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| Table E1. Associations between early pregnancy asthma medication use and isolated non-cardiac birth defects and simple isolated congenital heart defects, National Birth Defects Prevention Study 1997–2011. | | | | | | |
| **Birth Defect** | **All Cases** | | | **Isolated Cases** | | |
| **Unexposed** | **Exposed** | **aOR/cOR (95% CI)** a | **Unexposed** | **Exposed** | **aOR/cOR (95% CI)** a |
| *Controls* | 10,445 | 449 |  | 10,445 | 449 |  |
| *Non-cardiac Birth Defects* |  |  |  |  |  |  |
| Amniotic band sequence | 292 | 15 | 1.13 (0.66, 1.93) | 244 | 13 | 1.17 (0.66, 2.08) |
| Anencephaly | 593 | 25 | 1.07 (0.71, 1.62) | 530 | 22 | 1.05 (0.68, 1.63) |
| Spina bifida | 1,137 | 47 | 0.99 (0.73, 1.36) | 999 | 42 | 1.01 (0.73, 1.41) |
| Encephalocele | 202 | 6 | 0.76 (0.33, 1.72) | 150 | 3 | 0.47 (0.10, 1.40) |
| Holoprosencephaly | 146 | 10 | 1.62 (0.82, 3.22) | 102 | 10 | **2.31 (1.15, 4.64)** |
| Dandy-Walker malformation | 157 | 9 | 1.27 (0.62, 2.63) | 98 | 7 | 1.83 (0.84, 4.00) |
| Hydrocephaly | 444 | 21 | 1.06 (0.67, 1.68) | 308 | 14 | 1.07 (0.62, 1.84) |
| Cerebellar hypoplasia | 51 | 5 | 2.19 (0.86, 5.56) | 29 | 4 | 3.21 (0.82, 9.19) |
| Ano/microphthalmia | 205 | 6 | 0.69 (0.31, 1.58) | 124 | 4 | 0.75 (0.20, 1.98) |
| Congenital cataracts | 313 | 14 | 0.92 (0.52, 1.63) | 279 | 13 | 0.94 (0.52, 1.70) |
| Glaucoma b | 163 | 5 | 0.75 (0.31, 1.84) | 136 | 3 | 0.52 (0.11, 1.56) |
| Ano/microtia b | 631 | 22 | 0.97 (0.62, 1.53) | 16 | 441 | 1.04 (0.61, 1.76) |
| Choanal atresia | 136 | 11 | 1.79 (0.95, 3.35) | 9 | 71 | **2.70 (1.33, 5.49)** |
| Cleft palate only c | 1,415 | 78 | 1.17 (0.91, 1.50) | 1,141 | 63 | 1.14 (0.86, 1.50) |
| Cleft lip only c | 962 | 58 | 1.31 (0.99, 1.74) | 897 | 56 | **1.38 (1.04, 1.84)** |
| Cleft lip with cleft palate c | 1,819 | 86 | 1.10 (0.87, 1.40) | 1,550 | 73 | 1.08 (0.84, 1.40) |
| Esophageal atresia | 640 | 36 | 1.28 (0.81, 2.01) | 266 | 19 | 1.56 (0.96, 2.52) |
| Duodenal atresia/stenosis | 192 | 12 | 1.48 (0.81, 2.68) | 117 | 8 | 1.63 (0.79, 3.38) |
| Small intestinal atresia/stenosis | 416 | 22 | 1.28 (0.81, 2.01) | 355 | 19 | 1.31 (0.81, 2.14) |
| Colonic atresia/stenosis | 51 | 1 | NC | 45 | 1 | NC |
| Anorectal atresia/stenosis | 960 | 31 | 0.71 (0.49, 1.05) | 415 | 12 | 0.61 (0.33, 1.11) |
| Biliary atresia | 176 | 11 | 1.53 (0.82, 2.85) | 150 | 9 | 1.50 (0.75, 2.97) |
| Hypospadiasd | 2,242 | 105 | 1.02 (0.79, 1.30) | 2,022 | 94 | 1.03 (0.80, 1.33) |
| Renal agenesis/hypoplasia | 169 | 8 | 1.10 (0.54, 2.27) | 118 | 7 | 1.32 (0.61, 2.87) |
| Bladder exstrophy | 61 | 5 | 1.64 (0.65, 4.11) | 45 | 3 | 1.55 (0.31, 4.86) |
| Cloacal exstrophy | 91 | 3 | 0.77 (0.15, 2.33) | 54 | 1 | NC |
| Longitudinal limb deficiency e | 458 | 37 | **1.81 (1.27, 2.58)** | 260 | 25 | **2.11 (1.38, 3.22)** |
| Transverse limb deficiency | 643 | 29 | 1.00 (0.67, 1.48) | 539 | 22 | 0.91 (0.58, 1.43) |
| Craniosynostosis | 1,412 | 63 | 0.93 (0.71, 1.23) | 1,277 | 56 | 0.91 (0.68, 1.21) |
| Diaphragmatic hernia | 764 | 22 | 0.67 (0.43, 1.03) | 591 | 17 | 0.67 (0.41, 1.09) |
| Omphalocele | 382 | 18 | 1.05 (0.65, 1.71) | 227 | 10 | 0.97 (0.51, 1.86) |
| Gastroschisis | 1,216 | 74 | 1.31 (0.99, 1.75) | 1,101 | 69 | **1.39 (1.03, 1.86)** |
| Sacral agenesis | 96 | 3 | 0.73 (0.15, 2.20) | 9 | 1 | NC |
| *Congenital Heart Defects* |  |  |  |  |  |  |
