted the establishment of congenital anomaly registration to understand the causes of congenital anomalies, the COVID-19 pandemic amplified the need to be able to identify and protect individuals living with conditions that may put them at increased risk compared to the general population. NCARDRS' congenital anomaly register collates information across the full patient pathway as the pregnancy progresses and the child grows. The value of this dataset in supporting clinical audits and evaluating service delivery is proven. This population-based national register – currently the largest data collection of its kind globally – has a critical role in supporting the epidemiology and monitoring of disease trends, investigating the causes of these conditions, evaluating the outcome and providing this crucial information to parents, patients and clinicians and to clinical and service commissioners so these children have what they need as they grow.



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Figure 1 The regional structure of NCARDRS and the proportion of the birth population of England that was covered by congenital anomaly registration.

Figure 2 : Schematic describing the multisource registration process used for congenital anomalies in England.

Figure 3 The prevalence of anomaly groups in England compared to EUROCAT registers excluding English registers (2018-2020) [data downloaded 24th April 2023 from EUROCAT, 1st August 2022 NCARDRS]

Table 1 The number of pregnancies, babies and anomalies recorded registered since NCARDRS has been in operation until 2020 Data extracted 13th June 2023.

| | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 |
|---|---|---|---|---|---|---|
| Number of regions reporting | 4 | 7 | 7 | 10 | 10 | 10 |
| Number of pregnancies with babies with a congenital anomaly of any status | 2,915 | 9,524 | 9,882 | 20,036 | 19,636 | 18,440 |
| Number of babies with a congenital anomaly of any status | 2,932 | 9,574 | 9,937 | 20,145 | 19,767 | 18,541 |
| Number of mothers | 2,908 | 9,506 | 9,868 | 20,007 | 19,611 | 18,416 |
| Total number of anomalies | 5,902 | 18,839 | 18,803 | 35,483 | 34,500 | 33,344 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Total number of confirmed and probable anomalies | 5,432 | 15,819 | 15,316 | 28,282 | 25,988 | 25,617 |
| Birth population with active congenital anomaly registration | 141,474 | 329,301 | 320,013 | 628,171 | 614,952 | 589,454 |

NOTE : the numbers may differ from published estimates at point of reporting because of continued accumulation of data



Table 2: Summary of key data items available for each congenital anomaly registration

| **Mother** | **Pregnancy** | **Baby** | **Anomaly** | **Test**[1] |
|---|---|---|---|---|
| Patient identifier | Pregnancy identifier | Patient identifier | Anomaly identifier | Test date |
| NHS number | Expected Delivery Date | NHS number | Confirmation Status of anomaly[2] | Test type |
| Date of birth | Pregnancy outcome | Sex | ICD 10 & BPA extension code | Test result(s) |
| Ethnicity | Delivery information | Date of birth | Description of the anomaly | Test provider |
| Country of birth | Screening details | Gestational length at delivery | Gestation first suspected | Test requestor |
| Vital status | Body Mass Index | Birth weight (g) | Gestation at confirmation | Ultrasound markers |

| | | | | |
|---|---|---|---|---|
| Previous births and pregnancies | Smoking status at booking, alcohol and substance use | Birth order if from a multiple pregnancy | Diagnostic method | Indication |
| | Maternal illness status | Method of delivery | Aetiology of the anomaly/ies | |
| | Folic acid intake | Surgical status | | |
| | Assisted conception status | Date of death | | |
| | Number of fetuses | Postmortem status | | |
| | Consanguinity | | | |
| | Deprivation (derived from postcode of residence at delivery) | | | |
| | Postcode at booking and at delivery | | | |

[1] Test information is only consistently registered for conditions with enhanced registration

[2] Confirmation status: Anomalies are registered according to varying degrees of certainty depending on the clinical evidence available (*confirmed, probable or suspected)*. Anomalies remain at the level of *suspected* until the evidence supporting the diagnosis of the anomaly attains agreed confirmation criteria

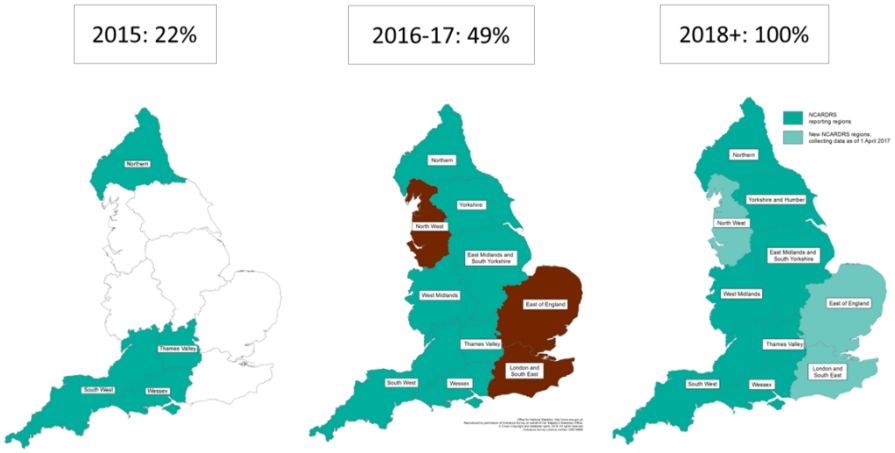


Figure 1 The regional structure of NCARDRS and the proportion of the birth population of England that was covered by congenital anomaly registration.

855x481mm (38 x 38 DPI)

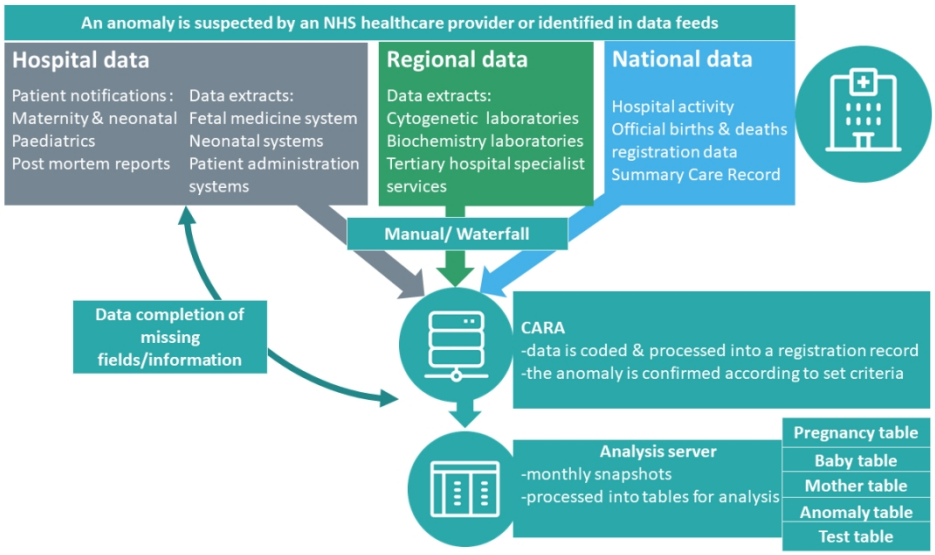


Figure 2 : Schematic describing the multisource registration process used for congenital anomalies in England.

855x481mm (38 x 38 DPI)

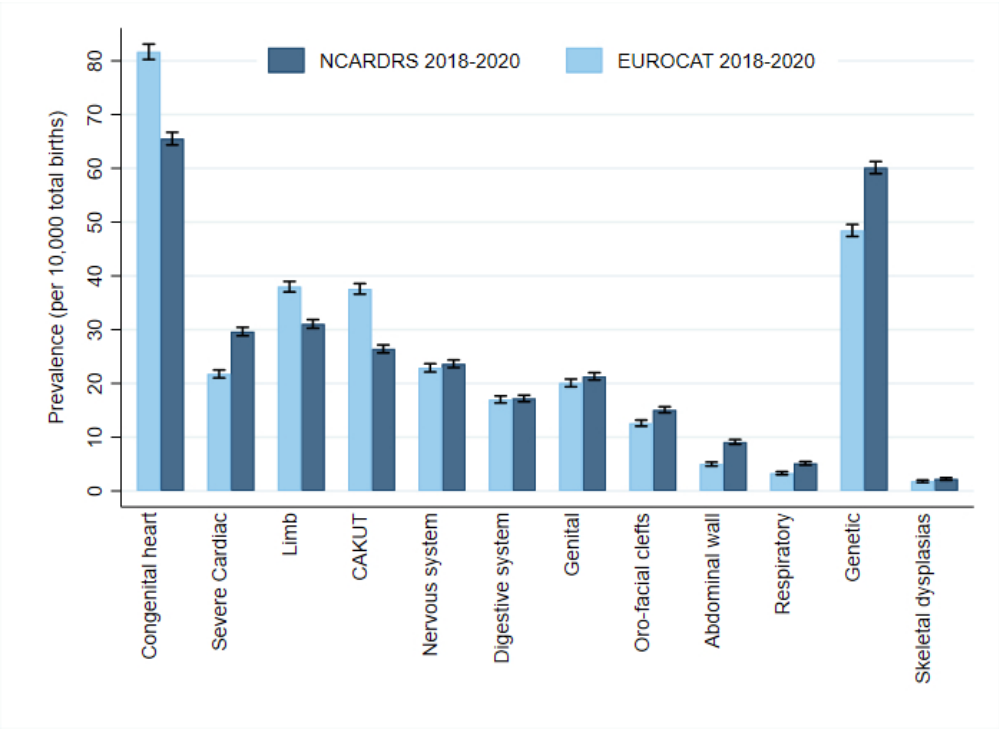


Figure 3 The prevalence of anomaly groups in England compared to EUROCAT registers excluding English registers (2018-2020) [data downloaded 24th April 2023 from EUROCAT, 1st August 2022 NCARDRS]

466x338mm (38 x 38 DPI)

**Table S1 NCARDRS inclusion and exclusion criteria for registerable congenital anomalies**

| Anomaly type | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Nervous system anomalies | Q00-Q07 Congenital malformations of the nervous system | MEASUREMENT / SEVERITY<br>Q02 Microcephaly<br>Q03.8 (part) Congenital ventriculomegaly [of lateral ventricle(s)]<br>Q04.32 Reduction anomalies of cerebellum<br><br>CLINICAL SIGNIFICANCE<br>Q04.61 (part) Arachnoid cyst | EXCLUDE IN ISOLATION<br>Q0780 Jaw-winking syndrome<br>Q0782 Crocodile tears<br><br>EXCLUDE always<br>Q04.6 (part) Porencephaly | Q04.6 (part) Porencephaly - EUROCAT inclusion but NCARDRS excludes<br><br>Q04.61 Single congenital cerebral cyst - EUROCAT exclusion in isolation but NCARDRS includes Arachnoid cyst | YES<br>Q00* Anencephaly and similar malformations<br>Q01* Encephalocele<br>Q05* Spina bifida |
| Eye anomalies | Q10-Q15 Congenital malformations of eye | NA | EXCLUDE IN ISOLATION<br>Q10.1 Congenital ectropion, Q10.2 Congenital entropion, Q10.3 Other congenital malformations of eyelid, Q10.5 Congenital stenosis or stricture of lacrimal duct<br>Q13.2 (part) Anisocoria, congenital, Q13.5 Blue sclera<br>Minor anomalies and dysmorphic features | NA | NO |

| Anomaly type | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Ear, face and neck anomalies | Q16 Congenital malformations of ear causing impairment of hearing | CLINICAL SIGNIFICANCE Q18.3 Webbing of neck | EXCLUDE IN ISOLATION Q17* Other congenital malformations of ear Q18.0-Q18.2 Branchial cleft malformations, Q18.4-Q18.9 Macrostomia, Microstomia, Macrocheilia, Microcheilia, Other congenital malformations of face and neck, Dysmorphic features NOS Minor anomalies and dysmorphic features | NA | NO |

| Anomaly type | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Heart and circulatory system anomalies | Q20-Q28 Congenital malformations of circulatory system | PERSISTENCE<br>Q21.10 Ostium secundum atrial septal defect (type II)<br><br>CLINICAL SIGNIFICANCE<br>Q24.8 Other specified congenital malformations of heartQ28.8 Other specified congenital malformations of circulatory system<br><br>GESTATIONAL AGE AT DELIVERY & PERSISTENCE / SURGERY / SEVERITYQ25.0 Patent ductus arteriosus, Q25.6 Stenosis of pulmonary artery | EXCLUDE IN ISOLATION<br>Q21.11 Patent foramen ovale<br>Q24.6 Congenital heart block<br>Q25.41 Persistent right aortic arch<br>Q26.1 Persistent left superior vena cava,<br>Q26.8 (part) Absence of superior vena cava, Interrupted inferior vena cava<br>Q27.0 Congenital absence and hypoplasia of umbilical artery | NA | YES<br>SERIOUS CARDIAC ANOMALIES<br><br>Q20.0 Common arterial trunk<br>Q20.1 Double outlet right ventricle<br>Q20.3 Transposition of the great arteries<br>Q20.4 Double inlet ventricle<br>Q21.2* Atrioventricular septal defect<br>Q21.3, Q21.82 Tetralogy of Fallot<br>Q22.0 Pulmonary valve atresia<br>Q22.4 Congenital tricuspid stenosis<br>Q22.5 Ebstein's anomaly<br>Q22.6 Hypoplastic right heart syndrome<br>Q23.0 Congenital stenosis of aortic valve<br>Q23.2, Q23.3 Congenital mitral stenosis and insufficiency<br>Q23.4 Hypoplastic left heart<br>Q25.1* Coarctation of aorta<br>Q25.2 Aortic atresia, interrupted aortic arch<br>Q26.2 Total anomalous pulmonary venous connection |

| Anomaly type | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Respiratory system anomalies | Q30-Q34 Congenital malformations of respiratory system | CLINICAL SIGNIFICANCE<br>Q30.8 Other congenital malformations of nose<br><br>CAUSE<br>Q33.6 Hypoplasia and dysplasia of lung | EXCLUDE IN ISOLATION<br>Q31.5 Congenital laryngomalacia<br>Q32.0 Congenital tracheomalacia<br>Q32.2* Congenital bronchomalacia<br>Q33.00 Congenital single lung cyst<br>Q33.1* Accessory lobe of lung | NA | NO |
| Orofacial clefts | Q35-Q37 Cleft lip and cleft palate | MINOR FORMS<br>Q35-Q37 Cleft lip and cleft palate | EXCLUDE IN ISOLATION<br>Q35.7 Cleft uvula | NA | YES<br>Q36*, Q37* Cleft lip with/without cleft palate |
| Gastrointestinal anomalies | Q38-Q45 Other congenital malformations of the digestive system | CLINICAL SIGNIFICANCE<br>Q38.3 Other congenital malformations of tongue<br>Q44.5 Other congenital malformations of bile ducts<br><br>GESTATIONAL AGE AT DIAGNOSIS & SURGERY<br>Q43.30 Malrotation of colon<br><br>SURGERY<br>Q43.5 Ectopic anus | EXCLUDE IN ISOLATION<br>Q38.1 Ankyloglossia, Q38.2 Macroglossia, Q38.3 (part) Microglossia, Q38.4 (part) Congenital ranula, Q38.50 High arched palate<br>Q40.0 Congenital hypertrophic pyloric stenosis, Q40.1 Congenital hiatus hernia, Q40.21 Dysmotility of stomach<br>Q43.0* Meckel's diverticulum, Q43.20 Large intestinal dysmotility, Q43.81 Small intestinal dysmotility, Q43.82 Generalised intestinal dysmotility<br>Q44.4 Choledochal cyst<br>Q45.83 Congenital mesenteric cyst | NA | NO |

