Medication use in children with congenital anomalies as a measure of co-morbidities

Protocol for WP4 Morbidity Study II

1. **Background:**

The focus of EUROlinkCAT Work Package 4 is to expand knowledge on the health and clinical course of children with congenital anomalies (CAs) up to the first 10 years of life and to evaluate different treatments in prenatal, neonatal and childhood care in Europe in order to optimize diagnosis, treatment and health for these children. The Morbidity I study focuses on evaluation of the long-term morbidity of children with CAs by assessing the number of days in hospital, occurrence of surgery and days in intensive care units based on linked data from seventeen EUROCAT registries. The Morbidity II study focuses on evaluating rates of prescription medications as these are indications of the occurrence of infections outside hospital and the need for daily medication for a chronic disease, and can thus be used as a measure of co-morbidities in children with CAs. The objective of the study is to compare prescription rates of selected medications in children with CAs (cases) compared to children without CAs (controls) in order to describe the additional burden for children with CAs.

Infections due to bacterial causes are commonly treated by antibiotics. A Danish population study assessing age-specific rates of prescribed antibiotics reported the highest prescribed rates in children aged under 5 years of age and in people aged 65 years and older based on the Danish national prescription database (Aabenhus et al 2017). In Danish children, the highest incident rate of antibiotic prescriptions was observed in children under two years of age, while the highest prevalence rate was found in children 0-1 years of age (Pottegård et al 2015). Among children exposed to antibiotics in Denmark, 56% had received one prescription, 24% two, and 10% three or more (Jensen et al 2016). In the Netherlands, the highest proportion (29%) of antibiotic prescriptions was observed in children aged 2 years and the lowest (16%) in children aged 14 years based on data from a primary care network in Utrecht (Dekker et al 2017).

A study assessing antibiotic prescription rates in seven paediatric cohorts found over seven-fold differences in rates between countries. Children in South Korea had 3.4 prescribed courses of antibiotics per child-year during the first two years of life, compared to 1.6 in Lazio Italy and 1.4 in Pedianet Italy, 1.5 in Spain, 1.0 in Germany and 0.5 in Norway (Youngster et al 2017). In addition, differences were found in the type of antibiotic prescribed. First-line penicillin accounted for 64.8% of antibiotic prescriptions in Norway, compared with 38.2% in Germany, 27.7% in Spain, 25.1% in the Italian Pedianet population, and 8% in the Italian Lazio population (Youngster et al 2017).

Data from the US 2001–2016 National Health Interview Survey for children aged 0–17 years including information on routine care visits, hospitalization, missed school days, self-management education, and asthma medication use reported that asthma was more prevalent in children aged five years and older (approx. 10%) compared to children aged less than 5 years (3.8%), (Zahran et al 2018). However, the prevalence of asthma attacks (62.4%), emergency department or urgent care visits (31.1%), and hospitalization (10.4%) were higher among children with asthma aged 0–4 years than among children aged 5-11 years and 12–17 years (Zahran et al 2018).

Using data from Danish population-based medical and prescription databases, 11,101 children with a diagnosis of congenital heart defects (CHD) before age 15 years were identified between 1995 and 2012. The overall cumulative incidence of cardiovascular medication (ATC codes beginning with C01-C03, C07-C09) use by age 15 was 25% (95% CI: 24-26). Diuretics (ATC code: C03x) were used by most children with CHD, with a cumulative incidence of 19% (95% CI: 18-20). Beta blocking agents (ATC code: C07x) were used by 2.3% (95% CI: 1.9-2.7) and calcium channel blockers (ATC code: C08x) by 0.9% (95% CI: 0.6-1.2). Cardiac therapy (ATC code: C01x) was used by 1.4% (95% CI: 1.1-1.7), (Olsen and Madsen, 2016)

Among 379 children with hydrocephalus, 86 (23%) developed epilepsy (mean age at onset was 2.7 years); and among children who underwent surgery, surgical infection doubled the risk of epilepsy (risk ratio= 2.0, 95% confidence interval= 1.4 to 3.0), (Tully et al 2016).