| Truncus arteriosus | 112 | 9 | 1.78 (0.89, 3.55) | 77 | 4 | 1.21 (0.32, 3.24) |
| Tetralogy of Fallot | 1,082 | 50 | 0.95 (0.69, 1.30) | 854 | 40 | 0.98 (0.70, 1.39) |
| D-TGA | 679 | 28 | 0.94 (0.63, 1.38) | 507 | 20 | 0.90 (0.57, 1.42) |
| DORV-TGA | 181 | 4 | 0.51 (0.14, 1.35) | 49 | 0 | NC |
| Conoventricular VSD f | 102 | 6 | 1.12 (0.45, 2.78) | 47 | 2 | NC |
| Atrioventricular septal defect | 328 | 17 | 1.05 (0.63, 1.75) | 153 | 11 | 1.30 (0.68, 2.48) |
| TAPVR | 277 | 12 | 1.09 (0.61, 1.97) | 234 | 9 | 0.96 (0.49, 1.89) |
| Hypoplastic left heart syndrome | 591 | 26 | 1.01 (0.68, 1.52) | 528 | 20 | 0.87 (0.55, 1.37) |
| Coarctation of the aorta | 1,044 | 38 | 0.83 (0.59, 1.17) | 494 | 20 | 0.90 (0.57, 1.43) |
| Aortic valve stenosis | 455 | 23 | 1.08 (0.70, 1.67) | 297 | 19 | 1.34 (0.83, 2.16) |
| Pulmonary atresia | 237 | 14 | 1.43 (0.82, 2.47) | 148 | 8 | 1.22 (0.59, 2.51) |
| Pulmonary valve stenosis g | 1,371 | 63 | 0.99 (0.75, 1.30) | 919 | 47 | 1.09 (0.80, 1.50) |
| Tricuspid atresia | 158 | 11 | 1.82 (0.97, 3.40) | 65 | 4 | 1.43 (0.38, 3.87) |
| Ebstein anomaly | 163 | 8 | 1.17 (0.57, 2.40) | 100 | 4 | 0.93 (0.25, 2.47) |
| Perimembranous VSD f | 1,261 | 53 | 0.91 (0.67, 1.25) | 772 | 31 | 0.84 (0.57, 1.26) |
| Muscular VSD h | 172 | 7 | 0.78 (0.32, 1.93) | 130 | 5 | 0.87 (0.33, 2.32) |
| Secundum ASD | 2,703 | 136 | 1.14 (0.93, 1.39) | 1,352 | 73 | 1.20 (0.92, 1.56) |
| aOR = adjusted odds ratio, cOR=crude odds ratio, CI = confidence interval, NC = not calculated, TGA = transposition of the great arteries, DORV = double outlet right ventricle, VSD = ventricular septal defect, TAPVR = total anomalous pulmonary venous return, ASD = atrial septal defect. Bold font indicates a statistically significant finding.  a For defects with 5+ exposed cases, estimates were adjusted for maternal age (continuous), race/ethnicity, BMI, smoking, folic acid-containing supplement use, and parity. Counts in the adjusted analysis were slightly lower due to missing values for some covariates. Crude ORs and exact 95% CIs are presented for defects groups with 3-4 exposed cases. Estimates are not presented when < 3 exposed cases.  b 8,883 unexposed controls, 379 exposed controls.  c 10,316 unexposed controls, 446 exposed controls.  d 5,306 unexposed controls, 221 exposed controls.  e Includes longitudinal and intercalary limb deficiencies.  f 6,145 unexposed controls, 260 exposed controls.  g 10,015 unexposed controls, 429 exposed controls.  h 654 unexposed controls, 31 exposed controls. | | | | | | |

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| Table E2. Associations between any early pregnancy albuterol use and birth defects, National Birth Defects Prevention Study 1997–2011. | | | | | |
| **Birth Defect** | **Unexposed** | **Any Bronchodilator Use** | | **Any Albuterol Use** | |
| **Exposed** | **aOR/cOR (95% CI)** a | **Exposed** | **aOR/cOR (95% CI)** a |
| *Controls* | 10,445 | 364 |  | 312 |  |
| *Non-cardiac Birth Defects* |  |  |  |  |  |
| Amniotic band sequence | 292 | 15 | 1.36 (0.80, 2.33) | 14 | 1.45 (0.83, 2.54) |
| Anencephaly | 593 | 25 | 0.94 (0.58, 1.53) | 17 | 1.03 (0.63, 1.71) |
| Spina bifida | 1,137 | 47 | 1.03 (0.74, 1.45) | 38 | 1.17 (0.83, 1.65) |
| Encephalocele | 202 | 6 | 0.92 (0.41, 2.10) | 6 | 1.07 (0.47, 2.43) |
| Holoprosencephaly | 146 | 10 | 1.75 (0.84, 3.61) | 7 | 1.52 (0.66, 3.48) |