| Anomaly type | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Reproductive system anomalies | Q50-Q56 Congenital malformations of genital organs | CLINICAL SIGNIFICANCE<br>Q55.6 Other congenital malformations of penis | EXCLUDE IN ISOLATION<br>Q50.1* Developmental ovarian cyst, Q50.2 Congenital torsion of ovary, Q50.5 Embryonic cyst of broad ligament, Q52.3 Imperforate hymen, Q52.4 (part) Congenital hypertrophy of hymen, Q52.5 Fusion of labia<br>Q52.7 (part) Minor other congenital malformations of vulva<br>Q54.4 Congenital chordee<br>Q55.20 Retractile testis, Q55.21 Bifid scrotum<br><br>EXCLUDE always<br>Q53* Undescended testicle | Q52.7 (part) Congenital rectovulval fistula - EUROCAT exclusion in isolation but NCARDRS includes | NO |
| Congenital anomalies of the kidney and urinary tract | Q60-Q64 Congenital malformations of the urinary system | MEASUREMENT / SEVERITY<br>Q62.0 Congenital hydronephrosis<br><br>CLINICAL SIGNIFICANCE<br>Q63.8 Other specified congenital malformations of kidney | EXCLUDE IN ISOLATION<br>Q61.0 Congenital single renal cyst<br>Q62.7* Congenital vesico-uretero-renal reflux<br>Q63.3 Hyperplastic and giant kidney | NA | YES<br>Q60.1 Bilateral renal agenesis |

| Anomaly type | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Congenital deformities of the musculoskeletal system | Q65-Q68 Congenital musculoskeletal deformities | PERSISTENCE<br>Q65.80 & Q65.81 Dysplastic hip<br><br>CAUSE<br>Q68.8 (part) Arthrogryposis, not otherwise specified | EXCLUDE IN ISOLATION<br>Q65.3-Q65.5 Congenital subluxation of hip, Q65.6* Unstable hip<br>Q66.1-Q66.9 Congenital deformities of feet (except include talipes equinovarus)<br>Q67* Congenital musculoskeletal deformities of head, face, spine and chest<br>Q68.0 Congenital deformity of sternocleidomastoid muscle, Q68.10 Clinodactyly, Q68.21 Genu recurvatum, Q68.3-Q68.5 Congenital bowing of femur, tibia and fibula | Q65.80 & Q65.81 Dysplastic hip - EUROCAT exclusion in isolation but NCARDRS includes | NO |
| Congenital malformations of the limbs | Q69-Q74 Congenital malformations of limb(s) | CLINICAL SIGNIFICANCE<br>Q70.2 Fused toes<br>Q703 Webbed toes, Q70.9 Syndactyly, unspecified<br>Q74.2 Other congenital malformations of lower limb(s), including pelvic girdle<br>Q74.82 Congenital undergrowth of limb(s) | EXCLUDE IN ISOLATION<br>Q74.0 (part) Congenital cubitus valgus, Q74.00 Accessory carpal bone | NA | NO |

| Anomaly type | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Congenital malformations of other parts of the musculoskeletal system | Q75-Q79 Other congenital malformations of musculoskeletal system | CAUSE<br>Q75.02 Trigonocephaly<br><br>CLINICAL SIGNIFICANCE<br>Q75.8* Other specified congenital malformations of skull and face bones<br>Q76.4 Other congenital malformations of spine, not associated with scoliosis<br><br>GESTATIONAL AGE AT DIAGNOSIS<br>Q79.5 (part) Congenital abdominal wall defect not otherwise specified<br><br>CONSEQUENCE<br>Q79.80 Congenital constriction bands | EXCLUDE IN ISOLATION<br>Q75.00 (part) Brachycephaly, Q75.2 Hypertelorism, Q75.3* Macrocephaly<br>Q76.0 Spina bifida occulta, Q76.43 Congenital lordosis, postural, Q76.5 Cervical rib, Q76.60 Congenital absence of rib, Q76.62 Accessory rib, Q76.71 Sternum bifidum<br>Q79.5 (part) - Congenital divarication of recti | NA | YES<br>Q77*/Q78* (part) Lethal and severe skeletal dysplasias e.g. Thanatophoric dysplasia, Short rib-polydactyly syndrome<br>Q79.0* Congenital diaphragmatic hernia<br>Q79.2 Exomphalos<br>Q79.3 Gastroschisis |

| Anomaly type | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Integument anomalies | Q80-Q84 Congenital malformations of integument | NA | EXCLUDE IN ISOLATION Q82.5* Congenital non-neoplastic naevus, Q82.8 (part) Dermatoglyphic anomalies, Q82.80 Abnormal palmar creases, Q82.81 Accessory skin tagsQ83.3 Accessory nippleQ84.2 (part) Persistent lanugo, Q84.5 (part) Enlarged or hypertrophic nails, Q84.6 Other congenital malformations of nails | NA | NO |
| Phakomatoses, not elsewhere classified | Q85 Phakomatoses, not elsewhere classified | NA | NA | NA | NO |

| Anomaly type | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Teratogenic syndromes | Q86* Congenital malformation syndromes due to known exogenous causes, not elsewhere classified | MATERNAL HISTORY & CONSEQUENCE<br>Q86.0 Fetal alcohol syndrome<br><br>KNOWN AETEOLOGY & CONSEQUENCE<br>Q86.1-Q86.8* Fetal hydantoin syndrome, Fetal warfarin syndrome, Other congenital malformation syndromes due to known exogenous causes | NA | NA | NO |
| Other congenital malformation syndromes | Q87* Other specified congenital malformation syndromes (multiple systems) | NA | EXCLUDE IN ISOLATION<br>Q87.4 (part) Arachnodactyly not otherwise specified | NA | NO |
| Other anomalies | Q89* Other congenital malformations, not elsewhere classified | NA | EXCLUDE IN ISOLATION<br>Q89.9 Congenital malformation, unspecified | NA | NO |

| Anomaly type | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Chromosomal | Q90-Q99 Chromosomal | IF REGISTRABLE ANOMALY Q95* Balanced rearrangements and structural markers, not elsewhere classified | EXCLUDE always Q95.0 Balanced translocation and insertion in normal individual, Q95.1 Chromosome inversion in normal individual, Q95.4 Individuals with marker heterochromatin, Q95.5 Individuals with autosomal fragile site | NA | YES Q90* Down's syndrome Q91* Edwards' syndrome and Patau's syndrome |
| Congenital neoplasms | D15.1 Cardiac rhabdomyoma D18.10 Cystic hygroma (congenital) D21.5 Sacrococcygeal teratoma, Sacral teratoma D21.9 Rhabdomyoma of other organs [i.e. not heart] D48.7 Teratoma, not elsewhere classified | CLINICAL SIGNIFICANCE D18.0 Haemangioma, any site, D18.1 Lymphangioma, any site | NA | EUROCAT exclusion but NCARDRS includes D15.1 Cardiac rhabdomyoma, D18.0 Haemangioma, any site, D18.1 Lymphangioma, any site, D21.9 Rhabdomyoma of other organs [i.e. not heart], D48.7 Teratoma, not elsewhere classified | NO |
| Di George syndrome | D82.1 Di George syndrome | NA | NA | NA | NO |

| Anomaly type | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Waardenburg syndrome | E70.30 Waardenburg syndrome | NA | NA | NA | NO |
| Cystic fibrosis | E84* Cystic fibrosis | NA | NA | EUROCAT exclusion but NCARDRS includes | NO |
| Spinal muscular atrophy | G12* Spinal muscular atrophy and related syndromes | NA | NA | EUROCAT exclusion but NCARDRS includes | NO |
| Congenital chylothorax | NA | NA | EXCLUDE IN ISOLATION<br>I89.8 Chylothorax (lymphatic);<br>J94.0 Chylothorax (chylous) | NA | NO |
| Paralysis of vocal cords and larynx | NA | NA | EXCLUDE IN ISOLATION<br>J38.0 Paralysis of vocal cords and larynx | NA | NO |
| Micrognathia | | SEVERITY<br>K07.0 Micrognathia | NA | NA | NO |
| Placental transfusion syndromes | P02.3 Fetus and newborn affected by placental transfusion syndromes | INCLUDE IN ISOLATION<br>P02.3 (part) Twin reversed arterial perfusion sequence<br><br>IF REGISTRABLE ANOMALY<br>P02.3 (part) Twin-to-twin transfusion syndrome | NA | NA | NO |

| Anomaly type | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Congenital infections | P35.8 Congenital zika virus infection | IF REGISTRABLE ANOMALY<br>P35.0 Congenital rubella syndrome, P35.1 Congenital cytomegalovirus infection, P37.1 Congenital toxoplasmosis | NA | NA | NO |
| Hydrops fetalis | P83.2 Hydrops fetalis not due to haemolytic disease | NA | EXCLUDE always<br>P56* Hydrops fetalis due to haemolytic disease | EUROCAT exclusion but NCARDRS includes | NO |
| Congenital hypotonia | NA | NA | EXCLUDE always<br>P94.2 Congenital hypotonia | NA | NO |

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# COHORT PROFILE : THE NATIONAL CONGENITAL ANOMALY REGISTRATION DATASET IN ENGLAND



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|---|---|
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# COHORT PROFILE : THE NATIONAL CONGENITAL ANOMALY REGISTRATION DATASET IN ENGLAND

Jennifer M Broughan, Ben Wreyford, Danielle Martin, Gabriella Melis, Kay Randall, Ewoma Obaro, John Broggio, Nicholas Aldridge , Sylvia Stoianova, Chloe Johnson, Donna Gibbard, Sarah Stevens & Kate Fleming

National Congenital Anomaly and Rare Disease Registration Service, National Disease Registration Service, Data and Analytics Directorate, NHS England, 7 Wellington Pl, Whitehall Rd, Leeds LS1 4EG, UK.

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Jennifer M Broughan, Jennifer.Broughan@nhs.net
Ben Wreyford, ben.wreyford@nhs.net
Danielle Martin, Danielle.Martin17@nhs.net
Gabriella Melis, Gabriella.Melis1@nhs.net
Kay Randall, kay.randall@nhs.net
Ewoma Obaro, ewoma.obaro@nhs.net
John Broggio, john.broggio@nhs.net
Nicholas Aldridge, nicholas.aldridge@nhs.net
Sylvia Stoianova, Sylvia.Stoianova@bristol.ac.uk
Chloe Johnson, Chloe.Johnson6@dhsc.gov.uk
Donna Gibbard, donna.gibbard@nhs.net
Sarah Stevens, sarah.stevens1@nhs.net
Kate M Fleming, kate.fleming5@nhs.net

Correspondence to:
Jennifer Broughan, PhD
National Disease Registration Service
NHS England
7 and 8 Wellington Pl,

Whitehall Rd,

Leeds

LS1 4EG,

UK.

Jennifer.Broughan@nhs.net

Tel +44 7769282928

ORCID 0000-0002-4450-2147

# ABSTRACT

## Purpose

The National Congenital Anomaly and Rare Disease Registration Service (NCARDRS), part of National Disease Registration Service (NDRS) in NHS England, quality assures, curates and analyses individual data on the pregnancies, fetuses, babies, children and adults with congenital anomalies and rare diseases across England. The congenital anomaly (CA) register provides a resource for patients and their families, clinicians, researchers, and public health professionals in furthering the understanding of CAs.

## Participants

NCARDRS registers CAs occurring in babies born alive and stillborn, fetal losses and terminations in England. NCARDRS collects data from secondary and tertiary health care providers, private providers and laboratories covering fetal medicine, maternity or paediatric services. Data describe the pregnancy, mother, baby, and anomaly. Established in 2015, NCARDRS expanded CA registration coverage from 22% of total births in England in 2015 until national coverage was achieved in 2018. Prior to 2015, data collection was performed independently by regional registers in England; this data is also held by NCARDRS.

## Findings to date:

NCARDRS registers approximately 21,000 babies with CAs per year with surveillance covering 600,000 total births, making it the register with the largest birth coverage globally. Data on prevalence, risk factors and survival for children with CAs are available. Data has been used in several peer-reviewed publications. Birth prevalence statistics, including public health indicators such as the association with maternal age, infant and perinatal mortality, are published annually. NCARDRS supports clinical audit for screening programmes and service evaluation.

## Future plans:

NCARDRS provides a valuable resource for the understanding of the epidemiology, surveillance, prevention and treatment of CAs. Currently, approximately 21,000 new registrations of babies or fetuses with suspected or confirmed CAs are added each year. Identifiers are collected, enabling linkage to routinely-collected healthcare and population statistics, further enhancing the value of the data.

## Key words

Epidemiology, Public Health, Registries, neonatology, paediatrics

## Strengths and limitations

- NCARDRS is one of the largest congenital anomaly registers in the world. Since 2018, coverage of congenital anomalies has been national across England (approximately 21,000 anomalies registered from 600,000 total births per year). This enables the calculation of accurate estimates of prevalence even for rare congenital anomalies. Legacy congenital anomaly registration data is held for some regions for births since 1985.
- NCARDRS collects personal identifiers and data are linked to other routinely collected administrative and health care data, allowing assessment of long-term outcome and survival over the life course of the baby, as well as associations with health inequalities and other risk factors.
- Information in NCARDRS can be linked to other national data sources, allowing the exploration of societal factors such as equity of access to treatment and clinical outcomes.
- NCARDRS provides data on all birth outcomes, including live births, stillbirths, fetal losses and terminations.

- Case-ascertainment is high for severe conditions, or those that are more frequently diagnosed antenatally or in the neonatal period. Registration and case ascertainment in NCARDRS regions that initiated congenital anomaly registration from 2018 continues to develop and is progressing well.

# INTRODUCTION

Congenital anomalies are a significant source of morbidity, mortality and long-term care needs in children. Approximately 2-3% of children born in Europe have a congenital anomaly(1) which are defined as conditions present at birth and include structural, chromosomal, genetic and biochemical conditions. Some congenital anomalies are detected during pregnancy, some are found at birth, while others are diagnosed only as a baby grows older. In England and Wales, congenital anomalies were the most common cause of death in the post neonatal period in 2020, accounting for 36.3% of deaths(2). Globally it is estimated that 240,000 new-borns die within the neonatal period as a result of congenital anomalies(3).

Registration of congenital anomalies became established in many countries from the 1960s and 70s as a consequence of the thalidomide tragedy and serves multiple purposes supporting epidemiology and public health(4). The National Congenital Anomaly and Rare Disease Registration Service (NCARDRS) is part of the National Disease Registration Service (NDRS) of NHS England which collects, quality assures and analyses data on all people living in England with cancer(5), congenital anomalies and rare diseases. NCARDRS curates a population-based congenital anomaly registry, collecting data on the pregnancies, fetuses, babies, children and adults with congenital anomalies across the whole of England. Data is collected to further the understanding of the causes of congenital anomalies, to inform the commission of public services, to audit health and social care and to provide information for patients, their carers and clinicians on their condition. To achieve this NCARDRS collects data

from heath care settings across England. In England, health care is publicly funded and delivered in a centralised and universal way by the National Health Service (NHS).

The UK Rare Disease Strategy, developed in 2013, aimed to improve the lives of those with rare diseases, focusing on patient empowerment, identification and prevention, diagnosis and treatment and the role of research and recommended the expansion of existing data collections(6, 7). Established in 2015 in response, NCARDRS assumed responsibility for congenital anomaly registration in regions with an existing register and expanded geographically to provide congenital anomaly registration across the whole country(8) (Figure 1). Prior to 2015, data collection was performed independently by regional registers operating across some areas of England, covering up to 32% of births. NCARDRS continues to host the regional registers' legacy registration data. A national congenital anomaly surveillance system was attempted by the UK Office of National Statistics (ONS) but this was closed in 2010 following concerns about data quality and completeness(9). NCARDRS national coverage for registration and reporting has been in place for babies born since 2018(10).