Infections and chronic conditions such as asthma, diabetes, epilepsy and CHD require medications to manage these conditions. To the author’s knowledge, medication rates for these conditions have never been evaluated to assess the burden of co-morbidities in children with CAs. Furthermore, studies assessing prescription rates in children do not differentiate between children with and without CA, or those born prematurely. The current study will assess the occurrence of co-morbidities in children up to ten years of age with CAs by evaluating prescription rates for select medications in children with CAs compared to control children with no CAs. It will also investigate if there are geographical differences in age-specific prescription rates, as well as geographical differences in types of medications prescribed for children up to ten years of age across Europe.

Aim: To evaluate specific medication use as an indication of the presence of co-morbidities in children up to 10 years of age with CA

1. **Description of data and data sources**

**2.1 Inclusion criteria**

This study is conducted on a sub-set of 13 registries contributing to the WP4 morbidity studies. Thirteen EUROCAT registries can link to local prescription databases and are included in the study: Odense (Denmark), England (five registries under BINOCAR), Finland, Emilia Romagna and Tuscany (Italy), Northern Netherlands, Basque Country and Valencia Region (Spain), and Wales (Table 1).

Cases for the study are all live born infants with a major congenital anomaly (CA) as defined in EUROCAT Guide 1.4 born between 1995 and 2014, in the 13 participating registries. Cases are included up to their 10th birthday.

**2.2 Controls**

Where possible, the controls will be all children in the population without CA, born in the same geographical area and within the same time period as the children recorded in the EUROCAT registry. We recognize that some control children in the general population may have other chronic conditions such as cerebral palsy or were born preterm hence these children will also be taking medications.

In some registry areas, data from a sample of matched control children without CA born in the same time period and in the same geographical area as the cases will be randomly selected, irrespective of the presence or absence of other chronic conditions (Table 2). The control children will be matched on the following variables if possible: age of child, gender, gestational age at birth, socioeconomic status (multiple deprivation index) and maternal age at birth.

**2.3 Exclusion criteria**

None

**2.4 Data file from the EUROCAT registry (cases)**

In April 2018, a CA case file was extracted from the EUROCAT central database for each registry contributing to the EUROlinkCAT study. The EUROCAT variables extracted are listed in Table 3. This case file is archived locally by all registries.

**2.5 Variables from hospital episodes/ health care databases (Morbidity Study I)**

All live born CA cases in the registry case file will be linked to local health care databases with data on morbidity. The registry or the data provider will send a short report outlining the number of CA cases that were linked / unlinked to the health care database and the reasons for non-linkage to Ulster University (UU). The linked EUROCAT-Hospital episodes data file will include the following:

* All CA cases linked to health care/ morbidity data
* All control children in health care/ morbidity data
* All CA cases not linked to health care/ morbidity data

Table 4 lists the variables requested for the Morbidity Study I. These variables will also be used for the prescription study.

**2.6 Prescription databases**

The linked EUROCAT-Hospital episodes data file will then be linked to the prescription database using either personal ID number or linked through common variables (date of birth, gestational age, birth weight, sex, maternal age/date of birth). For each child, data will be extracted up to the first 10 years of life or up to the latest available year in the prescription database. The registry or the data provider will produce a short report outlining the number of cases that were linked / unlinked to the prescription database and the reasons for non-linkage. This report should be sent to UU before any data tables are prepared.

Variables to include are listed in Table 5 and will be defined for each registry by the Standardisation Committee. Co-morbidity will be measured by the number of prescriptions for the following specific medications:

* Asthma (ATC codes beginning with R03)
* Cardiac (ATC codes beginning with C01-C03, C07-C09)
* Diabetes (ATC codes beginning with A10)
* Epilepsy (ATC codes beginning with N03)
* Infections (ATC codes beginning with J01-J05).

Variables on risk factors such as preterm birth, very low birth weight (VLBW), age of child, maternal age, and maternal socio-economic status are already collected for Morbidity Study I.

**2.7 The linked data**

The linked data file will be stored securely, either within the local registry or within the organisation doing the linkage. The registries will be provided with a set of instructions (syntax script, see section 3 below) to create pre-specified tables and perform analysis on the data and the aggregated tables and analytic results will be transmitted to the Central Results Repository (CRR) at UU. No individual case data will be transmitted to the CRR.

