**Online appendix**

**Table 1A:** **Study population (births) by country and year.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Country | Years included  | Years included in medication analysis | 1982-1991 | 1992-2001 | 2002-2011 | Total study years 1982-2011 |
| Denmark (Odense) | 1982-2011 | 1995-2011 | 49,475 | 5,7936 | 52,184 | 159,595 |
| France (Paris) | 1982-1011 | 2001-2011 | 365,807 | 361,464 | 267,343 | 994,614 |
| Netherlands(Northern) | 1982-2011 | 1995-2001 | 124,583 | 196,761 | 184,777 | 506,121 |
| Switzerland (Vaud) | 1989-2011 | 1997-2001 | 23,120 | 76,232 | 74,810 | 174,162 |
| Malta | 1986-2010 | 1996-2011 | 32,491 | 47,238 | 35,984 | 115,713 |
| Belgium (Antwerp) | 1990-2011 | 1997-2011 | 8,428 | 135,969 | 197,176 | 341,573 |
| Germany (Saxony) | 1987-2011 | 2000-2011 | 72,877 | 106,958 | 173,009 | 352,844 |
| Ukraine | 2005-2011 | 2005-2011 |  |  | 208,772 | 208,772 |
| Ireland\* | 1996-2011 | 1996-2011 |  | 74,817 | 157,571 | 232,388 |
| Italy\* | 1982-2011 | 1995-2011 | 315,353 | 507,186 | 674,268 | 1,496,807 |
| UK (Wales) | 1998-2011 | 1998-2011 |  | 128,106 | 338195 | 466,301 |
| Spain\* | 1990-2010 | 1995-2011 | 32,729 | 163,572 | 399,121 | 595,422 |
| Total | 1982-2011 | 1995-2011 | 1,024,863 | 1,856,239 | 2,763,210 | 5,644,312 |
| Ireland = Cork and Kerry 1996-2010 & SE Ireland 1997-2010 \* Italy = Tuscany 1982-2011 & Emilia Romagna 1982-2011\*Spain = Basque Country 1990-2010 & Valencia 2007-2010 |

**Table 2A: ICD9 /10 codes and Drug (ACT) codes used in the analysis**

|  |  |  |  |
| --- | --- | --- | --- |
| Disease / Condition / Anomaly | ICD10 | ICD9 | ACT |
| Ebstein’s anomaly | Q22.5 | 746.2 |  |
|  |  |  |  |
| Beta-thalassemia | D561 | 282.4 |  |
| Haemorrhage in pregnancy | O20\* | 640\* |  |
| Genitourinary infection in pregnancy | O23\* | 646.6 |  |
| Depression | F32/33 | 311\* |  |
| Anxiety | F41\* | 300\* |  |
| Mental illness | F\* | 29\*/30\*/31\* |  |
| Diabetes | E10\*/11\*/12\*/13\*/14\* | 249\*250\* |  |
| Gestational Diabetes | 0244/9 | 6480/8 |  |
| Antibiotics |  |  | J01\* |
| Psycholeptics |  |  | N05\* |
| Antidepressants |  |  | N06A\* |
| SSRI |  |  | N06AB\* |

**Table 3A: Genetic and teratogenic syndromes diagnosed in Ebstein’s Anomaly cases who were excluded from the case malformed control study.**

|  |  |  |
| --- | --- | --- |
| Case  | Diagnosis | Karyotype |
| 1 | Additional marker autosomes | Unknown |
| 2 | Other loss of autosomal material | Unknown |
| 3 | Down syndrome | 47,XY,+21 |
| 4 | Down syndrome | Unknown |
| 5 | Turner syndrome | Unknown |
| 6 | Partial trisomy | 46,XY,der(20)t(2;20) |
| 6 | Down syndrome | 47, XY, +21  |
| 8 | Down syndrome | Unknown |
| 9 | Down syndrome | 47, XX + 21 |
| 10 | Down syndrome | 47,XX,+21 |
| 11 | Down syndrome | 47,XX+21 |
| 12 | Prader-Willi syndrome | unknown |
| 13 | Pena Shokeir syndrome | unknown |
| 14 | Maternal cytomegalovirus | - |

**Table 3A: Number of Ebstein’s anomaly cases with relevant family history**

|  |  |  |
| --- | --- | --- |
| Family History | No. of EA cases | Remarks |
| Co-twin with EA | 2 (I twin pair) | Twin to twin transfusion |
| EA | 1 | Cousin (not in our data) |
| Pena Shokeir syndrome | 1 (case 13) | Sibling without EA |
| Congenital Cardiac anomaly | 2 | First degree relatives |
| Congenital Cardiac anomaly | 9 | Second degree relatives |
| Chromosomal anomaly | 1 | Co-twin without EA |