# COHORT DESCRIPTION

## Study population

NCARDRS registers congenital anomalies that occur in babies that are live born and stillborn, fetal losses and terminations at any gestation delivered in England. NCARDRS does not have a minimum gestation for fetal loss and registers all fetal losses reported, although in line with international standards(11) only anomalies that occur in live births, stillbirths, terminations at any gestation and fetal losses between 20-24 completed weeks of gestation are included in

prevalence reporting(12, 13). There are approximately 600,000 live births and stillbirths in England every year. There is no upper age limit and information can be added for children as they grow older Information on survival and vital status is updated at least annually.

Inclusion and exclusion criteria for registration of congenital anomalies in NCARDRS follow internationally recognised formats(11) and all registrations are coded to international standards. Anomalies are clinically coded to international standards using the World Health Organisation's International Classification of Diseases 10th revision (ICD-10)(14) with the British Paediatric Association (BPA) Adaptation, which gives supplementary one-digit extensions to ICD-10 codes to allow greater specificity of coding(11). Inclusion criteria are based on international guidance(11) predominantly covering the Q chapter in ICD-10. A detailed summary of the current inclusion and exclusion criteria is presented in Table S1 in the supplementary materials. NCARDRS excludes cases with an isolated minor anomaly as specified by the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT)(11). However, if minor anomalies occur in association with other anomalies, then these are registered.

Denominator data is obtained from the UK Office for National Statistics (ONS). Individual level birth data are available and are aggregated according to requirements.

## Registration model and source data

NCARDRS employs a multisource, event-based registration model. Over the life course of a patient, NCARDRS can be notified antenatally, at birth or in the neonatal period and beyond as the child is treated by various paediatric specialist services. Registration data are processed, held on a custom-built live data management application, and regularly cloned to a separate PostgreSQL database which creates regular snapshots of data for analysis, reporting and data release (Figure 2).

The data collected by NCARDRS come from a range of sources including maternity units, multidisciplinary team meetings, postmortem reports, molecular testing results, treatment records, hospital patient administration systems, clinical data systems, national data sets describing hospital activity, clinical biochemistry and genetics laboratories. Hospital trusts, including all trusts with a maternity or paediatric service, submit data which are processed and combined by trained registration officers into a comprehensive clinical record of each baby and anomaly.

Data can be submitted at the individual case-level or in large data extracts from clinical management data systems. Custom-built extracts from neonatal clinical data management systems (BadgerNet), including remote access to the record itself, are available for 94% of the trusts with a neonatal unit in England. Extracts of relevant data from fetal medicine software systems including fetal medicine (Viewpoint; Astraia) and specific services (HeartSuite) have been developed in conjunction with software suppliers; these extracts are produced and submitted to NCARDRS by the provider.

Information from providers is combined with routinely collected national data utilised for both data quality and case-ascertainment purposes. Linkage is conducted through NHS number or through date of birth, full name and address. Cases with defined ICD-10 codes that have been validated for accuracy are identified from Hospital Episode Statistics (HES) for ascertainment purposes. HES consists of routinely recorded, administrative data describing each hospital admission in the NHS(15). As well as demographic information on the patient, the primary reason for admission and any co-morbidities are recorded using ICD-10 codes. Death certificate data from the Office for National Statistics (ONS) is provided to NCARDRS monthly for children born alive after 1st January 2018 and where a relevant ICD-10 coded condition (within a specified range) is listed as a cause of death. Information about babies that were born alive or stillborn after 24 weeks gestation (civilly registrable in England) is supplemented using birth registration information supplied by the ONS. Survival for all patients recorded is updated at least annually by linkage with the NHS Personal Demographics Service

(PDS) on NHS Spine, a collection of national databases that holds electronic records of important patient information and demographics.

## Data processing

Once received, identifiable patient data are processed by trained registration officers. Processing involves manual extraction of clinical information from clinical reports and letters or free text comments in clinical software systems. Registration officers require detailed knowledge of congenital anomalies, clinical coding and clinical pathways for the range of different conditions collected. As NCARDRS is a multisource register, patient identifiers are required to ensure that there is no duplication, and that incoming data is linked to the correct baby and pregnancy. Where cases are entered manually, patient identifiers are checked manually using the Summary Care Record on NHS Spine. Further information is requested from the relevant clinician or obtained by direct, manual interrogation of patient records by registration officers via secure remote access to a hospital's clinical software systems or clinical documents where this is available.

Data are input onto the data management system in two ways: 1) data on individual patients submitted by providers are assessed by trained registration officers and manually entered or 2) data from electronic sources are loaded via a semi-automatic process known as the data waterfall (Figure 2). The data waterfall is a process which loads data from electronic sources. Its purpose is to perform basic validations on the data, confirm the patient's demographic information (via NHS Spine), match the patient to an existing patient (or create a new patient record) and create records, such as a screening or diagnostic test event which can be processed by registry staff. Most cases consist of information processed by both manual and automatic methods.

Anomalies are registered according to varying degrees of certainty depending on the clinical evidence available; confirmed, probable or suspected. Anomalies remain at the level of suspected until the evidence supporting the diagnosis of the anomaly attains agreed confirmation criteria. These criteria have been established with clinical input and consider the method by which the diagnosis is made, the specialism and confidence of the reporting clinician, the gestational or postnatal age at which the anomaly was identified, and the reliability of data sources. Criteria are different for each type of anomaly and a baby can have multiple anomalies, each with different statuses, depending on the level of evidence available for each one. Not all anomalies can be confirmed by the gold standard diagnostic test. Where there is a confident diagnosis by a relevant specialist in the field and the evidence is well described a probable confirmation status is used. Only data on probable and confirmed cases are used for routine reporting and analysis purposes and both are considered reportable.

## Data structure

Registration is framed at the level of the anomaly, baby, pregnancy and birth mother. The data are organised into over 600 raw tables which are in turn further organised into a series of approximately 100 custom-built analytical views, tables and lookup tables reflecting five main thematic groups, mother, pregnancy, baby, anomaly and test, with one-to-many relationships across all. Each table contains a primary key that uniquely identifies records within that table and allows joins between tables. A baby and a mother are each assigned a unique identifier. Registration records are never closed and new events can be added if new information is submitted.

## Key data fields

Detailed clinical and demographic information on the mother, baby, anomaly and pregnancy is recorded (Table 1). Multiple anomalies can be registered against a baby, each with different evidence and confirmation status.

NCARDRS works closely with the NHS Fetal Anomaly Screening Programme (FASP) to audit the detection of 15 conditions groups and these conditions are subject to enhanced registration. To facilitate this audit, more extensive information on antenatal screening and the nature and timing of diagnostic testing is collected for these conditions and other closely related or similar conditions. The conditions that are covered by this enhanced registration include severe cardiac anomalies, trisomy 13, trisomy 18 and trisomy 21, neural tube defects, lethal skeletal dysplasia, cleft lip+/palate, bilateral renal agenesis, abdominal wall anomalies and congenital diaphragmatic hernia (see Table S1 in the supplementary materials). These 15 condition groups reflected 35% (n=4501) of the 13,065 babies registered with a confirmed or probable congenital anomaly in 2020.

## Data Quality

Automatic and manual quality checks are embedded into the registration process at points of entry, at the level of the individual record and on the birth cohort as a whole prior to finalisation of the data for reporting. As well as internal data quality indicators (DQIs), the data are evaluated against DQIs for international bodies against known targets(16). For example, the prevalence of anencephaly is reported as an indicator of ascertainment of conditions detected at earlier gestations. Other DQIs focus on the accuracy of diagnosis, for example the number of babies with more than one anomaly, or the prevalence of selected codes that have used the BPA extension code in addition to the ICD-10 code.

## Patient and public involvement

Patient groups and third sector organisations representing patients were involved in the design of this register-based cohort and were members of an expert committee of stake holders made up of academics, clinicians, third sector organisation and patient interest groups that oversaw the formation of NCARDRS.

## Ethical approval and governance arrangements

NCARDRS has legal permission to collect patient-level data on those with a confirmed or suspected congenital anomaly or rare disease for specified purposes, without consent, to use it to protect the health of the population. Data are collected under legal instructions known as Directions, from the Secretary of State for Health and Social Care, made in accordance with section 254 of the Health and Social Care Act 2012 (2012 Act)(17). Strict technical and contractual controls are put in place to prevent unauthorized access and use of the data, with staff undergoing regular training on data protection and information governance.

## FINDINGS TO DATE

As of June 2023, NCARDRS held information on 117,682 mothers and 121,184 babies born in England since 2015. Table 2 shows the number of babies and other characteristics registered in regions with full congenital anomaly registration coverage by year of birth.

NCARDRS currently collects data on more than 1,000 different congenital anomalies, many of which are rare diseases, and provides expert analysis and interpretation of the data across a wide range of national and international functions. The data are available as a source of

intelligence for clinicians, public health, health-care performance, basic and applied research, patient groups, academics and commissioning and industry partners. A summary of the data is published each year describing congenital anomalies in England in the context of prevalence reported by anomaly group, timing of diagnosis and important public health indicators such as maternal age and infant mortality(10, 13, 18-21). In 2020, NCARDRS reported a total of 13,065 babies with one or more confirmed or probable congenital anomalies in 589,454 total births (live births and stillbirths), giving an overall birth prevalence of 221.7 per 10,000 total births (95% confidence intervals (CI) 217.9 - 225.5) or 1 for every 45 births(13). The rate of perinatal mortality associated with a congenital anomaly was highest for genetic disorders (3.1 per 10,000 total births, 95% CI 2.7-3.6), followed by congenital heart anomalies (2.8 per 10,000 total births, 95% CI 2.4-3.2). Infant mortality rate was highest for congenital heart anomalies (4.9 per 10,000 live births, 95% CI 4.4-5.5), followed by genetic conditions (3.0 per 10,000 live births, 95% CI 2.6-3.5). The rate of genetic conditions in babies born to women over 40 years old was almost 7 times higher relative to babies born to mothers under 20 years old (risk ratio equal to 6.9, 95% CI 5.2-9.2).

Congenital anomaly registration data for England is submitted to international bodies to allowing pooling of data across a wider geographical area to support analysis into causes of these rare conditions and how to prevent them. Data is submitted annually to EUROCAT and to the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR). Surveillance is performed annually using internationally recognised tools to identify potential clusters of anomalies and changes in trends(22).

NCARDRS works closely with NHS Screening Programmes delivering service evaluation for antenatal and new-born screening services. NCARDRS audits the detection of the conditions included in the Fetal Anomaly Screening Programme (FASP) (see Table S1 in the supplementary materials) and, to enable this, these conditions are subject to enhanced registration and active ascertainment. By linking information at patient level, NCARDRS creates a longitudinal record of the screening and diagnostic pathway for each mother, fetus,

or baby, enabling analysis of the efficacy of the tests, the behavioural choices on the pathway, and the operational standards of the service. NCARDRS have recently published the first national study of fetal anomaly ultrasound scan detection rates in England (23). The data is used to provide reliable information about the quality of screening services at local, regional and national level and contributes towards the safety and effectiveness of screening services. Each screening provider receives a report detailing hospital-level detection rates and also individual case-level detection status to allow further clinical audit and identify training requirements. NCARDRS is supporting the NHS evaluative roll-out of non-invasive prenatal testing (NIPT) for Edwards' syndrome, Patau's syndrome, and Down's syndrome in England(24). Routine laboratory surveillance is conducted on a monthly, quarterly and annual level, and test performance will be evaluated by linking laboratory and registration data.

At the start of the COVID-19 pandemic, NCARDRS informed the production of the Shielded Patient List (SPL)(25) by identifying individuals living with congenital anomalies and selected rare diseases that may have been at increased risk from COVID-19 infection and NCARDRS will support the continued evaluation of vaccines against COVID-19 in pregnancy(26).

Many publications use datasets that predate NCARDRS including the legacy regional registers. NCARDRS data has been used to examine the epidemiology of congenital anomalies across Europe including Dandy-Walker syndrome(27), VACTERL association (28, 29) , neural tube defects (30), aplasia cutis(31) achondroplasia(32) and vascular disruption anomalies(33). Studies aim to improve outcomes of babies with a congenital anomaly and to inform policy so that some may be prevented, for example to justify the fortification of flour with folic acid. Recently, the UK government announced plans for the fortification of flour with folic acid to reduce neural tube defects(34). NCARDRS will support the evaluation and monitoring of the impact of implementation of this policy(35).

## STRENGTHS AND LIMITATIONS:

## National Coverage

The key strength of the NCARDRS data set is its national coverage across a large birth population. NCARDRS is the largest register in Europe(36) in both size of population and representativeness. With complete population coverage of pregnancies from 2018 onwards, the data are representative and comprehensive, capitalising on the centralised nature of English health care. Registration records are never closed, and data can continue to passively accumulate, enriching each record and facilitating the potential identification of future syndromes or providing more information on the phenotypic manifestations of genetic differences identified later in life.

## Multisource ascertainment

An NCARDRS congenital anomaly record can be made up of multiple difference sources, some automatically added and manually verified. Clinical information, often obtained by the treating clinician, is combined with cytogenetic laboratory data, data from routinely collected hospital activity and national statistics, and extracts from clinical systems to make a cohesive and comprehensive record detailing the phenotype. A registration record is never closed, allowing for the possibility of adding further genomic data as it becomes available with the wider use of whole genome sequencing.

## Standardised disease coding and data entry

The development of NCARDRS has demonstrated that it is possible to conduct national registration on a large population using standardised approaches to data collection and management, disease coding, data classification, analysis and reporting. Data are coded consistently across the country and regions can be compared, allowing the identification of

clusters and geographical disparities which may be a result of population demographics, social determinants of health or local exposure.

## Ascertainment

National prevalence in England for 2018-2020 is consistent with European surveillance data for the same time period (excluding data for England) across most major congenital anomaly groups (Figure 3). The prevalence of severe anomalies, such as severe congenital heart, abdominal wall, oro-facial cleft, respiratory and genetic conditions was higher than the European average. These anomaly subgroups include FASP-conditions and so are subject to enhanced registration. Their higher prevalence reflects the integration of clinical audit in NCARDRS and demonstrates the impact of clinical engagement on data quality and ascertainment. The England national prevalence estimates for all cardiac conditions, limb anomalies and congenital anomalies of the kidney and urinary tract (CAKUT) conditions are lower than the average for other European registers. This likely reflects some under-ascertainment of anomalies that are predominantly confirmed postnatally in regions of NCARDRS new to reporting(10).

Within England, there is some variation in the prevalence of different anomaly groups depending on the length of time registration has been established, reflecting developing ascertainment in regions new to congenital anomaly registration particularly for anomalies that are more frequently identified postnatally or for those anomalies that are less severe(10, 21). As registration becomes embedded and ascertainment increases, differences in prevalence because of data collection should dissipate, revealing true regional differences, if they exist.

## Risk factor information

Information on the demographics of the mother is collected for each pregnancy and include ethnicity, Body Mass Index, illnesses or medications, folic acid intake and other lifestyle factors

such as smoking. This information can be supplemented using data linkage to examine other factors, including social deprivation measured at the area-level through deprivation scores for mother's residential address at delivery,

### Timeliness of data collection

Babies with a congenital anomaly are first registered by NCARDRS approximately 12 months after their expected date of delivery. This time lag allows for the notification of outcome of the pregnancy and a confirmatory diagnosis after delivery along with the notification of other relevant postnatal information and follow-up if required. Finalised delivery year cohorts are available approximately 18 months to two years following the end of a delivery year e.g., babies delivered in 2021 would be reported on in early 2024. Recent advances in the automated processing of defined data feeds (e.g. fetal medicine software system extracts) aim to improve the timeliness of data by reducing the time lag.

## FUTURE WORK

Planned improvements to the timeliness of data reporting and continued improvement to developing ascertainment for new regions and completeness of fields will further improve data quality. Proximity to the more established cancer registration service allows the register to build on synergies in data management, analytical infrastructure and data liaison.