**2.8 Calculate prescription rates**

Calculate the number of prescriptions per year for overall medication use by type e.g. antibiotics, and then sub-categories of medication type e.g. type of antibiotic. According to the European Centre for Disease Prevention, this method is a more realistic way to evaluate antibiotic prescribing than the traditional measure calculated as number of DDD per 1,000 inhabitants per day since dose depends on a patient’s body weight and we only have the weight of the child at birth.

We can estimate three measures of medication use, censored at death, emigration, or 31 Dec 2014:

* risk of at least one medication prescription up to age 10 years, using Kaplan-Meier cumulative incidence
* rate of repeat prescriptions per child
* medication burden, equal to the number of total days on prescribed medication treatment during infancy/ childhood

The five selected medication groups are different which necessitates different analytical approaches i.e. the method used will depend on the specific medication being analysed. This will be programmed into the syntax script for each registry.

Antibiotics: frequency and duration of antibiotic use; age at onset; lower dose prophylactic treatment; antibiotics for respiratory infection, urinary infection, viral infection and fungal infections. We will assume that antibiotic prescriptions in a two-week period are for the same infection.

Asthma medications: analyse in two groups: any prescription and more than one prescription. There will be a close association to use of antibiotics. Prescription of inhaled steroids is the best predictor of a chronic disease and daily use of medication.

Cardiac medications: analyse if medication is stopped or started in relation to cardiac surgery. Before surgery, diuretics and ace-inhibitors may be used for cardiac failure. After surgery there may be a need for anti-arythmic medications. Describe fluctuations in medication use up to 10 years of age.

Anti-epileptics: describe age at start and number of months or years on treatment; monotherapy or polytherapy.

Anti-diabetics: age at the first prescription (check that there is more than one prescription). Most children will have type-1 diabetes and use insulin. A few school children may be diagnosed with type 2 diabetes.

Each registry/data provider will provide a short report about the validity of the data based on a pre-defined template, that is: Can they link to hospital prescribing data? Is it possible to get information on indications for antibiotic prescribing?

**3. Local analyses**

A detailed analysis plan will be written by WP4 leaders with support from statisticians from Queen Mary University London (QMUL) and tested in a few databases before being released to the registries. UU and QMUL will produce common syntax scripts, which will conform to a common data model to ensure that all variables/proxy variables are standardised across all registries. Registries will use the syntax scripts specific to their registry to generate the tables/ results outlined in the analysis plan. A data "dictionary" of every variable in the linked dataset with its name, description/definition, coding instructions/values (in English) will be created and uploaded to the website. The quality of the data linkage will be investigated and data quality checks will be conducted for unlikely results and outliers across registries (UU) and a report produced.

Analysis will include all cases with congenital anomalies (EUROCAT subgroup al1: all anomalies) and on all relevant EUROCAT subgroups as defined in Guide 1.4 chapter 3.3, as well as an additional 27 subgroups as defined in the morbidity protocol (Table 6).

**4. Data transmission to the Central Results Repository (CRR) and to WP4**

The tables and results created by each registry using the supplied syntax scripts will be submitted in Excel, SPSS or STATA file formats, or other commercially available packages, to UU via the secure project portal (members’ area on the EUROlinkCAT website). All data submitted will be aggregated - no individual case data will be sent to UU.

UU will then:

1. Import the tables from each participating registry to the CRR
2. Perform data quality checks
3. Generate extracts of data from the CRR required for this study

**WP4 Analyses and milestones:**

Ulster University will perform meta-analyses on the data from the CRR to explore specific medication use (antibiotics, asthma, cardiac, diabetes, epilepsy) as an indication of the presence of co-morbidities in children up to 10 years of age with congenital anomalies. Results will be discussed at a subgroup meeting and a first draft of papers arising from the study will be circulated for comments. A Report will be submitted to the EU by month 51.

**5. Publication of results**

At least 5 papers will be published (one for each type of medication: antibiotics, anti-asthmatics, anti-diabetics, anti-epileptics, and cardiac medications) in high-impact peer-review journals with open access and with authorship according to EUROlinkCAT criteria.