| Dandy-Walker malformation | 157 | 9 | 1.15 (0.50, 2.63) | 6 | 1.30 (0.57, 3.00) |
| Hydrocephaly | 444 | 21 | 0.91 (0.53, 1.57) | 12 | 0.90 (0.50, 1.62) |
| Cerebellar hypoplasia | 51 | 5 | **2.70 (1.06, 6.85)** | 5 | **3.14 (1.23, 8.00)** |
| Ano/microphthalmia | 205 | 6 | 0.56 (0.15, 1.47) | 3 | 0.49 (0.10, 1.47) |
| Congenital cataracts | 313 | 14 | 1.13 (0.64, 1.99) | 13 | 1.31 (0.74, 2.32) |
| Glaucoma b | 163 | 5 | 0.52 (0.11, 1.57) | 3 | 0.61 (0.12, 1.83) |
| Ano/microtia b | 631 | 22 | 0.92 (0.55, 1.54) | 15 | 1.01 (0.60, 1.73) |
| Choanal atresia | 136 | 11 | 1.44 (0.66, 3.11) | 6 | 1.46 (0.64, 3.36) |
| Cleft palate only c | 1,415 | 78 | 1.30 (0.99, 1.69) | 64 | **1.43 (1.08, 1.88)** |
| Cleft lip only c | 962 | 58 | **1.37 (1.01, 1.87)** | 43 | **1.40 (1.01, 1.95)** |
| Cleft lip with cleft palate c | 1,819 | 86 | 1.03 (0.79, 1.35) | 61 | 1.13 (0.85, 1.49) |
| Esophageal atresia | 640 | 36 | 1.18 (0.79. 1.77) | 24 | 1.25 (0.81, 1.91) |
| Duodenal atresia/stenosis | 192 | 12 | 1.35 (0.68, 2.67) | 9 | 1.57 (0.79, 3.10) |
| Small intestinal atresia/stenosis | 416 | 22 | 1.04 (0.60, 1.80) | 13 | 1.04 (0.58, 1.88) |
| Colonic atresia/stenosis | 51 | 1 | NC | 1 | NC |
| Anorectal atresia/stenosis | 960 | 31 | 0.67 (0.43, 1.04) | 22 | 0.75 (0.48, 1.17) |
| Biliary atresia | 176 | 11 | 1.52 (0.77, 3.01) | 6 | 1.17 (0.51, 2.68) |
| Hypospadiasd | 2,242 | 105 | 0.94 (0.72, 1.24) | 70 | 0.98 (0.72, 1.31) |
| Renal agenesis/hypoplasia | 169 | 8 | 1.01 (0.44, 2.31) | 6 | 1.18 (0.51, 2.70) |
| Bladder exstrophy | 61 | 5 | 2.05 (0.82, 5.16) | 5 | 2.40 (0.85, 6.05) |
| Cloacal exstrophy | 91 | 3 | NC | 2 | NC |
| Longitudinal limb deficiency e | 458 | 37 | **2.04 (1.41, 2.96)** | 31 | **2.16 (1.46, 3.19)** |
| Transverse limb deficiency | 643 | 29 | 1.05 (0.68, 1.61) | 21 | 1.07 (0.67, 1.69) |
| Craniosynostosis | 1,412 | 63 | 0.94 (0.69, 1.28) | 46 | 1.00 (0.72, 1.39) |
| Diaphragmatic hernia | 764 | 22 | 0.64 (0.39, 1.05) | 17 | 0.75 (0.46, 1.23) |
| Omphalocele | 382 | 18 | 1.23 (0.75, 2.03) | 14 | 1.19 (0.69, 2.06) |
| Gastroschisis | 1,216 | 74 | 1.34 (0.98, 1.83) | 53 | 1.34 (0.96, 1.87) |
| Sacral agenesis | 96 | 3 | 0.90 (0.18, 2.72) | 3 | 1.05 (0.21, 3.18) |
| *Congenital Heart Defects* |  |  |  |  |  |
| Truncus arteriosus | 112 | 9 | **2.21 (1.10, 4.42)** | 9 | **2.59 (1.29, 5.19)** |
| Tetralogy of Fallot | 1,082 | 35 | 0.86 (0.60, 1.24) | 31 | 0.89 (0.60, 1.31) |
| D-TGA | 679 | 23 | 0.96 (0.62, 1.47) | 23 | 1.12 (0.73, 1.73) |
| DORV-TGA | 181 | 3 | 0.48 (0.10, 1.42) | 2 | NC |
| Conoventricular VSD f | 102 | 5 | 1.12 (0.40, 3.09) | 5 | 1.31 (0.47, 3.62) |
| Atrioventricular septal defect | 328 | 15 | 1.13 (0.65, 1.95) | 14 | 1.22 (0.69, 2.15) |
| TAPVR | 277 | 11 | 1.22 (0.66, 2.26) | 10 | 1.29 (0.68, 2.46) |
| Hypoplastic left heart syndrome | 591 | 22 | 1.05 (0.68, 1.63) | 19 | 1.05 (0.66, 1.69) |
| Coarctation of the aorta | 1,044 | 33 | 0.90 (0.63, 1.29) | 31 | 0.99 (0.68, 1.44) |
| Aortic valve stenosis | 455 | 18 | 1.06 (0.65, 1.72) | 17 | 1.17 (0.71, 1.93) |
| Pulmonary atresia | 237 | 13 | 1.63 (0.92, 2.88) | 10 | 1.44 (0.76, 2.76) |
| Pulmonary valve stenosis g | 1,371 | 56 | 1.06 (0.79, 1.42) | 50 | 1.09 (0.80, 1.49) |
| Tricuspid atresia | 158 | 10 | **2.03 (1.06, 3.90)** | 8 | 1.88 (0.91, 3.89) |
| Ebstein anomaly | 163 | 6 | 1.07 (0.47, 2.45) | 5 | 1.04 (0.42, 2.56) |
