

**EUROlinkCAT WP4 - Medication use in children with congenital anomalies as a measure of co-morbidities**

**Statistical analysis plan for WP4 Morbidity Study II – VERSION 1.2**

**Aim**: To evaluate specific medication use as an indication of the presence of co-morbidities in children up to 10 years of age with and without congenital anomalies

***Medication exposure data***

The medications of interest are:

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

***Age categories of children***

<1 years, 1-4 years and 5-9 years.

***Congenital anomaly groups***

Unless specified otherwise the CA groups used in the below tables are:

* 1. All anomalies subgroup (al1)
  2. Isolated anomalies[[1]](#footnote-1) (mult\_malf=A,R,N,I) (spina bifida, hydrocephalus, severe microcephaly, CHD, severe CHD, transposition of the great vessels, VSD, ASD, Tetralogy of Fallot, coarctation of the aorta, PDA, cleft lip with or without cleft palate, cleft palate, oesophageal atresia, anorectal atresia, diaphragmatic hernia, gastroschisis, multicystic renal dysplasia, congenital hydronephrosis, hypospadias, limb reduction defects, club foot, hip dislocation and craniosynostosis)
  3. Chromosomal anomalies – Down syndrome (all, with CHD, without CHD), Turner syndrome
  4. Rare anomalies - anomalies of the Corpus Callosum and Di George syndrome.

***Risk factors***

The following risk factors will be investigated:

* time period, sex, gestational age, maternal age, maternal non-resident/migrant status, and SES.

**Statistical analysis**

**Background data for paper – as per morbidity**

Number of cases (all anomalies, CA subgroups, and isolated CA) and controls, by 3 time periods (2000-2004, 2005-2009, 2010-2014).

**Frequency tables (descriptive stats) for study subjects**

1. Denominator tables
2. Total number, and number in each risk factor category, for controls and congenital anomalies by EUROCAT subgroup.
3. Total number of person years of follow-up, and person-years in each risk factor category, for controls and congenital anomalies by EUROCAT subgroup

**Stage I analysis:**

**Note: If cell counts are low, age groups will be collapsed**

**ANTI-INFECTIVES**

**Note:** When 2 or more prescriptions are redeemed with ≤14 day’s interval, we will count them as 1 treatment episode. The last antibiotic prescribed in this interval will be used in the analysis – it is assumed this is the appropriate antibiotic to treat the infection.

The anti-infective categories used in the below tables are:

* Any anti-infective (J01-J05)
* Antibacterials for systemic use (J01)
  + Amphenicols (J01B)
  + Beta-lactam antibacterials, penicillin’s (J01C)
  + Sulfonamides and Trimethoprim (J01E)
  + Macrolides, Lincosamides and Streptogramins (J01F)
  + Quinolone antibacterials (J01M)
  + Other antibacterials (J01X)
* Antimycotic for systemic use (J02)
* Antimycobacterials (J04)
* Antivirals for systemic use (J05)

Table 2 a-i Number of children with a prescription (can be used with table 1 to calculate period prevalence), number of prescriptions per person-year (annual prescription rate) and median and 95% CI number of prescriptions per person-yearfor a J01 anti-infective medication (above categories) across risk factors by age at prescription (<1 years, 1-4 years and 5-9 years of age). For the drug groups J02, J04 and J05, only the number of children with a prescription by age at prescription (<1 years, 1-4 years and 5-9 years of age) will be examined.

Table 3 A-C Cumulative incidence (1-Kaplan-Meier survival estimate) of at least one prescription for an anti-infective medication (by categories) for cases and controls a) <1 year; b) 1-4 years and c) 5-9 years.