The deliverable in the Horizon 2020 contract is:

D4.2: Report on Infections and use of antibiotics during the first 5 years of life [51]

Table 1: Prescription Databases in registries contributing to Morbidity II study on medication use

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Denmark - Odense | Finland | Italy - Emilia Romagna |  Italy - Tuscany | Netherlands | Spain (Basque Country) | Spain (Valencia Region) | Wales | BINOCAR (England) |
| Database for medicine use data | The Danish National Prescription Registry | KELA Register on reimbursed medication (Social Insurance Institution) | AFT “Pharmaceutical territorial assistance” | AFT “Pharmaceutical territorial assistance”FED “Pharmaceutical hospital prescribing”) | IADB.nl | Presbide & eOsabide, Osakidetza (Basque Health Service) | Valencia Health Agency – claims  | Secure Anonymised Information linkage (SAIL) | Clinical Practice Research Datalink (CPRD) |
| Coverage | All of Denmark | All of Finland, reimbursed medication only | 4,200,000 | 3,700,000 | Regional, ~0.5 million | 100% of 2.2 million inhabitants | 5 million inhabitants |  ~70% of Wales  | ~8% of the UK population |
| Data on congenital anomalies from 1995  | Yes | Yes | Yes | Yes | Yes | Yes | From 2007 | From 1998 | For some, but not all English registries |
| Data on medication use from 1995 (primary care/ community pharmacies) | Prescriptions for children were issued under the name of the mother until 1996, and then under the child’s name\*Year 2000 will be the start year. | Yes | From 2003 | From 2003 | Yes | From 2012 | From 2007 | 2000 for comprehensive data.  | ? |
| Hospital prescribing (i.e. medications dispensed during a hospital stay) | No | No | From 2008(outpatient clinics only) | From 2004(outpatient clinics only) | No | From 2012 | ? | No | No |
| Coding  | ATC | ATC | ATC | ATC | ATC | ATC | ATC | Read | Read / BNF |
| Information on risk factors available | Yes  | Yes, Medical Birth Register, Hospital Discharge Register | Yes | Yes | No | No | No | Yes  | Yes  |
| Information on co-morbidities in child | Yes  | Yes, Medical Birth Register, Hospital Discharge Register | ? | Yes | No | Yes | No | GP diagnoses, reasons for hospital admissions.  | Yes – GP diagnoses and referrals |
| Information on indication  |  | No |  | No |  | Could link prescription data with information of diagnoses and other episodes registered in the medical records | No |  |  |

\* <https://academic.oup.com/ije/article/46/3/798/2447869> ; Kildemoes et al (2011)

**Table 2: Type of controls planned for the 13 registries**

|  |  |
| --- | --- |
| **Registry name** | **Type of controls** |
| Basque Country, Spain | Population |
| Emilia Romagna, Italy | Population |
| England, five registries | Matched controls |
| Finland | Population |
| Funen, Denmark | Population |
| Northern Netherlands | Population |
| Tuscany, Italy | Population |
| Valencia Region, Spain | Population |
| Wales | Population |