| Perimembranous VSD f | 1,261 | 47 | 0.99 (0.71, 1.39) | 42 | 1.03 (0.73, 1.47) |
| Muscular VSD h | 172 | 4 | 0.63 (0.16, 1.88) | 3 | 0.52 (0.10, 1.76) |
| Secundum ASD | 2,703 | 108 | 1.12 (0.89, 1.40) | 98 | 1.17 (0.93, 1.49) |
| Single ventricle | 162 | 4 | 0.71 (0.19, 1.87) | 3 | 0.62 (0.13, 1.86) |
| Heterotaxy | 304 | 15 | 1.39 (0.80, 2.41) | 13 | 1.38 (0.76, 2.49) |
| aOR = adjusted odds ratio, cOR=crude odds ratio, CI = confidence interval, NC = not calculated, TGA = transposition of the great arteries, DORV = double outlet right ventricle, VSD = ventricular septal defect, TAPVR = total anomalous pulmonary venous return, ASD = atrial septal defect. Bold font indicates a statistically significant finding.  a For defects with 5+ exposed cases, estimates were adjusted for maternal age (continuous), race/ethnicity, BMI, smoking, folic acid-containing supplement use, and parity. Counts in the adjusted analysis were slightly lower due to missing values for some covariates. Crude ORs and exact 95% CIs are presented for defects groups with 3-4 exposed cases. Estimates are not presented when < 3 exposed cases.  b 8,883 unexposed controls, 269 albuterol exposed controls.  c 10,316 unexposed controls, 309 albuterol exposed controls.  d 5,306 unexposed controls, 160 albuterol exposed controls.  e Includes longitudinal and intercalary limb deficiencies.  f 6,145 unexposed controls, 184 albuterol exposed controls.  g 10,015 unexposed controls, 301 albuterol exposed controls.  h 654 unexposed controls, 22 albuterol exposed controls. | | | | | |

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| Table E3. Associations between early pregnancy use of specific asthma medication components and birth defects, National Birth Defects Prevention Study 1997–2011. | | | | | | | | | | | | | | | | | | | | | |
| Birth Defect | Salmeterol | | Terbutaline | | Montelukast sodium | | | Beclomethasone | | Budesonide | | Fluticasone | | Methylprednisolone | | | | | Prednisone | | |
| N | aOR/cOR (95% CI)a | N | cOR  (95% CI)a | N | aOR/cOR (95%CI)a | | N | cOR  (95%CI)a | N | aOR/cOR (95%CI)a | N | aOR/cOR (95%CI)a | | N | cOR (95%CI)a | | N | | aOR/cOR (95%CI)a | |
| *Controls* b | 62 |  | 6 |  | 40 | |  | 8 |  | 13 |  | 72 |  | | 6 |  | | 22 | | |  |
| Spina bifida | 6 | 1.0 (0.4, 2.3) |  |  | 5 | | 1.2 (0.5, 3.0) | 0 |  | 1 |  | 8 | 1.1 (0.5, 2.3) | | 0 |  | | 2 | |  | |
| Hydrocephaly | 4 | 1.5 (0.4, 4.1) |  |  | 2 | |  | 0 |  | 2 |  | 2 |  | | 0 |  | | 1 | |  | |
| Congenital cataracts d | 2 |  |  |  | 1 | |  | 0 |  | 0 |  | 3 | 1.4 (0.3, 4.2) | | 0 |  | | 2 | |  | |
| Cleft palate only d | 7 | 0.7 (0.3, 1.6) | 3 | 3.7 (0.6, 17.1) | 5 | | 0.9 (0.3, 2.2) | 1 |  | 0 |  | 6 | 0.5 (0.2, 1.2) | | 1 |  | | 4 | | 1.3 (0.3, 3.9) | |
| Cleft lip only d | 3 | 0.5 (0.1, 1.6) |  |  | 2 | |  | 4 | **6.1 (1.3, 24.1)** | 1 |  | 4 | 0.6 (0.2, 1.6) | | 1 |  | | 3 | | 1.5 (0.4, 4.9) | |
| Cleft lip with cleft palate d | 9 | 0.9 (0.5, 1.9) |  |  | 9 | | 1.3 (0.6, 2.8) | 1 |  | 2 |  | 10 | 0.9 (0.5, 1.7) | | 2 |  | 11 | | | **2.7 (1.2, 5.7)** | |
| Esophageal atresia | 3 | 0.8 (0.2, 2.4) |  |  | 3 | | 1.2 (0.2, 3.9) | 3 | **6.1 (1.0, 25.6)** | 0 |  | 5 | 1.1 (0.4, 2.6) | | 2 |  | | 1 | |  | |
| Anorectal atresia/stenosis | 4 | 0.7 (0.2, 1.9) |  |  | 4 | | 1.1 (0.3, 3.0) | 0 |  | 0 |  | 6 | 0.8 (0.3, 2.0) | | 0 |  | | 1 | |  | |