As the service matures, new data sources will be added to improve data quality or ascertainment. Transition to NHS England has situated NCARDRS closer to clinical providers and commissioning services which should improve data access and facilitate linkage to a wider network of data. Linkage with the Maternity Services Dataset, a routinely-collected national dataset describing maternity care in England(37), is underway and this aims to improve the completion of risk factor data items such as smoking, alcohol use as well as providing access to further information about the pregnancy. The inclusion of primary care

data would be an obvious improvement to the ascertainment of postnatally-diagnosed conditions as would clinical audit data such as paediatric intensive care (PICANET), cardiac surgery (NICOR), maternal and neonatal deaths (MBRACE) and NHS England commissioned Highly Specialised Services data.

Linkage to other datasets provides vital information on survival and health outcomes for these children throughout their life course. Cancer registration data collected by NDRS has been linked to the community prescriptions dataset(38) and linkage with the congenital anomaly registration data is in progress. This could provide information on possible drug interactions and potential teratogens. Linkage to other disease registers, subject to adequate consenting materials and approvals, is possible and could provide valuable information on health outcomes for children with congenital anomalies. NCARDRS currently contains data that only relates to the health outcomes of the child and further work should also include linkage to social and educational data.

## CONCLUSIONS

If the thalidomide scandal of the 1960s prompted the establishment of congenital anomaly registration to understand the causes of congenital anomalies, the COVID-19 pandemic amplified the need to be able to identify and protect individuals living with conditions that may put them at increased risk compared to the general population. NCARDRS' congenital anomaly register collates information across the full patient pathway as the pregnancy progresses and the child grows. The value of this dataset in supporting clinical audits and evaluating service delivery is proven. This population-based national register – currently the largest data collection of its kind globally – has a critical role in supporting the epidemiology and monitoring of disease trends, investigating the causes of these conditions, evaluating the

outcome and providing this crucial information to parents, patients and clinicians and to clinical and service commissioners so these children have what they need as they grow.

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**Details of contributions**

JMB led the drafting of the manuscript with advice from KMF, JB and SS as to the concept, structure and content. Additional sections were drafted by BW, DG, CJ, SyS, NA and KR. BW drafted the supplementary table (Table S1). KR, CJ, BW, DG, SyS provided advice on registration and/or data management system practice. Data analysis was performed by JMB, DM, GM and EO. All authors reviewed and commented on the manuscript and gave approval for publication.

**Competing interests statement**

No conflicts of interest have been declared.

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## Data availability statement

Permission to access congenital anomaly registration data can be granted to individuals who demonstrate that either there is a justified purpose for the data release, that there is an appropriate legal basis with safeguards in place to protect the data, or the data release is deemed to be anonymous (e.g. aggregate data). The access process for NDRS data is managed by Data Access Request Service (DARS) (https://digital.nhs.uk/services/data-access-request-service-dars) in NHS England. Full details, including data dictionaries, are available. Further details on the process of data access and associated costs are available on the DARS website [https://digital.nhs.uk/services/data-access-request-service-dars]. Data can also be made available by working in partnership with National Disease Registration Service and enquiries can be directed to ndrs.enquiries@nhs.net.

## Collaboration statement

NDRS supports collaborations with academic and other institutions to use the data for a justified purpose. Enquiries, requests for statistical code used and anonymised data should be directed to ndrs.enquiries@nhs.net.



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Figure 1 The regional structure of NCARDRS and the proportion of the birth population of England that was covered by congenital anomaly registration.

Figure 2 : Schematic describing the multisource registration process used for congenital anomalies in England.

Figure 3 The prevalence of anomaly groups in England compared to EUROCAT registers excluding English registers (2018-2020) [data downloaded 24th April 2023 from EUROCAT, 1st August 2022 NCARDRS]

Table 1: Summary of key data items currently available for each congenital anomaly registration in the NCARDRS congenital anomaly dataset. Data are available for all years.

| **Mother** | **Pregnancy** | **Baby** | **Anomaly** | **Test**[1] [3] |
|---|---|---|---|---|
| Patient identifier | Pregnancy identifier | Patient identifier | Anomaly identifier | Test date |
| NHS number | Expected Delivery Date | NHS number | Confirmation Status of anomaly[2] | Test type |
| Date of birth | Pregnancy outcome | Sex | ICD 10 & BPA extension code | Test result(s) |
| Ethnicity | Delivery information | Date of birth | Description of the anomaly | Test provider |
| Country of birth | Screening details [3] | Gestational length at delivery | Gestation first suspected | Test requestor |
| Vital status | Body Mass Index | Birth weight (g) | Gestation at confirmation | Ultrasound markers |
| Previous births and pregnancies | Smoking status at booking, alcohol and substance use | Birth order if from a multiple pregnancy | Diagnostic method | Indication |
| | Maternal illness status | Method of delivery | Aetiology of the anomaly/ies | |
| | Folic acid intake | Surgical status | | |
| | Assisted conception status | Date of death | | |
| | Number of fetuses | Postmortem status | | |
| | Consanguinity | | | |
| | Deprivation (derived from postcode of residence at delivery) | | | |
| | Postcode at booking and at delivery | | | |

[1] Test information is only consistently registered for conditions with enhanced registration (ie those conditions within the FASP audit)

[2] Confirmation status: Anomalies are registered according to varying degrees of certainty depending on the clinical evidence available (*confirmed, probable or suspected)*. Anomalies remain at the level of *suspected* until the evidence supporting the diagnosis of the anomaly attains agreed confirmation criteria

[3] Some fields may require additional Research Ethics Committee or other approvals on request



Table 2 The number of pregnancies, babies and anomalies recorded registered since NCARDRS has been in operation until 2020 Data extracted 13th June 2023.

| | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 |
|---|---|---|---|---|---|---|
| Number of regions reporting | 4 | 7 | 7 | 10 | 10 | 10 |
| Number of pregnancies with babies with a congenital anomaly of any status | 2,915 | 9,524 | 9,882 | 20,036 | 19,636 | 18,440 |
| Number of babies with a congenital anomaly of any status | 2,932 | 9,574 | 9,937 | 20,145 | 19,767 | 18,541 |
| Number of mothers | 2,908 | 9,506 | 9,868 | 20,007 | 19,611 | 18,416 |
| Total number of anomalies | 5,902 | 18,839 | 18,803 | 35,483 | 34,500 | 33,344 |
| Total number of confirmed and probable anomalies | 5,432 | 15,819 | 15,316 | 28,282 | 25,988 | 25,617 |
| Number of live and still births in regions with active congenital anomaly registration (denominator) | 141,474 | 329,301 | 320,013 | 628,171 | 614,952 | 589,454 |

NOTE : the numbers may differ from published estimates at point of reporting because of continued accumulation of data

Birth population calculated using ONS row level birth information available via the UKHSA DataLake.

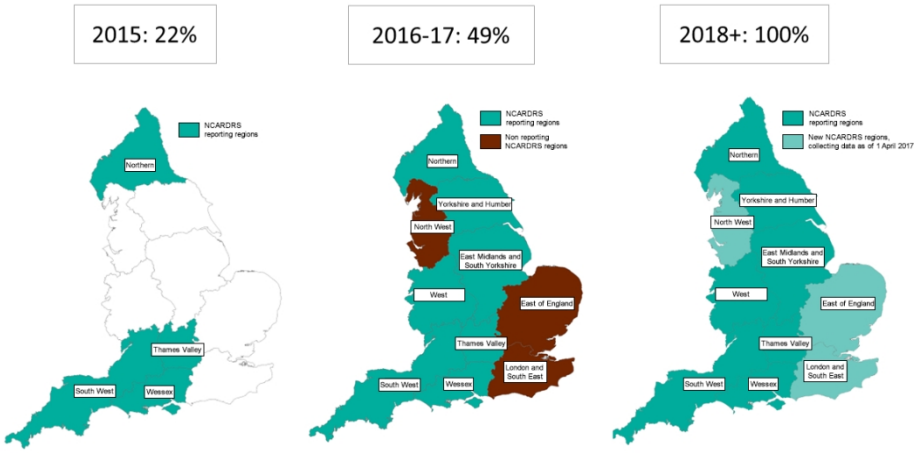


Figure 1 The regional structure of NCARDRS and the proportion of the birth population of England that was covered by congenital anomaly registration.

855x481mm (38 x 38 DPI)

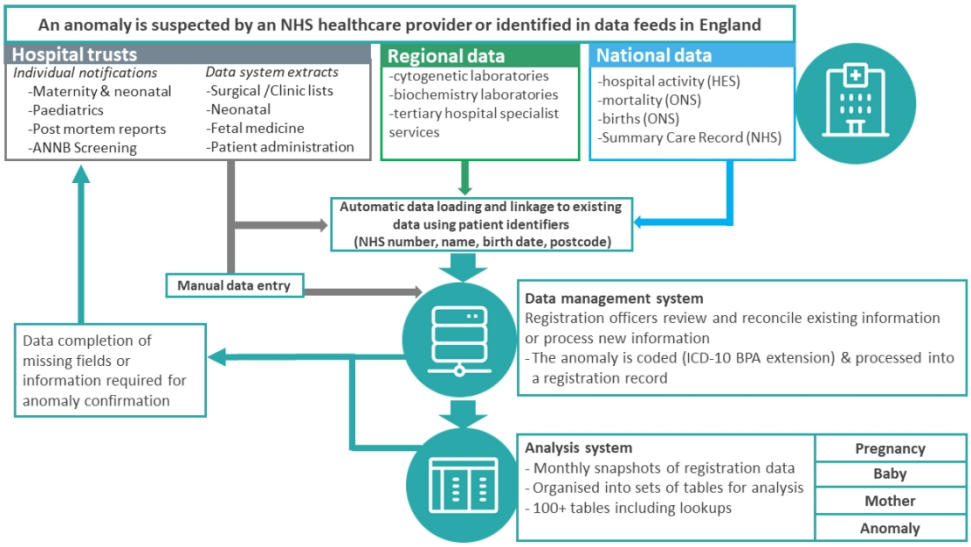


Figure 2 : Schematic describing the multisource registration process used for congenital anomalies in England.

855x481mm (38 x 38 DPI)

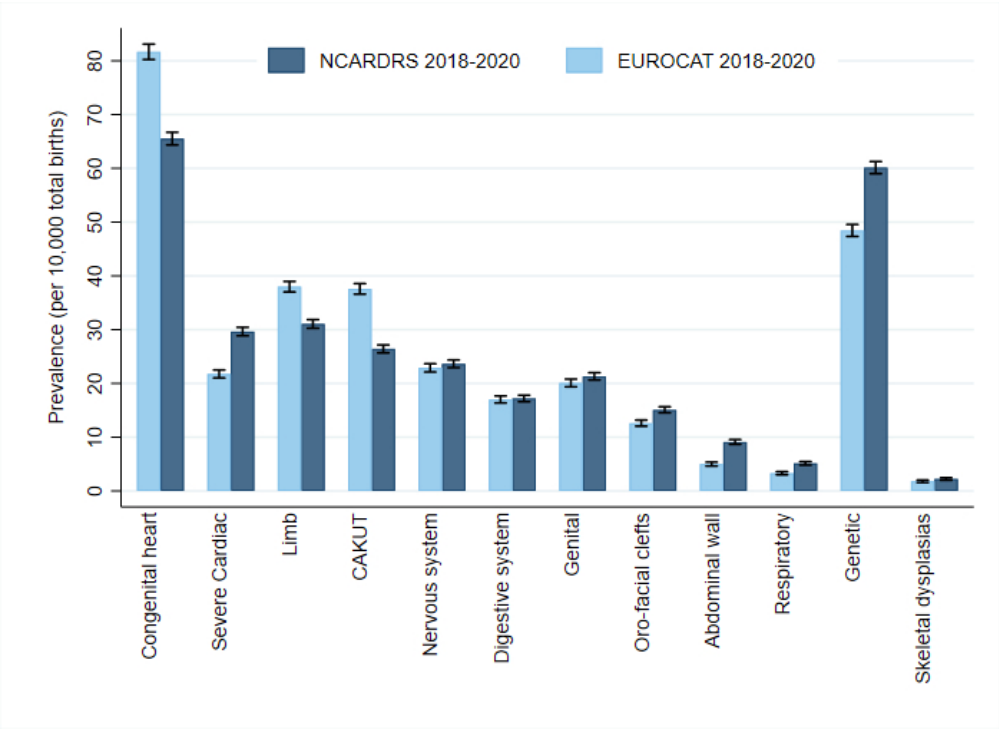


Figure 3 The prevalence of anomaly groups in England compared to EUROCAT registers excluding English registers (2018-2020) [data downloaded 24th April 2023 from EUROCAT, 1st August 2022 NCARDRS]

466x338mm (38 x 38 DPI)

**Table S1** **NCARDRS inclusion and exclusion criteria for registerable congenital anomalies**

| Anomaly type* | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Nervous system anomalies | Q00-Q07 Congenital malformations of the nervous system | MEASUREMENT / SEVERITY<br>Q02 Microcephaly<br>Q03.8 (part) Congenital ventriculomegaly [of lateral ventricle(s)]<br>Q04.32 Reduction anomalies of cerebellum<br><br>CLINICAL SIGNIFICANCE<br>Q04.61 (part) Arachnoid cyst | EXCLUDE IN ISOLATION<br>Q0780 Jaw-winking syndrome<br>Q0782 Crocodile tears<br><br>EXCLUDE always<br>Q04.6 (part) Porencephaly | Q04.6 (part) Porencephaly - EUROCAT inclusion but NCARDRS excludes<br><br>Q04.61 Single congenital cerebral cyst - EUROCAT exclusion in isolation but NCARDRS includes Arachnoid cyst | YES<br>Q00* Anencephaly and similar malformations<br>Q01* Encephalocele<br>Q05* Spina bifida |
| Eye anomalies | Q10-Q15 Congenital malformations of eye | NA | EXCLUDE IN ISOLATION<br>Q10.1 Congenital ectropion, Q10.2 Congenital entropion, Q10.3 Other congenital malformations of eyelid, Q10.5 Congenital stenosis or stricture of lacrimal duct<br>Q13.2 (part) Anisocoria, congenital, Q13.5 Blue sclera<br>Minor anomalies and dysmorphic features | NA | NO |

| Anomaly type* | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Ear, face and neck anomalies | Q16 Congenital malformations of ear causing impairment of hearing | CLINICAL SIGNIFICANCE Q18.3 Webbing of neck | EXCLUDE IN ISOLATION Q17* Other congenital malformations of ear Q18.0-Q18.2 Branchial cleft malformations, Q18.4-Q18.9 Macrostomia, Microstomia, Macrocheilia, Microcheilia, Other congenital malformations of face and neck, Dysmorphic features NOS Minor anomalies and dysmorphic features | NA | NO |

| Anomaly type* | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Heart and circulatory system anomalies | Q20-Q28 Congenital malformations of circulatory system | PERSISTENCE<br>Q21.10 Ostium secundum atrial septal defect (type II)<br><br>CLINICAL SIGNIFICANCE<br>Q24.8 Other specified congenital malformations of heartQ28.8 Other specified congenital malformations of circulatory system<br><br>GESTATIONAL AGE AT DELIVERY & PERSISTENCE / SURGERY / SEVERITYQ25.0 Patent ductus arteriosus, Q25.6 Stenosis of pulmonary artery | EXCLUDE IN ISOLATION<br>Q21.11 Patent foramen ovale<br>Q24.6 Congenital heart block<br>Q25.41 Persistent right aortic arch<br>Q26.1 Persistent left superior vena cava,<br>Q26.8 (part) Absence of superior vena cava, Interrupted inferior vena cava<br>Q27.0 Congenital absence and hypoplasia of umbilical artery | NA | YES<br>SERIOUS CARDIAC ANOMALIES<br><br>Q20.0 Common arterial trunk<br>Q20.1 Double outlet right ventricle<br>Q20.3 Transposition of the great arteries<br>Q20.4 Double inlet ventricle<br>Q21.2* Atrioventricular septal defect<br>Q21.3, Q21.82 Tetralogy of Fallot<br>Q22.0 Pulmonary valve atresia<br>Q22.4 Congenital tricuspid stenosis<br>Q22.5 Ebstein's anomaly<br>Q22.6 Hypoplastic right heart syndrome<br>Q23.0 Congenital stenosis of aortic valve<br>Q23.2, Q23.3 Congenital mitral stenosis and insufficiency<br>Q23.4 Hypoplastic left heart<br>Q25.1* Coarctation of aorta<br>Q25.2 Aortic atresia, interrupted aortic arch<br>Q26.2 Total anomalous pulmonary venous connection |

