Supplementary Table 1: Odds ratios (and 95% confidence intervals) for exposure to benzodiazepine medication in the month before through the third month of pregnancy and risk for specific isolated birth defects, National Birth Defects Prevention Study, 1997 – 2011

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Defect category | Any benzodiazepine | Alprazolam | Clonazepam | Diazepam | Lorazepam |
| Any neural tube defect | 1.2 [0.7, 2.1] | 1.5 [0.7, 3.3] | 1.3 [0.5, 3.6] | -- | -- |
| Anencephaly | 1.4 [0.5, 3.5] | -- | -- | -- | -- |
| Spina bifida | 0.9 [0.4, 2.1] | 1.1 [0.4, 3.1] | 1.5 [0.4, 5.0] | -- | -- |
| Hydrocephaly | -- | -- | -- | -- | -- |
| Dandy-Walker malformation | -- | -- | -- | -- | -- |
| Anophthalmia / microphthalmia | -- | -- | -- | -- | -- |
| Anotia / microtia | 2.3 [0.9, 5.9] | -- | 3.5 [1.0, 11.8] | -- | -- |
| Cleft lip with or without cleft palate | 1.1 [0.7, 1.8] | 0.8 [0.4, 1.7] | 1.1 [0.5, 2.9] | 1.2 [0.4, 3.2] | 2.4 [0.7, 8.2] |
| Cleft palate alone | 1.3 [0.7, 2.4] | 1.6 [0.7, 3.4] | -- | -- | -- |
| Esophageal atresia / stenosis | 3.0 [1.4, 6.2] | 4.5 [1.8, 11.3] | -- | -- | -- |
| Anorectal atresia / stenosis | -- | -- | -- | -- | -- |
| Hypospadias | 0.4 [0.2, 0.8] | 0.4 [0.1, 1.0] | 1.0 [0.3, 3.6] | -- | -- |
| Preaxial longitudinal limb deficiency | -- | -- | -- | -- | -- |
| Transverse limb deficiency | 1.0 [0.3, 2.6] | -- | -- | -- | -- |
| Craniosynostosis | 0.5 [0.3, 1.1] | -- | -- | -- | -- |
| Diaphragmatic hernia | -- | -- | -- | -- | -- |
| Omphalocele | 1.7 [0.5, 5.4] | -- | -- | -- | -- |
| Gastroschisis | 1.4 [0.7, 2.9] | 1.0 [0.3, 2.7] |  | -- | 3.9 [1.0, 15.1] |
| **Any NBDPS Congenital Heart Defect [CHD]** | 0.8 [0.5, 1.1] | 0.6 [0.3, 1.0] | 0.7 [0.4, 1.4] | 0.6 [0.3, 1.4] | 1.4 [0.6, 3.7] |
| Conotruncal CHD | 1.1 [0.7, 1.9] | 0.7 [0.3, 1.9] | 1.2 [0.4, 3.1] | 1.1 [0.3, 3.7] | 1.8 [0.5, 6.4] |
| D-transposition of the great arteries | 1.0 [0.4, 2.5] | -- | -- | -- | -- |
| Tetralogy of Fallot | 1.4 [0.7, 2.6] | 1.4 [0.6, 3.7] | 1.8 [0.5, 5.9] | -- | -- |
| Septal CHD | 0.7 [0.4, 1.2] | 0.5 [0.2, 1.3] | 0.8 [0.3, 2.5] | -- | -- |
| Perimembranous ventricular septal defect | 0.5 [0.2, 1.5] | -- | -- | -- | -- |
| Atrial septal defect [ASD] secundum or NOS | 0.8 [0.4, 1.5] | 0.8 [0.3, 2.2] | -- | -- | -- |
| Atrioventricular septal defect | 2.5 [0.8, 8.1] | -- | -- | -- | -- |
| Right ventricular outflow tract obstruction | 0.8 [0.4, 1.6] | 0.7 [0.2, 2.2] | -- | -- | 3.6 [0.9, 13.9] |
| Pulmonary valve stenosis [PVS] | 1.0 [0.5, 2.0] | 0.9 [0.3, 2.8] | -- | -- | 4.6 [1.2, 17.9] |
| Left ventricular outflow tract obstruction | 0.4 [0.2, 1.0] | -- | -- | -- | -- |
| Coarctation of the aorta | -- | -- | -- | -- | -- |
| Aortic stenosis | -- | -- | -- | -- | -- |
| Ventricular septal defect and ASD | -- | -- | -- | -- | -- |
| PVS and ASD | -- | -- | -- | -- | -- |

NOS = not otherwise specified

Supplementary Table 2: Odds ratios (and 95% confidence intervals) for exposure to benzodiazepine medication in the month before through the third month of pregnancy and risk for specific birth defects, stratified by antidepressant medication use, National Birth Defects Prevention Study, 1997 – 2011