| Biliary atresia | 1 |  |  |  | 2 | |  | 0 |  | 0 |  | 3 | 2.5 (0.5, 7.6) | | 0 |  | | 3 | | **8.1 (1.5, 27.3)** | |
| Hypospadias e | 22 | 0.4 (0.8, 2.5) |  |  | 12 | | 1.3 (0.6, 2.9) | 1 |  | 4 | 1.4 (0.3, 5.3) | 24 | 1.4 (0.8, 2.3) | | 2 |  | | 4 | | 1.0 (0.2, 3.3) | |
| Longitudinal limb deficiencyf | 3 | 1.1 (0.2, 3.4) |  |  | 2 | |  | 0 |  | 0 |  | 4 | 1.3 (0.3, 3.4) | | 0 |  | | 0 | |  | |
| Transverse limb deficiency | 4 | 1.1 (0.3, 2.8) |  |  | 2 | |  | 4 | 2.1 (1.8, 30.4) | 1 |  | 5 | 1.2 (0.5, 2.9) | | 0 |  | | 0 | |  | |
| Craniosynostosis | 8 | 0.8 (0.4, 1.7) |  |  | 5 | | 0.8 (0.3, 2.0) | 0 |  | 6 | **2.6 (1.0, 7.0)** | 10 | 0.8 (0.4, 1.7) | | 2 |  | | 2 | |  | |
| Diaphragmatic hernia | 1 |  |  |  | 3 | | 1.0 (0.2, 3.2) | 2 |  | 2 |  | 4 | 0.8 (0.2, 20.4) | | 0 |  | | 3 | | 1.9 (0.4, 6.2) | |
| Omphalocele | 3 | 1.3 (0.3, 4.1) |  |  | 2 | |  | 2 |  | 0 |  | 2 |  | | 0 |  | | 0 | |  | |
| Gastroschisis | 9 | 1.4 (0.6, 3.1) |  |  | 3 | | 0.6 (0.1, 2.0) | 3 | 3.2 (0.6, 13.4) | 2 |  | 11 | 1.6 (0.8, 3.4) | | 0 |  | | 3 | | 1.2 (0.2, 3.9) | |
| Tetralogy of Fallot | 6 | 0.9 (0.4, 2.2) |  |  | 0 | |  | 4 | **4.8 (1.1, 18.0)** | 1 |  | 6 | 0.8 (0.3, 1.8) | | 4 | **6.4 (1.3, 27.2)** | | 4 | | 1.8 (0.4, 5.2) | |
| D-TGA | 2 |  |  |  | 4 | | 1.5 (0.4, 4.3) | 1 |  | 2 |  | 4 | 0.9 (0.2, 2.3) | | 0 |  | | 2 | |  | |
| Hypoplastic heart syndrome | 0 |  |  |  | 3 | | 1.3 (0.3, 4.2) | 0 |  | 0 |  | 0 |  | | 0 |  | | 1 | |  | |
| Coarctation of the aorta | 4 | 0.7 (0.2, 1.7) |  |  | 3 | | 0.8 (0.2, 2.4) | 1 |  | 0 |  | 6 | 0.8 (0.3, 1.8) | | 0 |  | | 3 | | 1.4 (0.3, 4.6) | |
| Aortic valve stenosis | 5 | 1.6 (0.7, 4.1) |  |  | 1 | |  | 1 |  | 1 |  | 5 | 1.4 (0.1, 3.5) | | 1 |  | | 2 | |  | |
| Pulmonary atresia | 4 | 2.8 (0.8, 7.8) |  |  | 2 | |  | 1 |  | 0 |  | 4 | 2.5 (0.6, 6.6) | | 0 |  | | 0 | |  | |
| Pulmonary valve stenosis g | 8 | 0.9 (0.4, 1.9) |  |  | 8 | | 1.2 (0.6, 2.8) | 1 |  | 1 |  | 11 | 1.1 (0.6, 2.1) | | 1 |  | | 1 | |  | |
| Tricuspid atresia | 2 |  |  |  | 0 | |  | 0 |  | 0 |  | 3 | 2.8 (0.6, 8.5) | | 0 |  | | 0 | |  | |
| Perimembranous VSD h | 3 | 0.5 (0.1, 1.6) |  |  | 3 | | 1.0 (0.2, 3.5) | 1 |  | 1 |  | 8 | 1.1 (0.5, 2.4) | | 0 |  | | 2 | |  | |
| Secundum ASD | 14 | 0.9 (0.5, 1.7) |  |  | 13 | | 1.3 (0.7, 2.5) | 4 | 1.9 (0.4, 7.2) | 2 |  | 17 | 0.9 (0.5, 1.6) | | 2 |  | | 8 | | 1.5 (0.6, 3.3) | |
| aOR = adjusted odds ratio, cOR=crude odds ratio, CI = confidence interval, TGA = transposition of the great arteries, VSD = ventricular septal defect, ASD = atrial septal defect. Bold font indicates a statistically significant finding. Included in this table are birth defects that had at least 3 exposed cases to one of the asthma medication components.  a For defects with 5+ exposed cases, estimates were adjusted for maternal age, (continuous) race/ethnicity, BMI, smoking, folic acid-containing supplement use, and parity. Counts in the adjusted analysis were slightly lower due to missing values for some covariates. Crude ORs and exact 95% CIs are presented for defects groups with 3-4 exposed cases. Estimates are not presented when < 3 exposed cases.  b Unless stated, the number of unexposed cases and controls is the same as listed in Table 2 and Table 3.  c 8,883 unexposed controls, 62 fluticasone exposed controls.  d 10,316 unexposed controls, 61 salmeterol exposed controls, 7 beclomethasone exposed controls, 71 fluticasone exposed controls.  e 5,306 unexposed controls, 31 salmeterol exposed controls, 19 montelukast sodium exposed controls, 7 budesonide exposed controls, 35 fluticasone exposed controls, 10 prednisone exposed controls.  f Includes longitudinal and intercalary limb deficiencies.  g 10,105 unexposed controls, 39 montelukast sodium exposed controls.  h 6,145 unexposed controls, 30 salmeterol exposed controls, 15 montelukast sodium exposed controls, 33 fluticasone exposed controls. | | | | | | | | | | | | | | | | | | | | | |