| Anomaly type* | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Respiratory system anomalies | Q30-Q34 Congenital malformations of respiratory system | CLINICAL SIGNIFICANCE<br>Q30.8 Other congenital malformations of nose<br><br>CAUSE<br>Q33.6 Hypoplasia and dysplasia of lung | EXCLUDE IN ISOLATION<br>Q31.5 Congenital laryngomalacia<br>Q32.0 Congenital tracheomalacia<br>Q32.2* Congenital bronchomalacia<br>Q33.00 Congenital single lung cyst<br>Q33.1* Accessory lobe of lung | NA | NO |
| Orofacial clefts | Q35-Q37 Cleft lip and cleft palate | MINOR FORMS<br>Q35-Q37 Cleft lip and cleft palate | EXCLUDE IN ISOLATION<br>Q35.7 Cleft uvula | NA | YES<br>Q36*, Q37* Cleft lip with/without cleft palate |
| Abdominal wall | Q79.2 Exomphalos<br>Q79.3 Gastroschisis<br>Q79.5 Body Wall complex | | | NA | YES<br>Q79.2 Exomphalos<br>Q79.3 Gastroschisis |

| Anomaly type* | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Gastrointestinal anomalies | Q38-Q45 Other congenital malformations of the digestive system; Q79.0* Congenital diaphragmatic hernia | CLINICAL SIGNIFICANCE<br>Q38.3 Other congenital malformations of tongue<br>Q44.5 Other congenital malformations of bile ducts<br><br>GESTATIONAL AGE AT DIAGNOSIS & SURGERY<br>Q43.30 Malrotation of colon<br><br>SURGERY<br>Q43.5 Ectopic anus | EXCLUDE IN ISOLATION<br>Q38.1 Ankyloglossia, Q38.2 Macroglossia, Q38.3 (part) Microglossia, Q38.4 (part) Congenital ranula, Q38.50 High arched palate<br>Q40.0 Congenital hypertrophic pyloric stenosis, Q40.1 Congenital hiatus hernia, Q40.21 Dysmotility of stomach<br>Q43.0* Meckel's diverticulum, Q43.20 Large intestinal dysmotility, Q43.81 Small intestinal dysmotility, Q43.82 Generalised intestinal dysmotility<br>Q44.4 Choledochal cyst<br>Q45.83 Congenital mesenteric cyst | NA | YES<br>Q79.0* Congenital diaphragmatic hernia |

| Anomaly type* | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Reproductive system anomalies | Q50-Q56 Congenital malformations of genital organs | CLINICAL SIGNIFICANCE<br>Q55.6 Other congenital malformations of penis | EXCLUDE IN ISOLATION<br>Q50.1* Developmental ovarian cyst, Q50.2 Congenital torsion of ovary, Q50.5 Embryonic cyst of broad ligament, Q52.3 Imperforate hymen, Q52.4 (part) Congenital hypertrophy of hymen, Q52.5 Fusion of labia<br>Q52.7 (part) Minor other congenital malformations of vulva<br>Q54.4 Congenital chordee<br>Q55.20 Retractile testis, Q55.21 Bifid scrotum<br><br>EXCLUDE always<br>Q53* Undescended testicle | Q52.7 (part) Congenital rectovulval fistula - EUROCAT exclusion in isolation but NCARDRS includes | NO |
| Congenital anomalies of the kidney and urinary tract | Q60-Q64 Congenital malformations of the urinary system;<br>Q794 Prune Belly | MEASUREMENT / SEVERITY<br>Q62.0 Congenital hydronephrosis<br><br>CLINICAL SIGNIFICANCE<br>Q63.8 Other specified congenital malformations of kidney | EXCLUDE IN ISOLATION<br>Q61.0 Congenital single renal cyst<br>Q62.7* Congenital vesico-uretero-renal reflux<br>Q63.3 Hyperplastic and giant kidney | NA | YES<br>Q60.1 Bilateral renal agenesis |

| Anomaly type* | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Congenital deformities of the musculoskeletal system | Q65-Q68 Congenital musculoskeletal deformities | PERSISTENCE<br>Q65.80 & Q65.81 Dysplastic hip<br><br>CAUSE<br>Q68.8 (part) Arthrogryposis, not otherwise specified | EXCLUDE IN ISOLATION<br>Q65.3-Q65.5 Congenital subluxation of hip, Q65.6* Unstable hip<br>Q66.1-Q66.9 Congenital deformities of feet (except include talipes equinovarus)<br>Q67* Congenital musculoskeletal deformities of head, face, spine and chest<br>Q68.0 Congenital deformity of sternocleidomastoid muscle, Q68.10 Clinodactyly, Q68.21 Genu recurvatum, Q68.3-Q68.5 Congenital bowing of femur, tibia and fibula | Q65.80 & Q65.81 Dysplastic hip - EUROCAT exclusion in isolation but NCARDRS includes | NO |
| Congenital malformations of the limbs | Q69-Q74 Congenital malformations of limb(s) | CLINICAL SIGNIFICANCE<br>Q70.2 Fused toes<br>Q703 Webbed toes, Q70.9 Syndactyly, unspecified<br>Q74.2 Other congenital malformations of lower limb(s), including pelvic girdle<br>Q74.82 Congenital undergrowth of limb(s) | EXCLUDE IN ISOLATION<br>Q74.0 (part) Congenital cubitus valgus, Q74.00 Accessory carpal bone | NA | NO |

| Anomaly type* | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Congenital malformations of other parts of the musculoskeletal system | Q75-Q79 Other congenital malformations of musculoskeletal system | CAUSE<br>Q75.02 Trigonocephaly<br><br>CLINICAL SIGNIFICANCE<br>Q75.8* Other specified congenital malformations of skull and face bones<br>Q76.4 Other congenital malformations of spine, not associated with scoliosis<br><br>GESTATIONAL AGE AT DIAGNOSIS<br>Q79.5 (part) Congenital abdominal wall defect not otherwise specified<br><br>CONSEQUENCE<br>Q79.80 Congenital constriction bands | EXCLUDE IN ISOLATION<br>Q75.00 (part) Brachycephaly, Q75.2 Hypertelorism, Q75.3* Macrocephaly<br>Q76.0 Spina bifida occulta, Q76.43 Congenital lordosis, postural, Q76.5 Cervical rib, Q76.60 Congenital absence of rib, Q76.62 Accessory rib, Q76.71 Sternum bifidum<br>Q79.5 (part) - Congenital divarication of recti | NA | YES<br>Q77*/Q78* (part) Lethal and severe skeletal dysplasias e.g. Thanatophoric dysplasia, Short rib-polydactyly syndrome |

| Anomaly type* | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Integument anomalies | Q80-Q84 Congenital malformations of integument | NA | EXCLUDE IN ISOLATION Q82.5* Congenital non-neoplastic naevus, Q82.8 (part) Dermatoglyphic anomalies, Q82.80 Abnormal palmar creases, Q82.81 Accessory skin tagsQ83.3 Accessory nippleQ84.2 (part) Persistent lanugo, Q84.5 (part) Enlarged or hypertrophic nails, Q84.6 Other congenital malformations of nails | NA | NO |
| Phakomatoses, not elsewhere classified | Q85 Phakomatoses, not elsewhere classified | NA | NA | NA | NO |

| Anomaly type* | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Teratogenic syndromes | Q86* Congenital malformation syndromes due to known exogenous causes, not elsewhere classified | MATERNAL HISTORY & CONSEQUENCE<br>Q86.0 Fetal alcohol syndrome<br><br>KNOWN AETEOLOGY & CONSEQUENCE<br>Q86.1-Q86.8* Fetal hydantoin syndrome, Fetal warfarin syndrome, Other congenital malformation syndromes due to known exogenous causes | NA | NA | NO |
| Other congenital malformation syndromes | Q87* Other specified congenital malformation syndromes (multiple systems) | NA | EXCLUDE IN ISOLATION<br>Q87.4 (part) Arachnodactyly not otherwise specified | NA | NO |
| Other anomalies | Q89* Other congenital malformations, not elsewhere classified | NA | EXCLUDE IN ISOLATION<br>Q89.9 Congenital malformation, unspecified | NA | NO |

| Anomaly type* | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Chromosomal | Q90-Q99 Chromosomal | IF REGISTRABLE ANOMALY Q95* Balanced rearrangements and structural markers, not elsewhere classified | EXCLUDE always Q95.0 Balanced translocation and insertion in normal individual, Q95.1 Chromosome inversion in normal individual, Q95.4 Individuals with marker heterochromatin, Q95.5 Individuals with autosomal fragile site | NA | YES Q90* Down's syndrome Q91* Edwards' syndrome and Patau's syndrome |
| Congenital neoplasms | D15.1 Cardiac rhabdomyoma D18.10 Cystic hygroma (congenital) D21.5 Sacrococcygeal teratoma, Sacral teratoma D21.9 Rhabdomyoma of other organs [i.e. not heart] D48.7 Teratoma, not elsewhere classified | CLINICAL SIGNIFICANCE D18.0 Haemangioma, any site, D18.1 Lymphangioma, any site | NA | EUROCAT exclusion but NCARDRS includes D15.1 Cardiac rhabdomyoma, D18.0 Haemangioma, any site, D18.1 Lymphangioma, any site, D21.9 Rhabdomyoma of other organs [i.e. not heart], D48.7 Teratoma, not elsewhere classified | NO |
| Di George syndrome | D82.1 Di George syndrome | NA | NA | NA | NO |

| Anomaly type* | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Waardenburg syndrome | E70.30 Waardenburg syndrome | NA | NA | NA | NO |
| Cystic fibrosis | E84* Cystic fibrosis | NA | NA | EUROCAT exclusion but NCARDRS includes | NO |
| Spinal muscular atrophy | G12* Spinal muscular atrophy and related syndromes | NA | NA | EUROCAT exclusion but NCARDRS includes | NO |
| Congenital chylothorax | NA | NA | EXCLUDE IN ISOLATION<br>I89.8 Chylothorax (lymphatic);<br>J94.0 Chylothorax (chylous) | NA | NO |
| Paralysis of vocal cords and larynx | NA | NA | EXCLUDE IN ISOLATION<br>J38.0 Paralysis of vocal cords and larynx | NA | NO |
| Micrognathia | | SEVERITY<br>K07.0 Micrognathia | NA | NA | NO |
| Placental transfusion syndromes | P02.3 Fetus and newborn affected by placental transfusion syndromes | INCLUDE IN ISOLATION<br>P02.3 (part) Twin reversed arterial perfusion sequence<br><br>IF REGISTRABLE ANOMALY<br>P02.3 (part) Twin-to-twin transfusion syndrome | NA | NA | NO |

| Anomaly type* | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Congenital infections | P35.8 Congenital zika virus infection | IF REGISTRABLE ANOMALY<br>P35.0 Congenital rubella syndrome, P35.1 Congenital cytomegalovirus infection, P37.1 Congenital toxoplasmosis | NA | NA | NO |
| Hydrops fetalis | P83.2 Hydrops fetalis not due to haemolytic disease | NA | EXCLUDE always<br>P56* Hydrops fetalis due to haemolytic disease | EUROCAT exclusion but NCARDRS includes | NO |
| Congenital hypotonia | NA | NA | EXCLUDE always<br>P94.2 Congenital hypotonia | NA | NO |

* Anomaly type is organised according to ICD-10/BPA system[1] with some amendments to align with EUROCAT subgroup coding[2], but allowing greater granularity.

[1]World Health Organization. ICD-10: International Statistical Classification of Diseases and Related Health Problems. Geneva: World Health Organization; 2010.

[2]https://eu-rd-platform.jrc.ec.europa.eu/system/files/public/eurocat/Guide_1.5_Chapter_3.3.pdf

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# COHORT PROFILE : THE NATIONAL CONGENITAL ANOMALY REGISTRATION DATASET IN ENGLAND



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# COHORT PROFILE : THE NATIONAL CONGENITAL ANOMALY REGISTRATION DATASET IN ENGLAND

Jennifer M Broughan, Ben Wreyford, Danielle Martin, Gabriella Melis, Kay Randall, Ewoma Obaro, John Broggio, Nicholas Aldridge , Sylvia Stoianova, Chloe Johnson, Donna Gibbard, Sarah Stevens & Kate Fleming

National Congenital Anomaly and Rare Disease Registration Service, National Disease Registration Service, Data and Analytics Directorate, NHS England, 7 Wellington Pl, Whitehall Rd, Leeds LS1 4EG, UK.

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Jennifer M Broughan, Jennifer.Broughan@nhs.net
Ben Wreyford, ben.wreyford@nhs.net
Danielle Martin, Danielle.Martin17@nhs.net
Gabriella Melis, Gabriella.Melis1@nhs.net
Kay Randall, kay.randall@nhs.net
Ewoma Obaro, ewoma.obaro@nhs.net
John Broggio, john.broggio@nhs.net
Nicholas Aldridge, nicholas.aldridge@nhs.net
Sylvia Stoianova, Sylvia.Stoianova@bristol.ac.uk
Chloe Johnson, Chloe.Johnson6@dhsc.gov.uk
Donna Gibbard, donna.gibbard@nhs.net
Sarah Stevens, sarah.stevens1@nhs.net
Kate M Fleming, kate.fleming5@nhs.net

Correspondence to:
Jennifer Broughan, PhD
National Disease Registration Service
NHS England
7 and 8 Wellington Pl,

Whitehall Rd,

Leeds

LS1 4EG,

UK.

Jennifer.Broughan@nhs.net

Tel +44 7769282928

ORCID 0000-0002-4450-2147

# ABSTRACT

## Purpose

The National Congenital Anomaly and Rare Disease Registration Service (NCARDRS), part of National Disease Registration Service (NDRS) in NHS England, quality assures, curates and analyses individual data on the pregnancies, fetuses, babies, children and adults with congenital anomalies and rare diseases across England. The congenital anomaly (CA) register provides a resource for patients and their families, clinicians, researchers, and public health professionals in furthering the understanding of CAs.

## Participants

NCARDRS registers CAs occurring in babies born alive and stillborn, fetal losses and terminations in England. NCARDRS collects data from secondary and tertiary health care providers, private providers and laboratories covering fetal medicine, maternity or paediatric services. Data describe the pregnancy, mother, baby, and anomaly. Established in 2015, NCARDRS expanded CA registration coverage from 22% of total births in England in 2015 until national coverage was achieved in 2018. Prior to 2015, data collection was performed independently by regional registers in England; this data is also held by NCARDRS.

## Findings to date:

NCARDRS registers approximately 21,000 babies with CAs per year with surveillance covering 600,000 total births, making it the register with the largest birth coverage globally. Data on prevalence, risk factors and survival for children with CAs are available. Data has been used in several peer-reviewed publications. Birth prevalence statistics, including public health indicators such as the association with maternal age, infant and perinatal mortality, are published annually. NCARDRS supports clinical audit for screening programmes and service evaluation.

## Future plans:

NCARDRS provides a valuable resource for the understanding of the epidemiology, surveillance, prevention and treatment of CAs. Currently, approximately 21,000 new registrations of babies or fetuses with suspected or confirmed CAs are added each year. Identifiers are collected, enabling linkage to routinely-collected healthcare and population statistics, further enhancing the value of the data.