**Table 3:** Variables to extract from the EUROCAT Data Management Program (EDMP) for linkage to prescription database

|  |  |
| --- | --- |
|  | **EDMP Variables (Core variables shaded in blue)** |
| **Variable number** | **Variable Name** | **Variable explanation** |
| **Baby and Mother – Variables 1 to 18**  |
|  |  |  |
| 1 | CENTRE | Centre Number |
| 2 | NUMLOC | Local ID of case |
| 3 | BIRTH\_DATE | Date of Birth |
| 4 | SEX | Sex |
| 5\*\* | NBRBABY | Number of babies delivered |
| 6 | SP\_TWIN  | Specify twin type of birth, like or unlike, zygosity  |
| 7 | NBRMALF | Number of malformed in multiple set |
| 8 | TYPE | Type of birth |
| 9 | CIVREG | Civil registration status |
| 10 | WEIGHT | Birth weight |
| 11 | GESTLENGTH | Length of gestation in completed weeks |
| 12 | SURVIVAL | Survival beyond one week of age |
| 13 | DEATH\_DATE | Date of death |
| 14  | DATEMO  | Date of birth of mother  |
| 15 | AGEMO | Age of mother at delivery |
| 16\* | BMI  | Maternal Body Mass Index  |
| 17  | RESIDMO | Mother’s residence code  |
| **Diagnosis – Variables 19 to 57**  |
| 19\*\* | WHENDISC  | When discovered |
| 20 | CONDISC | Condition at discovery  |
| 21 | AGEDISC  | If prenatally diagnosed, gestational age at discovery |
| 22 | FIRST PRE | First positive prenatal test |
| 24 | KARYO  | Karyotype of infant/fetus  |
| 25 | SP\_KARYO  | Specify karyotype  |
| 26\* | GENTEST  | Genetic Test  |
| 27\* | SP\_GENTEST  | Specify genetic test  |
| 28 | PM  | Post mortem examination  |
| 29\*\* | SURGERY  | First surgery for malformation performed or planned  |
| 30 | SYNDROME  | Syndrome |
| 31 | SP\_SYNDROME  | Specify Syndrome  |
| 32 | MALFO1  | malformation |
| 33  | SP\_MALFO1  | Specify malformation  |
| 34  | MALFO2  | As MALFO1  |
| 35  | SP\_MALFO2  | Specify malformation  |
| 36  | MALFO3  | As MALFO1  |
| 37  | SP\_MALFO3  | Specify malformation  |
| 38  | MALFO4  | As MALFO1  |
| 39  | SP\_MALFO4  | Specify malformation  |
| 40  | MALFO5  | As MALFO1  |
| 41  | SP\_MALFO5  | Specify malformation  |
| 42 | MALFO6  | As MALFO1  |
| 43  | SP\_MALFO6  | Specify malformation  |
| 44  | MALFO7  | As MALFO1  |
| 45  | SP\_MALFO7  | Specify malformation  |
| 46  | MALFO8  | As MALFO1  |
| 47  | SP\_MALFO8  | Specify malformation  |
| 57# | OMIM  | OMIM code / Type of Mendelian Inheritance  |
| **Exposure and family history – variables 58 to 89** |
| 58\*\* | ASSCONCEPT | Assisted conception (where available) |
| 59##  | OCCUPMO  | Mother’s occupation at time of conception  |
| 60 | ILLBEF1 | Maternal illness before pregnancy 1 |
| 61 | ILLBEF2 | Maternal illness before pregnancy 2 |
| 64 | ILLDUR1 | Maternal illness during pregnancy 1 |
| 65 | ILLDUR2 | Maternal illness during pregnancy 2 |
| 79 | CONSANG | Consanguinity |
| 81 | SIBANOM | Sibs with congenital anomalies |
| 87 | MOANOM | Mother’s family with anomalies |
| 89 | FAANOM | Father’s family with anomalies |
| **Sociodemographic – Variables 91 to 94**  |
| 91 | MATEDU | Maternal education  |
| 92  | SOCM  | Socioeconomic status of mother  |
| 93  | SOCF  | Socioeconomic status of father  |
| 94  | MIGRANT  | Migrant status  |
| **EDMP-derived variables** |  |
|  | Byear | Year of birth |
|  | birth\_type | Definitions of stillbirths and spontaneous abortions vary between regions. This variable recodes birth type according to EUROCAT’s specifications: cases with gestational age ≥ 20 weeks are re-coded as “stillbirths” (irrespective of the local definition of stillbirth/spontaneous abortion). |
|  | Casestatus | Only cases with casestatus = 1 |
|  | al1-al114 | EUROCAT subgroups: (0 = No, 1 = Yes). Based on EUROCAT coding in Guide 1.4 |
|  | mult\_malf  | Algorithm for case classification into isolated and multiples |