**Table 5A**

**Table 5A: Non-CHD congenital anomalies seen in non-syndromic Ebstein’s anomaly cases**

|  |  |  |
| --- | --- | --- |
| Congenital anomaly | Multiple anomalies\*, no. and (%) of EA cases | Multiple anomalies\*, no. and (%) of non- EA CHD cases |
| Any non-CHD anomaly | 22(8.80) | 6326 (17.6) |
| Eye | 3 (1.20) | 347 (0.97) |
| Nervous system | 4 (1.60) | 1,113 (3.10) |
|  Hydrocephalus | 1 (0.40) | 299 (0.83) |
|  Microcephaly | 1 (0.40) | 215 (0.60) |
| Oro-facial clefts | 3 (1.20) | 593 (1.65) |
|  Cleft lip with or without palate | **2 (0.80)** | **323 (0.90)** |
|  Cleft palate | 1 (0.40) | 270 (0.75) |
| Ear face and neck | 3 (0.80) | 326 (0.91) |
| Respiratory | 3 (1.20) | 613 (1.71) |
| Digestive system | 6 (2.39) | 1,360 (3.79) |
|  Diaphragmatic hernia | 2 (0.80) | 189 ((0.53) |
| Urinary | 4 (1.20) | 1,345 (3.75) |
|  Congenital hydronephrosis | 2 (0.80) | 329 (0.92) |
| Genital | 3 (1.20) | 593 (1.65) |
|  hypospadias | 2 (0.80) | 397 (1.11) |
| Lmb | 3 (1.20) | 1,383 (3.85) |
|  Hip dislocation (non-isolated) | 1 (0.40) | 157 (0.44) |
|  Polydactyly | 2 (0.80) | 243 (0.68) |
|  Syndactyly | 1 (0.40) | 161 (0.45) |
| Craniosynostosis | 1 (0.40) | 70 (0.19) |

NB Ebstein’s anomaly cases may appear more than once in this table if they have more than one other major congenital anomaly

**Table 6A: Ebstein’s anomaly: Prevalence per 10,000 total births over time and by country 1982-2011**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Country | n | 1982-1991 | n | 1992-2001 | n | 2002-2011 | n | 1982-2011 |
| Denmark | 4 | 0.81 (0.30-2.15) | 5 | 0.86 (0.36-2.07) | 1 | 0.19 (0.03-1.36) | 10 | 0.63 (0.34-1.16) |
| France | 9 | 0.25 (0.13-0.47) | 24 | 0.66 (0.45-0.99) | 28 | 1.05 (0.72-1.52) | 61 | 0.61 (0.48-0.79) |
| Netherlands | 6 | 0.48 (0.22-1.07) | 9 | 0.46 (0.24-0.88) | 11 | 0.60 (0.33-1.07) | 26 | 0.51 (0.35-0.75) |
| Switzerland | 3 | 1.30 (0.42-4.02) | 6 | 0.79 (0.35-1.75) | 4 | 0.53 (0.20-1.42) | 13 | 0.75 (0.43-1.29) |
| Malta | 2 | 0.62 (0.15-2.46) | 4 | 0.85 (0.32-2.26) | 5 | 1.39 (0.58-3.34) | 11 | 0.95 (0.53-1.72) |
| Belgium | 1 | 1.19 (0.17-8.42) | 5 | 0.37 (0.15-0.88) | 6 | 0.30 (0.14-0.68) | 12 | 0.35 (0.20-0.62) |
| Germany | 0 | 0 | 3 | 0.28 (0.09-0.87) | 9 | 0.52 (0.27-1.00) | 12 | 0.34 (0.19-0.60) |
| Ukraine |  | - |  | - | 13 | 0.62 (0.36-1.07) | 13 | 0.62 (0.36-1.07) |
| Ireland |  | - | 4 | 0.53 (0.20-1.42) | 7 | 0.44 (0.21-0.93) | 11 | 0.47 (0.26-0.85) |
| Italy | 3 | 0.10 (0.03-0.29) | 22 | 0.43 (0.29-0.66) | 15 | 0.22 (0.13-0.37) | 40 | 0.27 (0.20-0.36) |
| Wales | 0 |  | 11 | 0.86 (0.48-1.55) | 21 | 0.62(0.40-0.95) | 32 | 0.69 (0.49-0.97) |
| Spain | 1 | 0.31 (0.04-2.17) | 10 | 0.61 (0.33-1.14) | 12 | 0.30 (0.17-0.53) | 23 | 0.39 (0.26-0.58) |
| Total | **29** | **0.29 (0.20-0.41)** | **103** | **0.55 (0.46-0.67)** | **132** | **0.48 (0.40-0.57)** | **264** | **0.47 (0.41-0.53)** |

**Figure 1A: Flowchart showing data used in each exclusions and numbers included in each group of analyses**

173 cases

51,024 non cardiac controls

78,678 non-cardiac controls

26,170 cardiac controls

35,904 cardiac controls

Used in the medication case malformed-control analyses

Used in the main case malformed-control analyses

250 cases

144,820

Babies/fetuses with other congenital anomalies

Controls

264

Babies/fetuses with Ebstein’s anomaly

Cases

Used in the prevalence analyses

145,084 babies/fetuses with of major congenital anomaly

Population

5,644,312 births