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| Table E4. Associations between early pregnancy asthma medication use and birth defects without women who reported only “as needed” asthma medication use, National Birth Defects Prevention Study 1997–2011. | | | | | | | | | |
| **Birth Defect** | **Unexposed** | **Any Asthma Medication Use** | | **Bronchodilator**  **Only Use** | | **Anti-Inflammatory Only use** | | **Bronchodilators & anti-inflammatories** | |
|  | **N** | **aOR/cOR**  **(95% CI)** a | **N** | **aOR/cOR**  **(95% CI)** a | **N** | **aOR/cOR**  **(95% CI)** a | **N** | **aOR/cOR**  **(95% CI)** a |
| *Controls* | 10,445 | 378 |  | 201 |  | 70 |  | 92 |  |
| *Non-cardiac Birth Defects* |  |  |  |  |  |  |  |  |  |
| Amniotic band sequence | 292 | 13 | 1.16 (0.65, 2.05) | 10 | 1.55 (0.80, 2.98) | 0 | NC | 3 | 1.17 (0.23, 3.55) |
| Anencephaly | 593 | 21 | 1.08 (0.69, 1.69) | 12 | 1.16 (0.64, 2.10) | 4 | 1.01 (0.27, 2.71) | 2 | NC |
| Spina bifida | 1137 | 39 | 0.98 (0.69, 1.37) | 19 | 0.91 (0.56, 1.47) | 6 | 0.86 (0.37, 2.00) | 12 | 1.27 (0.69, 2.33) |
| Encephalocele | 202 | 6 | 0.90 (0.40, 2.05) | 5 | 1.37 (0.55, 3.38) | 0 | NC | 1 | NC |
| Holoprosencephaly | 146 | 10 | 1.94 (0.97, 3.86) | 6 | **2.37 (1.03, 5.47)** | 1 | NC | 3 | 2.33 (0.47, 7.17) |
| Dandy-Walker malformation | 157 | 8 | 1.34 (0.62, 2.87) | 5 | 1.71 (0.69, 4.24) | 1 | NC | 0 | NC |
| Hydrocephaly | 444 | 18 | 1.07 (0.65, 1.76) | 6 | 0.70 (0.31, 1.58) | 5 | 1.44 (0.52, 3.99) | 5 | 1.32 (0.53, 3.27) |
| Cerebellar hypoplasia | 51 | 5 | **2.58 (1.02, 6.57)** | 4 | **4.08 (1.06, 11.2)** | 0 | NC | 1 | NC |
| Ano/microphthalmia | 205 | 4 | 0.54 (0.14, 1.41) | 3 | 0.76 (0.15, 2.29) | 1 | NC | 0 | NC |
| Congenital cataracts b | 313 | 10 | 0.74 (0.38, 1.45) | 5 | 0.76 (0.31, 1.87) | 0 | NC | 3 | 1.03 (0.21, 3.13) |
| Glaucoma b | 163 | 5 | 0.87 (0.35, 2.15) | 2 | NC | 2 | NC | 1 | NC |
| Ano/microtia | 631 | 20 | 1.06 (0.66, 1.70) | 11 | 1.16 (0.62, 2.17) | 5 | 1.58 (0.63, 3.99) | 2 | NC |
| Choanal atresia | 136 | 10 | **1.94 (1.01, 3.74)** | 6 | **2.35 (1.02, 5.43)** | 2 | NC | 0 | NC |
| Cleft palate only c | 1,415 | 60 | 1.05 (0.79, 1.40) | 40 | 1.32 (0.93, 1.89) | 3 | 0.88 (0.38, 2.05) | 14 | 0.98 (0.55, 1.77) |
| Cleft lip only c | 932 | 46 | 1.23 (0.89, 1.69) | 31 | **1.53 (1.04, 2.27)** | 6 | 1.46 (0.84, 2.53) | 8 | 0.91 (0.44, 1.89) |
| Cleft lip with cleft palate c | 1,819 | 76 | 1.16 (0.90, 1.49) | 35 | 0.98 (0.68, 1.42) | 16 | 1.46 (0.85, 2.54) | 21 | 1.35 (0.84, 2.19) |
| Esophageal atresia | 640 | 29 | 1.18 (0.80, 1.74) | 15 | 1.20 (0.71, 2.06) | 4 | 0.93 (0.25, 2.51) | 7 | 1.17 (0.54, 2.54) |
| Duodenal atresia/stenosis | 192 | 11 | 1.60 (0.86, 2.99) | 6 | 1.57 (0.69, 3.61) | 2 | NC | 2 | NC |
| Small intestinal atresia/stenosis | 416 | 20 | 1.38 (0.86, 2.21) | 12 | 1.47 (0.79, 2.74) | 4 | 1.43 (0.38, 3.67) | 3 | 0.82 (0.17, 2.49) |