\* New variable in Guide 1.4 from 2013

\*\* Variable compatible over time, but coding has been extended/modified

# Variable name change only

## Guide 1.4 use ISCO-08 classifications

**Table 4:** Variables from the Morbidity Study I protocol for cases and controls. Core variables shaded grey.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variable number** | **Variable Name** | **Variable Definition and Instructions** | **Variable Values/ format** | **Variable released to researcher** |
| 1 | L\_CH\_ID | Local ID number used to identify child | Unique identifier | No |
| 2 | L\_CH\_DATE\_B | Child’s date of birth  |  | No |
| 3 | L\_CH\_YEAR\_B | Child’s year of birth  | Four digits required e.g. 2005 | Yes |
| 4 | L\_CH\_SEX | Infant’s sex  | As recorded in the vital statistics or health care database | Yes |
| 5 | L\_DATE\_LOST | Date lost to follow-up/ linkage (i.e. due to emigration, adoption or other reason) |  | No |
| 6 | L\_YEAR\_LOST | Year child lost to follow-up/ linkage (i.e. due to emigration, adoption or other reason) | Four digits required e.g. 2005 | Yes |
| 7 | L\_AGEL\_D | Age at lost to follow-up in complete days | Numeric | Yes |
| 8 | L\_MORT\_MATCH | Match with vital statistics database (or, if not available, hospital episodes data) | 1= Matched 2= Not matched  | Yes |
| 9 | L\_CONFIDENCE | Strength of match with hospital episodes data | Please use your local data provider’s codes.If no local code available, a guideline on how to assess confidence in matching is found below# | Yes |
| 10 | L\_MAT\_CTRY\_B | Maternal country of birth/ place of birth/ country of origin | As recorded in the vital statistics or health care database | Yes |
| 11 | L\_MAT\_DOB | Maternal date of birth |  | No |
| 12 | L\_MAT\_YEAR\_B | Maternal year of birth | Four digits required e.g. 1980 | Yes |
| 13 | L\_MATAGE\_B\* | Maternal age at infant's birthCalculate maternal age (completed years) at infant’s date of birth  | Numeric | Yes |
| 14 | L\_MAT\_EDUC\* | Maternal education at infant’s birth | As recorded in the vital statistics or health care database | Yes |
| 15 | L\_MAT\_EMPL\* | Mother’s employment status at infant’s birth | As recorded in the vital statistics or health care database | Yes |
| 16 | L\_MAT\_OCC\* | Maternal occupation at infant’s birth | As recorded in the vital statistics or health care database | Yes |
| 17 | L\_MATDEPR\_IND | Quintile of Deprivation index of maternal residence at infant’s birth | As recorded in the vital statistics or health care database | Yes |
| 18 | L\_MATMAR\_STA | Maternal marital status at infant’s birth | As recorded in the vital statistics or health care database | Yes |
| 19 | L\_CH\_DATE\_D | Child’s date of death on the death certificate or in the mortality database |  | No |
| 20 | L\_CH\_YEAR\_D | Child’s year of death  | Four digits required e.g. 2006 | Yes |
| 21 | L\_CH\_AGED\_H | Age at death in complete hours for day 0 (first 24 hours) = applies to infants who died within the first 24 hours | 0 = Died <1 hour after birth1 = Died 1 complete hour after birth 2 = Died 2 complete hours after birth Etc23 = Died 23 complete hours after birth88 = Alive at 24 hours99 = Died within first 24 hours, but exact time unknown | Yes |