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Defect category | Any benzodiazepine | | Alprazolam | | Clonazepam | | Diazepam | | Lorazepam | |
| No AD | Any AD | No AD | Any AD | No AD | Any AD | No AD | Any AD | No AD | Any AD |
| Any neural tube defect | 1.1  [0.5, 2.2] | 0.8  [0.3, 2.0] | 1.7  [0.7, 4.1] | 0.3  [0, 2.6] | -- | -- | -- | -- | -- | -- |
| Anencephaly | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| Spina bifida | 0.8  [0.3, 2.3] | 0.7  [0.2, 2.5] | 1.3  [0.4, 4.2] | 0.5  [0.1, 4.2] | -- | -- | -- | -- | -- | -- |
| Hydrocephaly | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| Dandy-Walker malformation | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| Anophthalmia / microphthalmia | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| Anotia / microtia | 1.1  [0.3, 3.6] | 1.6  [0.5, 5.7] | -- | -- | -- | -- | -- | -- | -- | -- |
| Cleft lip with or without cleft palate | 1.2  [0.7, 2.2] | 1.2  [0.6, 2.3] | 1.2  [0.5, 2.8] | 0.9  [0.3, 2.6] | 1.1  [0.2, 5.1] | 1.0  [0.3, 3.1] | -- | -- | -- | -- |
| Cleft palate alone | 1.6  [0.8, 3.2] | 0.9  [0.3, 2.3] | -- | -- | -- | -- | -- | -- | -- | -- |
| Esophageal atresia / stenosis | 2.4  [1.1, 5.4] | 1.2  [0.4, 3.6] | 3.6  [1.3, 9.4] | 2.1  [0.6, 7.4] | -- | -- | -- | -- | -- | -- |
| Anorectal atresia / stenosis | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| Hypospadias | 0.6  [0.3, 1.4] | 0.3  [0.1, 1.0] | -- | -- | -- | -- | -- | -- | -- | -- |
| Preaxial longitudinal limb deficiency | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| Transverse limb deficiency | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| Craniosynostosis | 0.5  [0.2, 1.6] | 0.7  [0.3, 1.7] | -- | -- | -- | -- | -- | -- | -- | -- |
| Diaphragmatic hernia | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| Omphalocele | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| Gastroschisis | 1.5  [0.7, 3.1] | 0.4  [0.1, 1.6] | -- | -- | -- | -- | -- | -- | -- | -- |
| **Any NBDPS Congenital Heart Defect [CHD]** | 0.9  [0.6, 1.4] | 0.9  [0.6, 1.4] | 0.7  [0.4, 1.3] | 0.7  [0.3, 1.4] | 1.2  [0.5, 3.3] | 0.7  [0.3, 1.5] | 0.8  [0.4, 1.8] | 0.8  [0.2, 2.7] | 2.2  [0.6, 8.7] | 1.2  [0.3, 4.1] |
| Conotruncal CHD | 0.9  [0.4, 1.9] | 1.3  [0.7, 2.4] | 0.6  [0.2, 2.1] | 0.4  [0.1, 1.8] | -- | -- | -- | -- | -- | -- |
| D-transposition of the great arteries | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| Tetralogy of Fallot | 1.3  [0.6, 3.1] | 1.6  [0.7, 3.6] | -- | -- | -- | -- | -- | -- | -- | -- |
| Septal CHD | 1.2  [0.7, 2.0] | 0.7  [0.4, 1.4] | 0.9  [0.4, 2.0] | 0.7  [0.2, 1.8] | 1.8  [0.6, 5.6] | 0.8  [0.3, 2.1] | -- | -- | -- | -- |
| Perimembranous ventricular septal defect | 1.1  [0.5, 2.4] | 0.8  [0.3, 2.2] | -- | -- | -- | -- | -- | -- | -- | -- |
| Atrial septal defect [ASD] secundum or NOS2 | 1.5  [0.9, 2.7] | 0.7  [0.3, 1.6] | 1.2  [0.5, 2.9] | 1.0  [0.4, 2.8] | 1.6  [0.4, 6.4] | 0.2  [0, 1.8] | -- | -- | -- | -- |
| Atrioventricular septal defect | 2.1  [0.7, 6.9] | 2.0  [0.6, 7.0] | -- | -- | -- | -- | -- | -- | -- | -- |
| Right ventricular outflow tract obstruction | 0.8  [0.3, 1.8] | 1.3  [0.7, 2.5] | -- | -- | -- | -- | -- | -- | -- | -- |
| Pulmonary valve stenosis [PVS] | 1.0  [0.4, 2.3] | 1.3  [0.6, 2.7] | -- | -- | -- | -- | -- | -- | -- | -- |
| Left ventricular outflow tract obstruction | 0.8  [0.4, 1.8] | 0.5  [0.2, 1.2] | -- | -- | -- | -- | -- | -- | -- | -- |
| Coarctation of the aorta | 0.7  [0.2, 2.2] | 0.6  [0.2, 2.1] | -- | -- | -- | -- | -- | -- | -- | -- |
| Aortic stenosis | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| Ventricular septal defect and ASD | 1.4  [0.5, 3.8] | 1.3  [0.4, 4.4] | -- | -- | -- | -- | -- | -- | -- | -- |
| PVS and ASD | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |

AD = antidepressant medication; NOS = not otherwise specified