| Colonic atresia/stenosis | 51 | 1 | NC | 1 | NC | 0 | NC | 0 | NC |
| Anorectal atresia/stenosis | 960 | 27 | 0.73 (0.48, 1.10) | 14 | 0.77 (0.44, 1.33) | 4 | 0.62 (0.16, 1.67) | 6 | 0.60 (0.24, 1.49) |
| Biliary atresia | 176 | 9 | 1.49 (0.75, 2.95) | 2 | NC | 2 | NC | 5 | **3.50 (1.40, 8.76)** |
| Hypospadias d | 2,242 | 87 | 0.99 (0.75, 1.29) | 34 | 0.67 (0.45, 1.01) | 22 | 1.50 (0.84, 2.69) | 28 | 1.28 (0.78, 2.09) |
| Renal agenesis/hypoplasia | 169 | 8 | 1.29 (0.63, 2.67) | 6 | 1.77 (0.77, 4.07) | 2 | NC | 0 | NC |
| Bladder exstrophy | 61 | 4 | 1.81 (0.48, 4.92) | 1 | NC | 0 | NC | 3 | **5.58 (1.10, 17.6)** |
| Cloacal exstrophy | 91 | 3 | 0.91 (0.18, 2.77) | 2 | NC | 1 | NC | 0 | NC |
| Longitudinal limb deficiency e | 458 | 33 | **1.91 (1.31, 2.78)** | 23 | **2.54 (1.62, 3.97)** | 1 | NC | 7 | 1.49 (0.65, 3.44) |
| Transverse limb deficiency | 643 | 23 | 0.92 (0.59, 1.44) | 7 | 0.57 (0.27, 1.23) | 5 | 0.96 (0.35, 2.64) | 10 | 1.60 (0.80, 3.20) |
| Craniosynostosis | 1,412 | 54 | 0.96 (0.71, 1.29) | 27 | 0.95 (0.62, 1.44) | 10 | 0.84 (0.43, 1.63) | 15 | 1.07 (0.61, 1.86) |
| Diaphragmatic hernia | 764 | 21 | 0.75 (0.48, 1.18) | 9 | 0.61 (0.31, 1.19) | 6 | 1.16 (0.50, 2.69) | 5 | 0.74 (0.30, 1.82) |
| Omphalocele | 382 | 14 | 0.96 (0.56, 1.67) | 8 | 1.02 (0.50, 2.10) | 1 | NC | 5 | 1.43 (0.58, 3.56) |
| Gastroschisis | 1,216 | 64 | 1.35 (0.99, 1.84) | 36 | 1.35 (0.90, 2.01) | 7 | 0.97 (0.39, 2.41) | 15 | 1.49 (0.78, 2.82) |
| Sacral agenesis | 96 | 2 | NC | 1 | NC | 0 | NC | 1 | NC |
| *Congenital Heart Defects* |  |  |  |  |  |  |  |  |  |
| Truncus arteriosus | 112 | 7 | 1.64 (0.76, 3.58) | 5 | 2.24 (0.90, 5.60) | 0 | NC | 2 | NC |
| Tetralogy of Fallot | 1,082 | 42 | 0.92 (0.65, 1.30) | 14 | 0.57 (0.32, 1.02) | 8 | 1.06 (0.51, 2.21) | 12 | 1.22 (0.66, 2.24) |
| D-TGA | 679 | 24 | 0.95 (0.63, 1.45) | 12 | 0.91 (0.51, 1.64) | 3 | 0.66 (0.13, 2.02) | 8 | 1.31 (0.63, 2.71) |
| DORV-TGA | 181 | 3 | 0.46 (0.09, 1.37) | 2 | NC | 1 | NC | 0 | NC |
| Conoventricular VSD f | 102 | 6 | 1.43 (0.57, 3.58) | 4 | 2.19 (0.58, 5.94) | 1 | NC | 1 | NC |
| Atrioventricular septal defect | 328 | 15 | 1.08 (0.63, 1.87) | 10 | 1.39 (0.65, 2.55) | 2 | NC | 2 | NC |
| TAPVR | 277 | 12 | 1.30 (0.72, 2.36) | 10 | **2.01 (1.05, 3.86)** | 1 | NC | 1 | NC |
| Hypoplastic heart syndrome | 591 | 21 | 0.98 (0.62, 1.53) | 13 | 1.14 (0.65, 2.02) | 5 | 1.25 (0.50, 3.13) | 3 | 0.58 (0.12, 1.75) |
| Coarctation of the aorta | 1,044 | 31 | 0.81 (0.56, 1.18) | 14 | 0.71 (0.41, 1.23) | 3 | 0.43 (0.09, 1.31) | 12 | 1.27 (0.69, 2.34) |
| Aortic valve stenosis | 455 | 19 | 1.07 (0.66, 1.71) | 8 | 0.86 (0.42, 1.76) | 2 | NC | 6 | 1.38 (0.60, 3.18) |
| Pulmonary atresia | 237 | 12 | 1.45 (0.80, 2.62) | 6 | 1.35 (0.59, 3.09) | 0 | NC | 5 | 2.46 (0.99, 6.13) |
| Pulmonary valve stenosis g | 1,371 | 53 | 0.99 (0.73, 1.34) | 29 | 1.00 (0.67, 1.48) | 7 | 0.66 (0.29, 1.54) | 15 | 1.16 (0.67, 2.01) |
| Tricuspid atresia | 158 | 9 | 1.76 (0.89, 3.50) | 6 | 2.19 (0.95, 5.04) | 1 | NC | 2 | NC |
| Ebstein anomaly | 163 | 6 | 1.05 (0.46, 2.38) | 3 | 0.96 (0.19, 2.89) | 1 | NC | 2 | NC |
| Perimembranous VSD f | 1,261 | 44 | 0.99 (0.70, 1.39) | 25 | 1.01 (0.64, 1.60) | 8 | 1.00 (0.46, 2.16) | 10 | 1.05 (0.51, 2.18) |
| Muscular VSD h | 172 | 6 | 1.00 (0.36, 2.74) | 3 | 0.95 (0.17, 3.58) | 2 | NC | 1 | NC |