## Key words

Epidemiology, Public Health, Registries, neonatology, paediatrics

## Strengths and limitations

- Congenital anomaly registration coverage has been national across England since 2018 (approximately 21,000 anomalies registered from 600,000 total births per year), enabling the calculation of accurate estimates of prevalence, even for rare congenital anomalies.
- NCARDRS collects personal identifiers and data are linked to other routinely collected administrative and health care data, allowing assessment of long-term outcome and survival over the life course of the baby, as well as associations with health inequalities and other risk factors.
- NCARDRS provides data on all birth outcomes, including live births, stillbirths, fetal losses and terminations.
- Case-ascertainment is good for severe conditions, or those that are more frequently diagnosed antenatally or in the neonatal period.
- Registration and case ascertainment in NCARDRS regions that initiated congenital anomaly registration from 2018 continues to develop and is progressing well.

# INTRODUCTION

Congenital anomalies are a significant source of morbidity, mortality and long-term care needs in children. Approximately 2-3% of children born in Europe have a congenital anomaly(1) which are defined as conditions present at birth and include structural, chromosomal, genetic and biochemical conditions. Some congenital anomalies are detected during pregnancy, some are found at birth, while others are diagnosed only as a baby grows older. In England and Wales, congenital anomalies were the most common cause of death in the post neonatal period in 2020, accounting for 36.3% of deaths(2). Globally it is estimated that 240,000 new-borns die within the neonatal period as a result of congenital anomalies(3).

Registration of congenital anomalies became established in many countries from the 1960s and 70s as a consequence of the thalidomide tragedy and serves multiple purposes supporting epidemiology and public health(4). The National Congenital Anomaly and Rare Disease Registration Service (NCARDRS) is part of the National Disease Registration Service (NDRS) of NHS England which collects, quality assures and analyses data on all people living in England with cancer(5), congenital anomalies and rare diseases. NCARDRS curates a population-based congenital anomaly registry, collecting data on the pregnancies, fetuses, babies, children and adults with congenital anomalies across the whole of England. Data is collected to further the understanding of the causes of congenital anomalies, to inform the commission of public services, to audit health and social care and to provide information for patients, their carers and clinicians on their condition. To achieve this NCARDRS collects data from heath care settings across England. In England, health care is publicly funded and delivered in a centralised and universal way by the National Health Service (NHS).

The UK Rare Disease Strategy, developed in 2013, aimed to improve the lives of those with rare diseases, focusing on patient empowerment, identification and prevention, diagnosis and treatment and the role of research and recommended the expansion of existing data collections(6, 7). Established in 2015 in response, NCARDRS assumed responsibility for

congenital anomaly registration in regions with an existing register and expanded geographically to provide congenital anomaly registration across the whole country(8) (Figure 1). Prior to 2015, data collection was performed independently by regional registers operating across some areas of England, covering up to 32% of births. NCARDRS continues to host the regional registers' legacy registration data. A national congenital anomaly surveillance system was attempted by the UK Office of National Statistics (ONS) but this was closed in 2010 following concerns about data quality and completeness(9). NCARDRS national coverage for registration and reporting has been in place for babies born since 2018(10).

# COHORT DESCRIPTION

## Study population

NCARDRS registers congenital anomalies that occur in babies that are live born and stillborn, fetal losses and terminations at any gestation delivered in England. NCARDRS does not have a minimum gestation for fetal loss and registers all fetal losses reported, although in line with international standards(11) only anomalies that occur in live births, stillbirths, terminations at any gestation and fetal losses between 20-24 completed weeks of gestation are included in prevalence reporting(12, 13). There are approximately 600,000 live births and stillbirths in England every year. There is no upper age limit and information can be added for children as they grow older Information on survival and vital status is updated at least annually.

Inclusion and exclusion criteria for registration of congenital anomalies in NCARDRS follow internationally recognised formats(11) and all registrations are coded to international standards. Anomalies are clinically coded to international standards using the World Health

Organisation's International Classification of Diseases 10th revision (ICD-10)(14) with the British Paediatric Association (BPA) Adaptation, which gives supplementary one-digit extensions to ICD-10 codes to allow greater specificity of coding(11). Inclusion criteria are based on international guidance(11) predominantly covering the Q chapter in ICD-10. A detailed summary of the current inclusion and exclusion criteria is presented in Table S1 in the supplementary materials. NCARDRS excludes cases with an isolated minor anomaly as specified by the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT)(11). However, if minor anomalies occur in association with other anomalies, then these are registered.

Denominator data is obtained from the UK Office for National Statistics (ONS). Individual level birth data are available and are aggregated according to requirements.

## Registration model and source data

NCARDRS employs a multisource, event-based registration model. Over the life course of a patient, NCARDRS can be notified antenatally, at birth or in the neonatal period and beyond as the child is treated by various paediatric specialist services. Registration data are processed, held on a custom-built live data management application, and regularly cloned to a separate PostgreSQL database which creates regular snapshots of data for analysis, reporting and data release (Figure 2).

The data collected by NCARDRS come from a range of sources including maternity units, multidisciplinary team meetings, postmortem reports, molecular testing results, treatment records, hospital patient administration systems, clinical data systems, national data sets describing hospital activity, clinical biochemistry and genetics laboratories. Hospital trusts, including all trusts with a maternity or paediatric service, submit data which are processed and combined by trained registration officers into a comprehensive clinical record of each baby and anomaly.

Data can be submitted at the individual case-level or in large data extracts from clinical management data systems. Custom-built extracts from neonatal clinical data management systems (BadgerNet), including remote access to the record itself, are available for 94% of the trusts with a neonatal unit in England. Extracts of relevant data from fetal medicine software systems including fetal medicine (Viewpoint; Astraia) and specific services (HeartSuite) have been developed in conjunction with software suppliers; these extracts are produced and submitted to NCARDRS by the provider.

Information from providers is combined with routinely collected national data utilised for both data quality and case-ascertainment purposes. Linkage is conducted through NHS number or through date of birth, full name and address. Cases with defined ICD-10 codes that have been validated for accuracy are identified from Hospital Episode Statistics (HES) for ascertainment purposes. HES consists of routinely recorded, administrative data describing each hospital admission in the NHS(15). As well as demographic information on the patient, the primary reason for admission and any co-morbidities are recorded using ICD-10 codes. Death certificate data from the Office for National Statistics (ONS) is provided to NCARDRS monthly for children born alive after 1st January 2018 and where a relevant ICD-10 coded condition (within a specified range) is listed as a cause of death. Information about babies that were born alive or stillborn after 24 weeks gestation (civilly registrable in England) is supplemented using birth registration information supplied by the ONS. Survival for all patients recorded is updated at least annually by linkage with the NHS Personal Demographics Service (PDS) on NHS Spine, a collection of national databases that holds electronic records of important patient information and demographics.

## Data processing

Once received, identifiable patient data are processed by trained registration officers. Processing involves manual extraction of clinical information from clinical reports and letters

or free text comments in clinical software systems. Registration officers require detailed knowledge of congenital anomalies, clinical coding and clinical pathways for the range of different conditions collected. As NCARDRS is a multisource register, patient identifiers are required to ensure that there is no duplication, and that incoming data is linked to the correct baby and pregnancy. Where cases are entered manually, patient identifiers are checked manually using the Summary Care Record on NHS Spine. Further information is requested from the relevant clinician or obtained by direct, manual interrogation of patient records by registration officers via secure remote access to a hospital's clinical software systems or clinical documents where this is available.

Data are input onto the data management system in two ways: 1) data on individual patients submitted by providers are assessed by trained registration officers and manually entered or 2) data from electronic sources are loaded via a semi-automatic process known as the data waterfall (Figure 2). The data waterfall is a process which loads data from electronic sources. Its purpose is to perform basic validations on the data, confirm the patient's demographic information (via NHS Spine), match the patient to an existing patient (or create a new patient record) and create records, such as a screening or diagnostic test event which can be processed by registry staff. Most cases consist of information processed by both manual and automatic methods.

Anomalies are registered according to varying degrees of certainty depending on the clinical evidence available; confirmed, probable or suspected. Anomalies remain at the level of suspected until the evidence supporting the diagnosis of the anomaly attains agreed confirmation criteria. These criteria have been established with clinical input and consider the method by which the diagnosis is made, the specialism and confidence of the reporting clinician, the gestational or postnatal age at which the anomaly was identified, and the reliability of data sources. Criteria are different for each type of anomaly and a baby can have multiple anomalies, each with different statuses, depending on the level of evidence available for each one. Not all anomalies can be confirmed by the gold standard diagnostic test. Where there is a confident diagnosis by a relevant specialist in the field and the evidence is well described a probable confirmation status is used. Only data on probable and confirmed cases are used for routine reporting and analysis purposes and both are considered reportable.

## Data structure

Registration is framed at the level of the anomaly, baby, pregnancy and birth mother. The data are organised into over 600 raw tables which are in turn further organised into a series of approximately 100 custom-built analytical views, tables and lookup tables reflecting five main thematic groups, mother, pregnancy, baby, anomaly and test, with one-to-many relationships across all. Each table contains a primary key that uniquely identifies records within that table and allows joins between tables. A baby and a mother are each assigned a unique identifier. Registration records are never closed and new events can be added if new information is submitted.

## Key data fields

Detailed clinical and demographic information on the mother, baby, anomaly and pregnancy is recorded (Table 1). Multiple anomalies can be registered against a baby, each with different evidence and confirmation status.

NCARDRS works closely with the NHS Fetal Anomaly Screening Programme (FASP) to audit the detection of 15 conditions groups and these conditions are subject to enhanced registration. To facilitate this audit, more extensive information on antenatal screening and the nature and timing of diagnostic testing is collected for these conditions and other closely related or similar conditions. The conditions that are covered by this enhanced registration include severe cardiac anomalies, trisomy 13, trisomy 18 and trisomy 21, neural tube defects, lethal skeletal dysplasia, cleft lip+/palate, bilateral renal agenesis, abdominal wall anomalies and congenital diaphragmatic hernia (see Table S1 in the supplementary materials). These 15 condition groups reflected 35% (n=4501) of the 13,065 babies registered with a confirmed or probable congenital anomaly in 2020.

## Data Quality

Automatic and manual quality checks are embedded into the registration process at points of entry, at the level of the individual record and on the birth cohort as a whole prior to finalisation of the data for reporting. As well as internal data quality indicators (DQIs), the data are evaluated against DQIs for international bodies against known targets(16). For example, the prevalence of anencephaly is reported as an indicator of ascertainment of conditions detected at earlier gestations. Other DQIs focus on the accuracy of diagnosis, for example the number of babies with more than one anomaly, or the prevalence of selected codes that have used the BPA extension code in addition to the ICD-10 code.

## Patient and public involvement

Patient groups and third sector organisations representing patients were involved in the design of this register-based cohort and were members of an expert committee of stake holders made up of academics, clinicians, third sector organisation and patient interest groups that oversaw the formation of NCARDRS.

## Ethical approval and governance arrangements

NCARDRS has legal permission to collect patient-level data on those with a confirmed or suspected congenital anomaly or rare disease for specified purposes, without consent, to use it to protect the health of the population. Data are collected under legal instructions known as Directions, from the Secretary of State for Health and Social Care, made in accordance with section 254 of the Health and Social Care Act 2012 (2012 Act)(17). Strict technical and contractual controls are put in place to prevent unauthorized access and use of the data, with staff undergoing regular training on data protection and information governance.

## FINDINGS TO DATE

As of June 2023, NCARDRS held information on 117,682 mothers and 121,184 babies born in England since 2015. Table 2 shows the number of babies and other characteristics registered in regions with full congenital anomaly registration coverage by year of birth.

NCARDRS currently collects data on more than 1,000 different congenital anomalies, many of which are rare diseases, and provides expert analysis and interpretation of the data across a wide range of national and international functions. The data are available as a source of

intelligence for clinicians, public health, health-care performance, basic and applied research, patient groups, academics and commissioning and industry partners. A summary of the data is published each year describing congenital anomalies in England in the context of prevalence reported by anomaly group, timing of diagnosis and important public health indicators such as maternal age and infant mortality(10, 13, 18-21). In 2020, NCARDRS reported a total of 13,065 babies with one or more confirmed or probable congenital anomalies in 589,454 total births (live births and stillbirths), giving an overall birth prevalence of 221.7 per 10,000 total births (95% confidence intervals (CI) 217.9 - 225.5) or 1 for every 45 births(13). The rate of perinatal mortality associated with a congenital anomaly was highest for genetic disorders (3.1 per 10,000 total births, 95% CI 2.7-3.6), followed by congenital heart anomalies (2.8 per 10,000 total births, 95% CI 2.4-3.2). Infant mortality rate was highest for congenital heart anomalies (4.9 per 10,000 live births, 95% CI 4.4-5.5), followed by genetic conditions (3.0 per 10,000 live births, 95% CI 2.6-3.5). The rate of genetic conditions in babies born to women over 40 years old was almost 7 times higher relative to babies born to mothers under 20 years old (risk ratio equal to 6.9, 95% CI 5.2-9.2).

Congenital anomaly registration data for England is submitted to international bodies to allowing pooling of data across a wider geographical area to support analysis into causes of these rare conditions and how to prevent them. Data is submitted annually to EUROCAT and to the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR). Surveillance is performed annually using internationally recognised tools to identify potential clusters of anomalies and changes in trends(22).

NCARDRS works closely with NHS Screening Programmes delivering service evaluation for antenatal and new-born screening services. NCARDRS audits the detection of the conditions included in the Fetal Anomaly Screening Programme (FASP) (see Table S1 in the supplementary materials) and, to enable this, these conditions are subject to enhanced registration and active ascertainment. By linking information at patient level, NCARDRS creates a longitudinal record of the screening and diagnostic pathway for each mother, fetus,

or baby, enabling analysis of the efficacy of the tests, the behavioural choices on the pathway, and the operational standards of the service. NCARDRS have recently published the first national study of fetal anomaly ultrasound scan detection rates in England (23). The data is used to provide reliable information about the quality of screening services at local, regional and national level and contributes towards the safety and effectiveness of screening services. Each screening provider receives a report detailing hospital-level detection rates and also individual case-level detection status to allow further clinical audit and identify training requirements. NCARDRS is supporting the NHS evaluative roll-out of non-invasive prenatal testing (NIPT) for Edwards' syndrome, Patau's syndrome, and Down's syndrome in England(24). Routine laboratory surveillance is conducted on a monthly, quarterly and annual level, and test performance will be evaluated by linking laboratory and registration data.

At the start of the COVID-19 pandemic, NCARDRS informed the production of the Shielded Patient List (SPL)(25) by identifying individuals living with congenital anomalies and selected rare diseases that may have been at increased risk from COVID-19 infection and NCARDRS will support the continued evaluation of vaccines against COVID-19 in pregnancy(26).

Many publications use datasets that predate NCARDRS including the legacy regional registers. NCARDRS data has been used to examine the epidemiology of congenital anomalies across Europe including Dandy-Walker syndrome(27), VACTERL association (28, 29) , neural tube defects (30), aplasia cutis(31) achondroplasia(32) and vascular disruption anomalies(33). Studies aim to improve outcomes of babies with a congenital anomaly and to inform policy so that some may be prevented, for example to justify the fortification of flour with folic acid. Recently, the UK government announced plans for the fortification of flour with folic acid to reduce neural tube defects(34). NCARDRS will support the evaluation and monitoring of the impact of implementation of this policy(35).

## STRENGTHS AND LIMITATIONS:

## National Coverage

The key strength of the NCARDRS data set is its national coverage across a large birth population. NCARDRS is the largest register in Europe(36) in both size of population and representativeness. With complete population coverage of pregnancies from 2018 onwards, the data are representative and comprehensive, capitalising on the centralised nature of English health care. Registration records are never closed, and data can continue to passively accumulate, enriching each record and facilitating the potential identification of future syndromes or providing more information on the phenotypic manifestations of genetic differences identified later in life.