| 22 | L\_CH\_AGED\_D | Age at death in complete days (up to 10th birthday). Should be provided in days for infants who died after the first 24 hours.Subtract child’s date of birth from child’s date of death.If age at death in complete days is not available, please complete age at death in complete months (variable L\_CH\_AGED\_M) and/ or age at death in complete years (variable L\_CH\_AGED\_Y). | 0 = Died <1 complete day after birth1 = Died 1 complete day after birth 2 = Died 2 complete days after birth Etc8888 = Alive on 10th birthday9999 = Died before 10th birthday, but exact date unknown | Yes |
| 23 | L\_CH\_AGED\_M | Age at death in complete monthsOnly complete, if age at death in complete days (variable L\_CH\_AGED\_D) is not available | 0 = Died <1 complete month after birth1 = Died 1 complete months after birth 2 = Died 2 complete months after birth Etc888 = Alive on 10th birthday999 = Died before 10th birthday, but exact date unknown | No |
| 24 | L\_CH\_AGED\_Y | Age at death in complete yearsOnly complete, if age at death in complete days (variable L\_CH\_AGED\_D) is not available | 0 = Died <1 complete year after birth1 = Died 1 complete year after birth 2 = Died 2 complete years after birth Etc88 = Alive on 10th birthday99 = Died before 10th birthday, but exact date unknown | No |
| 25 | L\_CH\_GA\_B\* | Child’s gestational age at birth (in completed weeks) | As recorded in the vital statistics or health care database | Yes |
| 26 | L\_CH\_BW\* | Child’s birth weight (in grams) | As recorded in the vital statistics or health care database | Yes |
| 27 | L\_MULT\_BIRTH\* | Singleton or multiple birth  | As recorded in the vital statistics or health care database | Yes |
| 28 | L\_PARITY | Number of previous pregnancies | Numeric | Yes |
| 29 | L\_DATE\_ADM | Date of admission to hospital\* | Date | No |
| 30 | L\_YEAR\_ADM | Year of admission to hospital  | Four digits required e.g. 2005 | Yes |
| 31 | L\_DATE\_DIS | Date of discharge from hospital | Date | No |
| 32 | L\_HOSP\_DAYS | Length of stay in hospital (i.e. number of days) | Numeric | Yes |
| 33 | L\_CH\_AGE\_ADM\_D | Child’s age at hospital admission in complete days (up to 10th birthday). Subtract child’s date of birth from date of admission to hospital | Numeric | Yes |
| 34 | L\_DIAG\_DIS | Main diagnosis in ICD9 or ICD10 for the hospital stay | As recorded in the vital statistics or health care database | Yes |
| 35 | L\_DIAG\_SEC1 | Other diagnoses for the hospital stay (ICD9 or ICD10) | As recorded in the vital statistics or health care database | Yes |
| 36 | L\_DIAG\_SEC2 | Other diagnoses for the hospital stay (ICD9 or ICD10) | As recorded in the vital statistics or health care database | Yes |
| 37 | L\_DIAG\_SEC3 | Other diagnoses for the hospital stay (ICD9 or ICD10) | As recorded in the vital statistics or health care database | Yes |
| 38 | L\_DIAG\_SEC4 | Other diagnoses for the hospital stay (ICD9 or ICD10) | As recorded in the vital statistics or health care database | Yes |
| 39 | L\_DIAG\_SEC5 | Other diagnoses for the hospital stay (ICD9 or ICD10) | As recorded in the vital statistics or health care database | Yes |
| 40 | L\_DAYS\_ICU | Number of days in intensive care unit during hospital stay (Include Neonatal Intensive Care Unit, Paediatric Intensive Care Unit, or Intensive Care Unit) | Numeric | Yes |
| 41 | L\_DAYS\_VENT | Number of days on ventilator during hospital stay | Numeric  | Yes |
| 42 | L\_SURG\_CODE1 | Codes for surgery performed during hospital stay | As recorded in the vital statistics or health care database | Yes |
| 43 | L\_ SURG\_CODE2  | Codes for surgery performed during hospital stay | As recorded in the vital statistics or health care database | Yes |