# ASTHMA

The medication categories to be used are:

* Any asthma medication (R03)
  + Inhaled β2- agonists (R03AC)
  + Inhaled corticosteroids (R03BA)
  + Anticholinergic inhaled medications (R03BB)
  + Antiallergic agents, excl. corticosteroids (R03BC)
  + Xanthanes (R03DA)
  + Leukotriene receptor antagonists (R03DC)

**Note: We will not analyse the number of prescriptions for anti-asthmatics as treatment varies from occasional use to daily use). The below tables are based on at least two prescriptions for an R03 medication as these children are more likely to have asthma.**

Table 1 a-g Number of children with at least two prescriptions (can be used with table 1 to calculate period prevalence), for an anti-asthmatic medication (above categories) across risk factors by age at prescription (0-4 years and 5-9 years of age). 0-4 years used as asthma is difficult to diagnose <1.

Table 2 A-B Cumulative incidence (1-Kaplan-Meier survival estimate) of at least two prescriptions for an anti-asthmatic medication (by categories) for cases and controls a) 0-4 years; b) 5-9 years. 0-4 years used as asthma is difficult to diagnose <1.

# CARDIAC

**Note: the exploration of the use of cardiac medications will be restricted to controls, cardiac anomalies, Down syndrome with CHD, Turner syndrome and Di George syndrome.**

The cardiac medication categories to be used in the below tables are:

* Any cardiac medication (ATC C)
  + Cardiac therapy (C01)
  + Antihypertensives (C02) excluding all central α-blockers (C02AC) e.g. clonidine C02AC01/ C02AC02 guanfacine) because of their use in ADHD
  + Diuretics (C03)
  + Beta blocking agents (C07)
  + Calcium Channel Blockers (C08)
  + Agents acting on the renin-angiotensin system (C09)

1. a-g Number of children with a prescription (can be used with table 1 to calculate period prevalence for a cardiac medication (above categories) across risk factors by age at prescription (<1 years, 1-4 years and 5-9 years of age).
2. A-B Cumulative incidence (1-Kaplan-Meier survival estimate) of at least one prescription for a cardiac medication (by categories) for cases and controls a) <1 year; b) 1-4 years and c) 5-9 years.

# ANTI-EPILEPTICS

Note: **The below tables are based on at least two prescriptions in an attempt to ensure that only those with epilepsy are included.**

The anti-epileptic drug groups used in the below tables are:

* Any antiepileptic (ATC N03)
  + Barbiturates and derivatives (N03AA)
  + Hydantoin derivatives (N03AB)
  + Succinimide derivatives (N03AD)
  + Benzodiazepine derivatives (N03AE)
  + Carboxamide derivatives (N03AF)
  + Fatty acid derivatives (N03AG)
  + Other antiepileptics **(**N03AX)

1. a-h Number of children with at least two prescriptions (can be used with table 1 to calculate period prevalence) for an AED (above categories) across risk factors by age at prescription (<1 years, 1-4 years and 5-9 years of age).
2. A-C Cumulative incidence (Kaplan-Meier survival estimate) of at least two prescriptions for an AED (by categories) for cases and controls a) <1 year; b) 1-4 years and c) 5-9.

# ANTI-DIABETICS

The anti-diabetic medication categories used in the below tables are:

* Any antidiabetic medication (A10)
  + Insulins and analogues (A10A)
  + Blood glucose lowering drugs, excluding Insulins (A10B)

1. a-c Number of children with a prescription (can be used with table 1 to calculate period prevalence), across risk factors by age at prescription (0-4 years and 5-9 years of age). 0-4 years used as diabetes is rare in those <1.
2. A-B Cumulative incidence (1-Kaplan-Meier survival estimate) of at least one prescription for any antidiabetic medication (A10 categories) for cases and controls a) 0-4 years and b) 5-9 years. 0-4 years used as diabetes is rare in those <1.

**Pan European analysis**

To combine the prevalence of medication use in cases and controls across registries METAPROP or METAN (using the Freeman-Tukey Double Arcsine Transformation to stabilise the variance) will be used. The I2 statistic will describes the percentage of total variation across registries. The difference in risk could be examined using MVMETA again with the Freeman-Tukey Double Arcsine Transformation to stabilise the variance.

1. Anomalies selected based on a livebirth prevalence of ≥ 1.75 per 10,000 births [↑](#footnote-ref-1)