## Multisource ascertainment

An NCARDRS congenital anomaly record can be made up of multiple difference sources, some automatically added and manually verified. Clinical information, often obtained by the treating clinician, is combined with cytogenetic laboratory data, data from routinely collected hospital activity and national statistics, and extracts from clinical systems to make a cohesive and comprehensive record detailing the phenotype. A registration record is never closed, allowing for the possibility of adding further genomic data as it becomes available with the wider use of whole genome sequencing.

## Standardised disease coding and data entry

The development of NCARDRS has demonstrated that it is possible to conduct national registration on a large population using standardised approaches to data collection and management, disease coding, data classification, analysis and reporting. Data are coded consistently across the country and regions can be compared, allowing the identification of

clusters and geographical disparities which may be a result of population demographics, social determinants of health or local exposure.

## Ascertainment

National prevalence in England for 2018-2020 is consistent with European surveillance data for the same time period (excluding data for England) across most major congenital anomaly groups (Figure 3). The prevalence of severe anomalies, such as severe congenital heart, abdominal wall, oro-facial cleft, respiratory and genetic conditions was higher than the European average. These anomaly subgroups include FASP-conditions and so are subject to enhanced registration. Their higher prevalence reflects the integration of clinical audit in NCARDRS and demonstrates the impact of clinical engagement on data quality and ascertainment. The England national prevalence estimates for all cardiac conditions, limb anomalies and congenital anomalies of the kidney and urinary tract (CAKUT) conditions are lower than the average for other European registers. This likely reflects some under-ascertainment of anomalies that are predominantly confirmed postnatally in regions of NCARDRS new to reporting(10).

Within England, there is some variation in the prevalence of different anomaly groups depending on the length of time registration has been established, reflecting developing ascertainment in regions new to congenital anomaly registration particularly for anomalies that are more frequently identified postnatally or for those anomalies that are less severe(10, 21). As registration becomes embedded and ascertainment increases, differences in prevalence because of data collection should dissipate, revealing true regional differences, if they exist.

## Risk factor information

Information on the demographics of the mother is collected for each pregnancy and include ethnicity, Body Mass Index, illnesses or medications, folic acid intake and other lifestyle factors

such as smoking. This information can be supplemented using data linkage to examine other factors, including social deprivation measured at the area-level through deprivation scores for mother's residential address at delivery,

### Timeliness of data collection

Babies with a congenital anomaly are first registered by NCARDRS approximately 12 months after their expected date of delivery. This time lag allows for the notification of outcome of the pregnancy and a confirmatory diagnosis after delivery along with the notification of other relevant postnatal information and follow-up if required. Finalised delivery year cohorts are available approximately 18 months to two years following the end of a delivery year e.g., babies delivered in 2021 would be reported on in early 2024. Recent advances in the automated processing of defined data feeds (e.g. fetal medicine software system extracts) aim to improve the timeliness of data by reducing the time lag.

## FUTURE WORK

Planned improvements to the timeliness of data reporting and continued improvement to developing ascertainment for new regions and completeness of fields will further improve data quality. Proximity to the more established cancer registration service allows the register to build on synergies in data management, analytical infrastructure and data liaison.

As the service matures, new data sources will be added to improve data quality or ascertainment. Transition to NHS England has situated NCARDRS closer to clinical providers and commissioning services which should improve data access and facilitate linkage to a wider network of data. Linkage with the Maternity Services Dataset, a routinely-collected national dataset describing maternity care in England(37), is underway and this aims to improve the completion of risk factor data items such as smoking, alcohol use as well as providing access to further information about the pregnancy. The inclusion of primary care

data would be an obvious improvement to the ascertainment of postnatally-diagnosed conditions as would clinical audit data such as paediatric intensive care (PICANET), cardiac surgery (NICOR), maternal and neonatal deaths (MBRACE) and NHS England commissioned Highly Specialised Services data.

Linkage to other datasets provides vital information on survival and health outcomes for these children throughout their life course. Cancer registration data collected by NDRS has been linked to the community prescriptions dataset(38) and linkage with the congenital anomaly registration data is in progress. This could provide information on possible drug interactions and potential teratogens. Linkage to other disease registers, subject to adequate consenting materials and approvals, is possible and could provide valuable information on health outcomes for children with congenital anomalies. NCARDRS currently contains data that only relates to the health outcomes of the child and further work should also include linkage to social and educational data.

## CONCLUSIONS

If the thalidomide scandal of the 1960s prompted the establishment of congenital anomaly registration to understand the causes of congenital anomalies, the COVID-19 pandemic amplified the need to be able to identify and protect individuals living with conditions that may put them at increased risk compared to the general population. NCARDRS' congenital anomaly register collates information across the full patient pathway as the pregnancy progresses and the child grows. The value of this dataset in supporting clinical audits and evaluating service delivery is proven. This population-based national register – currently the largest data collection of its kind globally – has a critical role in supporting the epidemiology and monitoring of disease trends, investigating the causes of these conditions, evaluating the

outcome and providing this crucial information to parents, patients and clinicians and to clinical and service commissioners so these children have what they need as they grow.

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**Details of contributions**

JMB led the drafting of the manuscript with advice from KMF, JB and SS as to the concept, structure and content. Additional sections were drafted by BW, DG, CJ, SyS, NA and KR. BW drafted the supplementary table (Table S1). KR, CJ, BW, DG, SyS provided advice on registration and/or data management system practice. Data analysis was performed by JMB, DM, GM and EO. All authors reviewed and commented on the manuscript and gave approval for publication.

**Competing interests statement**

No conflicts of interest have been declared.

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## Data availability statement

Permission to access congenital anomaly registration data can be granted to individuals who demonstrate that either there is a justified purpose for the data release, that there is an appropriate legal basis with safeguards in place to protect the data, or the data release is deemed to be anonymous (e.g. aggregate data). The access process for NDRS data is managed by Data Access Request Service (DARS) (https://digital.nhs.uk/services/data-access-request-service-dars) in NHS England. Full details, including data dictionaries, are available. Further details on the process of data access and associated costs are available on the DARS website [https://digital.nhs.uk/services/data-access-request-service-dars]. Data can also be made available by working in partnership with National Disease Registration Service and enquiries can be directed to ndrs.enquiries@nhs.net.

## Collaboration statement

NDRS supports collaborations with academic and other institutions to use the data for a justified purpose. Enquiries, requests for statistical code used and anonymised data should be directed to ndrs.enquiries@nhs.net.



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Figure 1 The regional structure of NCARDRS and the proportion of the birth population of England that was covered by congenital anomaly registration.

Figure 2 : Schematic describing the multisource registration process used for congenital anomalies in England.

Figure 3 The prevalence of anomaly groups in England compared to EUROCAT registers excluding English registers (2018-2020) [data downloaded 24th April 2023 from EUROCAT, 1st August 2022 NCARDRS]

Table 1: Summary of key data items currently available for each congenital anomaly registration in the NCARDRS congenital anomaly dataset. Data are available for all years.

| **Mother** | **Pregnancy** | **Baby** | **Anomaly** | **Test**[1] [3] |
|---|---|---|---|---|
| Patient identifier | Pregnancy identifier | Patient identifier | Anomaly identifier | Test date |
| NHS number | Expected Delivery Date | NHS number | Confirmation Status of anomaly[2] | Test type |
| Date of birth | Pregnancy outcome | Sex | ICD 10 & BPA extension code | Test result(s) |
| Ethnicity | Delivery information | Date of birth | Description of the anomaly | Test provider |
| Country of birth | Screening details [3] | Gestational length at delivery | Gestation first suspected | Test requestor |
| Vital status | Body Mass Index | Birth weight (g) | Gestation at confirmation | Ultrasound markers |
| Previous births and pregnancies | Smoking status at booking, alcohol and substance use | Birth order if from a multiple pregnancy | Diagnostic method | Indication |
| | Maternal illness status | Method of delivery | Aetiology of the anomaly/ies | |
| | Folic acid intake | Surgical status | | |
| | Assisted conception status | Date of death | | |
| | Number of fetuses | Postmortem status | | |
| | Consanguinity | | | |
| | Deprivation (derived from postcode of residence at delivery) | | | |
| | Postcode at booking and at delivery | | | |

[1] Test information is only consistently registered for conditions with enhanced registration (ie those conditions within the FASP audit)

[2] Confirmation status: Anomalies are registered according to varying degrees of certainty depending on the clinical evidence available (*confirmed, probable or suspected)*. Anomalies remain at the level of *suspected* until the evidence supporting the diagnosis of the anomaly attains agreed confirmation criteria

[3] Some fields may require additional Research Ethics Committee or other approvals on request



Table 2 The number of pregnancies, babies and anomalies recorded registered since NCARDRS has been in operation until 2020 Data extracted 13th June 2023.

| | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 |
|---|---|---|---|---|---|---|
| Number of regions reporting | 4 | 7 | 7 | 10 | 10 | 10 |
| Number of pregnancies with babies with a congenital anomaly of any status | 2,915 | 9,524 | 9,882 | 20,036 | 19,636 | 18,440 |
| Number of babies with a congenital anomaly of any status | 2,932 | 9,574 | 9,937 | 20,145 | 19,767 | 18,541 |
| Number of mothers | 2,908 | 9,506 | 9,868 | 20,007 | 19,611 | 18,416 |
| Total number of anomalies | 5,902 | 18,839 | 18,803 | 35,483 | 34,500 | 33,344 |
| Total number of confirmed and probable anomalies | 5,432 | 15,819 | 15,316 | 28,282 | 25,988 | 25,617 |
| Number of live and still births in regions with active congenital anomaly registration (denominator) | 141,474 | 329,301 | 320,013 | 628,171 | 614,952 | 589,454 |

NOTE : the numbers may differ from published estimates at point of reporting because of continued accumulation of data

Birth population calculated using ONS row level birth information available via the UKHSA DataLake.

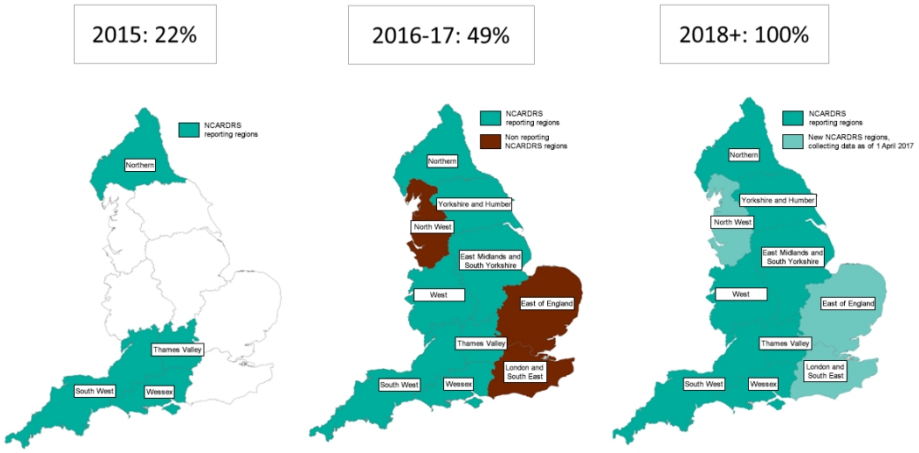


Figure 1 The regional structure of NCARDRS and the proportion of the birth population of England that was covered by congenital anomaly registration.

855x481mm (38 x 38 DPI)

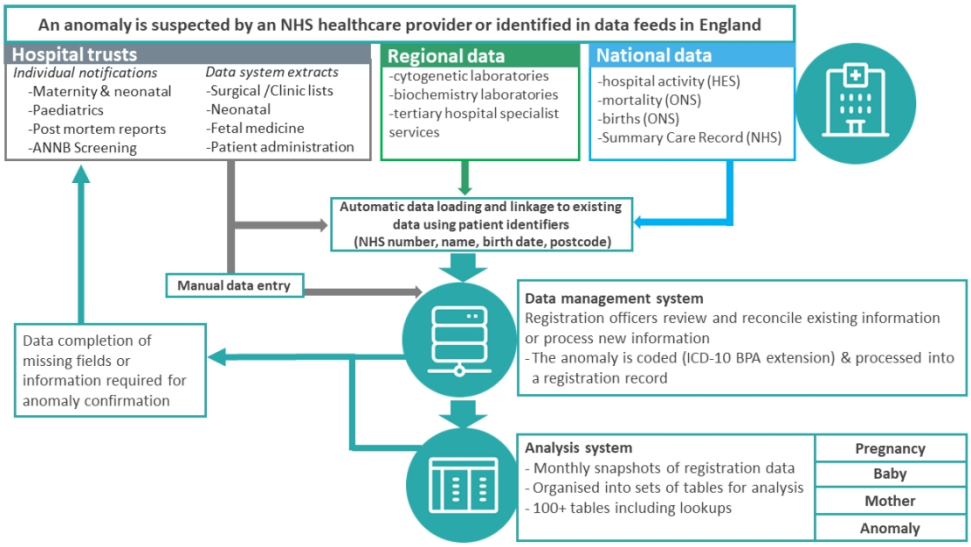


Figure 2 : Schematic describing the multisource registration process used for congenital anomalies in England.

855x481mm (38 x 38 DPI)

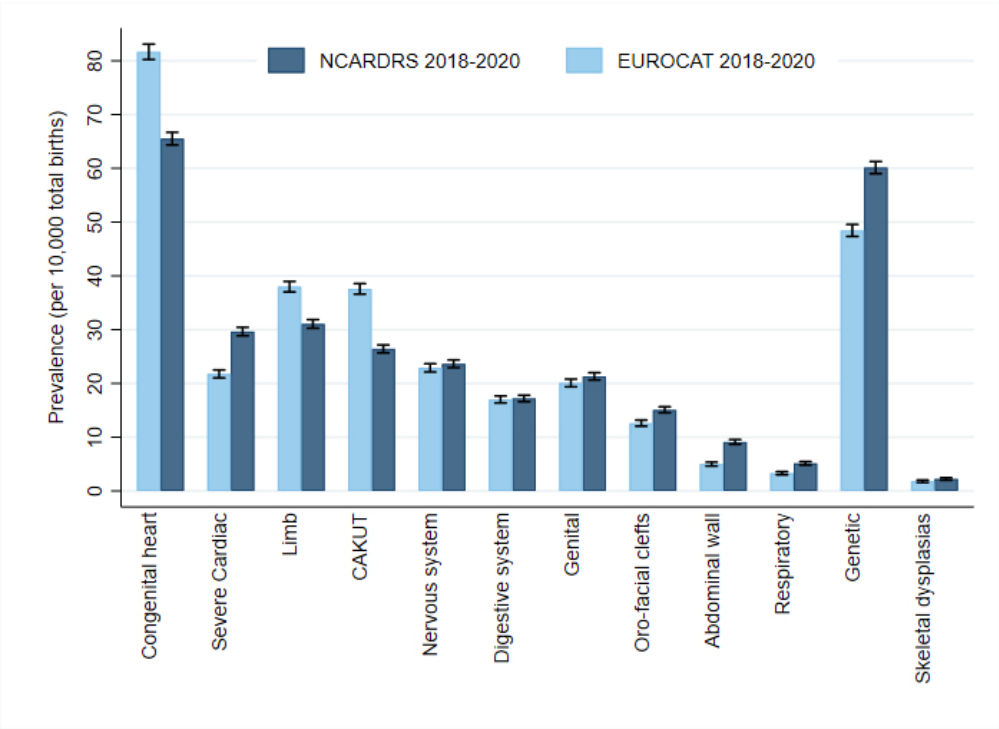


Figure 3 The prevalence of anomaly groups in England compared to EUROCAT registers excluding English registers (2018-2020) [data downloaded 24th April 2023 from EUROCAT, 1st August 2022 NCARDRS]