\* If variable is unavailable in the vital statistics or health care database, please use the equivalent EUROCAT variable (see Table 2)

Guideline for coding L\_CONFIDENCE variable (for matching cases in different datasets)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **All 3 variables available in both datasets for each individual child** | **Only 2 variables present in both datasets** **for each individual child** | **Only 1 variable available in both datasets for each individual child** |
| Unique ID | Matched | Not Matched | Matched | Matched | - | Matched | Matched | - | - | Matched | Not matched | Matched | - | - |
| Child’s date of birth | Matched | Matched | Not Matched | Matched | Matched | - | Matched | Matched | Not matched | - | - | - | Matched | - |
| Maternal age | Matched | Matched | Matched | Not Matched | Matched | Matched | - | Not matched | Matched | Not matched | matched | - | - | Matched |
| **Final code** | **Excellent** | **Fair** | **Fair** | **Good** | **Fair** | **Fair** | **Good** | **Poor** | **Not linked** | **Fair** | **Not linked** | **Fair** | **Poor** | **Not linked** |

The “-“ symbol = Not present

If all 3 variables present and matched, code=EXCELLENT

If 2 variables present and both matched, code=GOOD if the 2 variables are unique ID number and child’s DOB

If 2 variables present and both matched, code=FAIR if unique ID number is not one of the 2 variables

If 2 variables present and only 1 matched, code=FAIR if unique ID number is matched

If 2 variables present and only 1 matched, code=POOR if unique ID number is the unmatched variable

If 1 variable present and matched, code=FAIR if it is unique ID number

**Table 5 Variables from prescription databases for cases and controls. Core variables shaded grey.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variable number** | **Variable Name** | **Variable Definition and Instructions** | **Variable Values/ format** | **Variable released to researcher** |
| 44 | L\_AGE\_PX | Child’s age at prescription in complete days (up to 10th birthday). Subtract child’s date of birth from the date prescription was issued | Numeric | Yes |
| 45 | L\_DATE\_PX | Date prescription was issued/ dispensed\* # | Date | No |
| 46 | L\_DRUG\_CODE | Codes for medications (ATC, BNF or Read) | As recorded in prescription database | Yes |
| 47 | L\_MED\_DAYS | Number of days the product is to be taken | As recorded in prescription database | Yes |
| 48 | L\_MED\_PACKET | Number of packets/units of the product dispensed | As recorded in prescription database | Yes |
| 49 | L\_GP\_HOSP | Indicates if GP or hospital prescription (for Italian registries only) |  | No |

\*Note the difference in terminology between the UK and continental Europe - in the UK, information is available for when a prescription is issued by a General Practitioner, while in continental Europe, information is available for when a prescription is redeemed/ dispensed by the pharmacy.

# Please provide a record for each prescription issued for the following conditions:

* Asthma (ATC codes beginning with R03)
* Cardiac (ATC codes beginning with C01-C03, C07-C09)
* Diabetes (ATC codes beginning with A10)
* Epilepsy (ATC codes beginning with N03)
* Infections (ATC codes beginning with J01-J05).

13 registries:

ATC codes provided by 6 registries

BNF codes provided by 5 registries (BINOCAR)

Read codes provided by 1 registry

**Table 6: Additional congenital anomalies for analysis**

|  |  |  |
| --- | --- | --- |
|  | ICD10 | ICD9 |
| Structural anomalies |  |  |
| Anomalies of corpus callosum | Q040 | 74221 |
| Megalencephaly | Q045 | No code |
| Anomalies of intestinal fixation | Q433 | 7514 |
| Unilateral renal agenesis | Q600 | No code |
| Accessory kidney | Q630 | 75330 |
| Bladder exstrophy | Q641 | 7535 |
| Epispadia | Q640 | 75261 |
| Posterior urethral valves | Q6420 | 75360 |
| Prune Belly | Q794 | 75672 |
| Arthrogryposis multiplex congenita | Q743 | 75580 |
| Ectodermal dysplasia | Q824 | No code |
| Genetic syndromes |  |  |
| Alagille syndrome | Q4471 | No code |
| Meckel-Gruber syndrome | Q6190 | No code |
| Di George syndrome | D821 | 27910 |
| Goldenhar syndrome | Q8704 | 75606 |
| Cornelia de Lange syndrome | Q8712 | 759821 |
| Noonan syndrome | Q8714 | 759896 |
| Prader-Willi | Q8715 | 759872 |
| Holt-Oram syndrome | Q8720 | 759842 |
| Beckwith Wiedeman syndrome | Q8730 | 759874 |
| Williams syndrome | Q8784 | No code |
| Angelman syndrome | Q8785 | No code |
| Chromosomal anomalies |  |  |
| Wolff-Hirschhorn syndrome | Q933 | 75832 |
| Cri-du chat syndrome | Q934 | 75831 |
| Karyotype XXX | Q970 | 75885 |
| Sequences |  |  |
| Caudal regression sequence | Q8980 | No code |
| Pierre-Robin sequence | Q8708 | 75603 |

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