466x338mm (38 x 38 DPI)

**Table S1** **NCARDRS inclusion and exclusion criteria for registerable congenital anomalies**

| Anomaly type* | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Nervous system anomalies | Q00-Q07 Congenital malformations of the nervous system | MEASUREMENT / SEVERITY<br>Q02 Microcephaly<br>Q03.8 (part) Congenital ventriculomegaly [of lateral ventricle(s)]<br>Q04.32 Reduction anomalies of cerebellum<br><br>CLINICAL SIGNIFICANCE<br>Q04.61 (part) Arachnoid cyst | EXCLUDE IN ISOLATION<br>Q0780 Jaw-winking syndrome<br>Q0782 Crocodile tears<br><br>EXCLUDE always<br>Q04.6 (part) Porencephaly | Q04.6 (part) Porencephaly - EUROCAT inclusion but NCARDRS excludes<br><br>Q04.61 Single congenital cerebral cyst - EUROCAT exclusion in isolation but NCARDRS includes Arachnoid cyst | YES<br>Q00* Anencephaly and similar malformations<br>Q01* Encephalocele<br>Q05* Spina bifida |
| Eye anomalies | Q10-Q15 Congenital malformations of eye | NA | EXCLUDE IN ISOLATION<br>Q10.1 Congenital ectropion, Q10.2 Congenital entropion, Q10.3 Other congenital malformations of eyelid, Q10.5 Congenital stenosis or stricture of lacrimal duct<br>Q13.2 (part) Anisocoria, congenital, Q13.5 Blue sclera<br>Minor anomalies and dysmorphic features | NA | NO |

| Anomaly type* | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Ear, face and neck anomalies | Q16 Congenital malformations of ear causing impairment of hearing | CLINICAL SIGNIFICANCE Q18.3 Webbing of neck | EXCLUDE IN ISOLATION Q17* Other congenital malformations of ear Q18.0-Q18.2 Branchial cleft malformations, Q18.4-Q18.9 Macrostomia, Microstomia, Macrocheilia, Microcheilia, Other congenital malformations of face and neck, Dysmorphic features NOS Minor anomalies and dysmorphic features | NA | NO |

| Anomaly type* | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Heart and circulatory system anomalies | Q20-Q28 Congenital malformations of circulatory system | PERSISTENCE<br>Q21.10 Ostium secundum atrial septal defect (type II)<br><br>CLINICAL SIGNIFICANCE<br>Q24.8 Other specified congenital malformations of heartQ28.8 Other specified congenital malformations of circulatory system<br><br>GESTATIONAL AGE AT DELIVERY & PERSISTENCE / SURGERY / SEVERITYQ25.0 Patent ductus arteriosus, Q25.6 Stenosis of pulmonary artery | EXCLUDE IN ISOLATION<br>Q21.11 Patent foramen ovale<br>Q24.6 Congenital heart block<br>Q25.41 Persistent right aortic arch<br>Q26.1 Persistent left superior vena cava,<br>Q26.8 (part) Absence of superior vena cava, Interrupted inferior vena cava<br>Q27.0 Congenital absence and hypoplasia of umbilical artery | NA | YES<br>SERIOUS CARDIAC ANOMALIES<br><br>Q20.0 Common arterial trunk<br>Q20.1 Double outlet right ventricle<br>Q20.3 Transposition of the great arteries<br>Q20.4 Double inlet ventricle<br>Q21.2* Atrioventricular septal defect<br>Q21.3, Q21.82 Tetralogy of Fallot<br>Q22.0 Pulmonary valve atresia<br>Q22.4 Congenital tricuspid stenosis<br>Q22.5 Ebstein's anomaly<br>Q22.6 Hypoplastic right heart syndrome<br>Q23.0 Congenital stenosis of aortic valve<br>Q23.2, Q23.3 Congenital mitral stenosis and insufficiency<br>Q23.4 Hypoplastic left heart<br>Q25.1* Coarctation of aorta<br>Q25.2 Aortic atresia, interrupted aortic arch<br>Q26.2 Total anomalous pulmonary venous connection |

| Anomaly type* | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Respiratory system anomalies | Q30-Q34 Congenital malformations of respiratory system | CLINICAL SIGNIFICANCE<br>Q30.8 Other congenital malformations of nose<br><br>CAUSE<br>Q33.6 Hypoplasia and dysplasia of lung | EXCLUDE IN ISOLATION<br>Q31.5 Congenital laryngomalacia<br>Q32.0 Congenital tracheomalacia<br>Q32.2* Congenital bronchomalacia<br>Q33.00 Congenital single lung cyst<br>Q33.1* Accessory lobe of lung | NA | NO |
| Orofacial clefts | Q35-Q37 Cleft lip and cleft palate | MINOR FORMS<br>Q35-Q37 Cleft lip and cleft palate | EXCLUDE IN ISOLATION<br>Q35.7 Cleft uvula | NA | YES<br>Q36*, Q37* Cleft lip with/without cleft palate |
| Abdominal wall | Q79.2 Exomphalos<br>Q79.3 Gastroschisis<br>Q79.5 Body Wall complex | | | NA | YES<br>Q79.2 Exomphalos<br>Q79.3 Gastroschisis |

| Anomaly type* | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Gastrointestinal anomalies | Q38-Q45 Other congenital malformations of the digestive system; Q79.0* Congenital diaphragmatic hernia | CLINICAL SIGNIFICANCE<br>Q38.3 Other congenital malformations of tongue<br>Q44.5 Other congenital malformations of bile ducts<br><br>GESTATIONAL AGE AT DIAGNOSIS & SURGERY<br>Q43.30 Malrotation of colon<br><br>SURGERY<br>Q43.5 Ectopic anus | EXCLUDE IN ISOLATION<br>Q38.1 Ankyloglossia, Q38.2 Macroglossia, Q38.3 (part) Microglossia, Q38.4 (part) Congenital ranula, Q38.50 High arched palate<br>Q40.0 Congenital hypertrophic pyloric stenosis, Q40.1 Congenital hiatus hernia, Q40.21 Dysmotility of stomach<br>Q43.0* Meckel's diverticulum, Q43.20 Large intestinal dysmotility, Q43.81 Small intestinal dysmotility, Q43.82 Generalised intestinal dysmotility<br>Q44.4 Choledochal cyst<br>Q45.83 Congenital mesenteric cyst | NA | YES<br>Q79.0* Congenital diaphragmatic hernia |

| Anomaly type* | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Reproductive system anomalies | Q50-Q56 Congenital malformations of genital organs | CLINICAL SIGNIFICANCE<br>Q55.6 Other congenital malformations of penis | EXCLUDE IN ISOLATION<br>Q50.1* Developmental ovarian cyst, Q50.2 Congenital torsion of ovary, Q50.5 Embryonic cyst of broad ligament, Q52.3 Imperforate hymen, Q52.4 (part) Congenital hypertrophy of hymen, Q52.5 Fusion of labia<br>Q52.7 (part) Minor other congenital malformations of vulva<br>Q54.4 Congenital chordee<br>Q55.20 Retractile testis, Q55.21 Bifid scrotum<br><br>EXCLUDE always<br>Q53* Undescended testicle | Q52.7 (part) Congenital rectovulval fistula - EUROCAT exclusion in isolation but NCARDRS includes | NO |
| Congenital anomalies of the kidney and urinary tract | Q60-Q64 Congenital malformations of the urinary system;<br>Q794 Prune Belly | MEASUREMENT / SEVERITY<br>Q62.0 Congenital hydronephrosis<br><br>CLINICAL SIGNIFICANCE<br>Q63.8 Other specified congenital malformations of kidney | EXCLUDE IN ISOLATION<br>Q61.0 Congenital single renal cyst<br>Q62.7* Congenital vesico-uretero-renal reflux<br>Q63.3 Hyperplastic and giant kidney | NA | YES<br>Q60.1 Bilateral renal agenesis |

| Anomaly type* | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Congenital deformities of the musculoskeletal system | Q65-Q68 Congenital musculoskeletal deformities | PERSISTENCE<br>Q65.80 & Q65.81 Dysplastic hip<br><br>CAUSE<br>Q68.8 (part) Arthrogryposis, not otherwise specified | EXCLUDE IN ISOLATION<br>Q65.3-Q65.5 Congenital subluxation of hip, Q65.6* Unstable hip<br>Q66.1-Q66.9 Congenital deformities of feet (except include talipes equinovarus)<br>Q67* Congenital musculoskeletal deformities of head, face, spine and chest<br>Q68.0 Congenital deformity of sternocleidomastoid muscle, Q68.10 Clinodactyly, Q68.21 Genu recurvatum, Q68.3-Q68.5 Congenital bowing of femur, tibia and fibula | Q65.80 & Q65.81 Dysplastic hip - EUROCAT exclusion in isolation but NCARDRS includes | NO |
| Congenital malformations of the limbs | Q69-Q74 Congenital malformations of limb(s) | CLINICAL SIGNIFICANCE<br>Q70.2 Fused toes<br>Q703 Webbed toes, Q70.9 Syndactyly, unspecified<br>Q74.2 Other congenital malformations of lower limb(s), including pelvic girdle<br>Q74.82 Congenital undergrowth of limb(s) | EXCLUDE IN ISOLATION<br>Q74.0 (part) Congenital cubitus valgus, Q74.00 Accessory carpal bone | NA | NO |

| Anomaly type* | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Congenital malformations of other parts of the musculoskeletal system | Q75-Q79 Other congenital malformations of musculoskeletal system | CAUSE<br>Q75.02 Trigonocephaly<br><br>CLINICAL SIGNIFICANCE<br>Q75.8* Other specified congenital malformations of skull and face bones<br>Q76.4 Other congenital malformations of spine, not associated with scoliosis<br><br>GESTATIONAL AGE AT DIAGNOSIS<br>Q79.5 (part) Congenital abdominal wall defect not otherwise specified<br><br>CONSEQUENCE<br>Q79.80 Congenital constriction bands | EXCLUDE IN ISOLATION<br>Q75.00 (part) Brachycephaly, Q75.2 Hypertelorism, Q75.3* Macrocephaly<br>Q76.0 Spina bifida occulta, Q76.43 Congenital lordosis, postural, Q76.5 Cervical rib, Q76.60 Congenital absence of rib, Q76.62 Accessory rib, Q76.71 Sternum bifidum<br>Q79.5 (part) - Congenital divarication of recti | NA | YES<br>Q77*/Q78* (part) Lethal and severe skeletal dysplasias e.g. Thanatophoric dysplasia, Short rib-polydactyly syndrome |

| Anomaly type* | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Integument anomalies | Q80-Q84 Congenital malformations of integument | NA | EXCLUDE IN ISOLATION Q82.5* Congenital non-neoplastic naevus, Q82.8 (part) Dermatoglyphic anomalies, Q82.80 Abnormal palmar creases, Q82.81 Accessory skin tagsQ83.3 Accessory nippleQ84.2 (part) Persistent lanugo, Q84.5 (part) Enlarged or hypertrophic nails, Q84.6 Other congenital malformations of nails | NA | NO |
| Phakomatoses, not elsewhere classified | Q85 Phakomatoses, not elsewhere classified | NA | NA | NA | NO |

| Anomaly type* | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Teratogenic syndromes | Q86* Congenital malformation syndromes due to known exogenous causes, not elsewhere classified | MATERNAL HISTORY & CONSEQUENCE<br>Q86.0 Fetal alcohol syndrome<br><br>KNOWN AETEOLOGY & CONSEQUENCE<br>Q86.1-Q86.8* Fetal hydantoin syndrome, Fetal warfarin syndrome, Other congenital malformation syndromes due to known exogenous causes | NA | NA | NO |
| Other congenital malformation syndromes | Q87* Other specified congenital malformation syndromes (multiple systems) | NA | EXCLUDE IN ISOLATION<br>Q87.4 (part) Arachnodactyly not otherwise specified | NA | NO |
| Other anomalies | Q89* Other congenital malformations, not elsewhere classified | NA | EXCLUDE IN ISOLATION<br>Q89.9 Congenital malformation, unspecified | NA | NO |

| Anomaly type* | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Chromosomal | Q90-Q99 Chromosomal | IF REGISTRABLE ANOMALY Q95* Balanced rearrangements and structural markers, not elsewhere classified | EXCLUDE always Q95.0 Balanced translocation and insertion in normal individual, Q95.1 Chromosome inversion in normal individual, Q95.4 Individuals with marker heterochromatin, Q95.5 Individuals with autosomal fragile site | NA | YES Q90* Down's syndrome Q91* Edwards' syndrome and Patau's syndrome |
| Congenital neoplasms | D15.1 Cardiac rhabdomyoma D18.10 Cystic hygroma (congenital) D21.5 Sacrococcygeal teratoma, Sacral teratoma D21.9 Rhabdomyoma of other organs [i.e. not heart] D48.7 Teratoma, not elsewhere classified | CLINICAL SIGNIFICANCE D18.0 Haemangioma, any site, D18.1 Lymphangioma, any site | NA | EUROCAT exclusion but NCARDRS includes D15.1 Cardiac rhabdomyoma, D18.0 Haemangioma, any site, D18.1 Lymphangioma, any site, D21.9 Rhabdomyoma of other organs [i.e. not heart], D48.7 Teratoma, not elsewhere classified | NO |
| Di George syndrome | D82.1 Di George syndrome | NA | NA | NA | NO |

| Anomaly type* | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Waardenburg syndrome | E70.30 Waardenburg syndrome | NA | NA | NA | NO |
| Cystic fibrosis | E84* Cystic fibrosis | NA | NA | EUROCAT exclusion but NCARDRS includes | NO |
| Spinal muscular atrophy | G12* Spinal muscular atrophy and related syndromes | NA | NA | EUROCAT exclusion but NCARDRS includes | NO |
| Congenital chylothorax | NA | NA | EXCLUDE IN ISOLATION<br>I89.8 Chylothorax (lymphatic);<br>J94.0 Chylothorax (chylous) | NA | NO |
| Paralysis of vocal cords and larynx | NA | NA | EXCLUDE IN ISOLATION<br>J38.0 Paralysis of vocal cords and larynx | NA | NO |
| Micrognathia | | SEVERITY<br>K07.0 Micrognathia | NA | NA | NO |
| Placental transfusion syndromes | P02.3 Fetus and newborn affected by placental transfusion syndromes | INCLUDE IN ISOLATION<br>P02.3 (part) Twin reversed arterial perfusion sequence<br><br>IF REGISTRABLE ANOMALY<br>P02.3 (part) Twin-to-twin transfusion syndrome | NA | NA | NO |

| Anomaly type* | Routine inclusion (per ICD-10 code blocks) | Inclusions subject to criteria | Exclusions | Differences with EUROCAT | Enhanced registration |
|---|---|---|---|---|---|
| Congenital infections | P35.8 Congenital zika virus infection | IF REGISTRABLE ANOMALY<br>P35.0 Congenital rubella syndrome, P35.1 Congenital cytomegalovirus infection, P37.1 Congenital toxoplasmosis | NA | NA | NO |
| Hydrops fetalis | P83.2 Hydrops fetalis not due to haemolytic disease | NA | EXCLUDE always<br>P56* Hydrops fetalis due to haemolytic disease | EUROCAT exclusion but NCARDRS includes | NO |
| Congenital hypotonia | NA | NA | EXCLUDE always<br>P94.2 Congenital hypotonia | NA | NO |

* Anomaly type is organised according to ICD-10/BPA system[1] with some amendments to align with EUROCAT subgroup coding[2], but allowing greater granularity.

[1]World Health Organization. ICD-10: International Statistical Classification of Diseases and Related Health Problems. Geneva: World Health Organization; 2010.

[2]https://eu-rd-platform.jrc.ec.europa.eu/system/files/public/eurocat/Guide_1.5_Chapter_3.3.pdf