| Secundum ASD | 2,703 | 115 | 1.13 (0.91, 1.41) | 58 | 1.06 (0.78, 1.43) | 23 | 1.27 (0.77, 2.07) | 27 | 1.10 (0.71, 1.72) |
| Single ventricle | 162 | 5 | 0.71 (0.26, 1.93) | 2 | NC | 2 | NC | 1 | NC |
| Heterotaxy | 304 | 15 | 1.37 (0.79, 2.37) | 9 | 1.60 (0.81, 3.16) | 1 | NC | 5 | 1.63 (0.59, 4.49) |
| aOR = adjusted odds ratio, cOR= crude odds ratio, CI = confidence interval, NC = not calculated, TGA = transposition of the great arteries, DORV = double outlet right ventricle, VSD = ventricular septal defect, TAPVR = total anomalous pulmonary venous return, ASD = atrial septal defect. Bold font indicates a statistically significant finding.  a For defects with 5+ exposed cases, estimates were adjusted for maternal age (continuous), race/ethnicity, BMI, smoking, folic acid-containing supplement use, and parity. Counts in the adjusted analysis were slightly lower due to missing values for some covariates. Crude ORs and exact 95% CIs are presented for defects groups with 3-4 exposed cases. Estimates are not presented when < 3 exposed cases.  b 8,883 unexposed controls, 329 any asthma medication exposed controls, 177 bronchodilator only exposed controls, 83 bronchodilator and anti-inflammatory exposed controls.  c 10,316 unexposed controls, 376 any asthma medication exposed controls, 201 any bronchodilator exposed controls, 69 any anti-inflammatory exposed controls, 91 bronchodilator and anti-inflammatory exposed controls.  d 5,306 unexposed controls, 187 any asthma medication exposed controls, 109 any bronchodilator exposed controls, 28 any anti-inflammatory exposed controls, 46 bronchodilator and anti-inflammatory exposed controls.  e Includes longitudinal and intercalary limb deficiencies.  f 6,145 unexposed controls, 199 any asthma medication exposed controls, 110 any bronchodilator exposed controls, 38 any anti-inflammatory exposed controls, 40 bronchodilator and anti-inflammatory exposed controls.  g 10,015 unexposed controls, 361 any asthma medication exposed controls, 195 any bronchodilator exposed controls, 66 any anti-inflammatory exposed controls, 90 bronchodilator and anti-inflammatory exposed controls.  h 654 unexposed controls, 21 any asthma medication exposed controls, 12 any bronchodilator exposed controls. | | | | | | | | | |

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| Table E5. Association between early pregnancy bronchodilator use and birth defects, compared to late pregnancy bronchodilator use, National Birth Defects Prevention Study, 1997-2011. | | | | |
| **Birth Defect** | **Bronchodilator use in late pregnancy only**  **(Unexposed)** | | **Any Bronchodilators Use in**  **Early Pregnancy**  **(Exposed)** | |
| **N** | | **N** a | **OR (95% CI)** b |
| Controls | 133 | 358 | |  |
| *Non-cardiac birth defects* |  |  | |  |
| Amniotic band sequence c | 5 | 15 | | 1.11 (0.38, 4.00) |
| Anencephaly | 2 | 18 | | NC |
| Spina bifida | 13 | 39 | | 1.16 (0.59, 2.27) |
| Encephalocele | 2 | 6 | | NC |
| Holoprosencephaly | 1 | 9 | | NC |
| Dandy-Walker malformation | 4 | 6 | | 0.56 (0.13, 2.73) |
| Hydrocephaly | 7 | 14 | | 0.99 (0.36, 2.73) |
| Cerebellar hypoplasia | 0 | 5 | | NC |
| Ano/microphthalmia | 1 | 4 | | NC |
| Congenital cataracts d | 3 | 13 | | 1.66 (0.44, 9.22) |
| Glaucoma d | 3 | 3 | | 0.38 (0.05, 2.90) |
| Ano/microtia c | 6 | 16 | | 0.98 (0.37, 2.60) |
| Choanal atresia | 2 | 7 | | NC |
| Cleft palate only e | 7 | 70 | | **3.27 (1.45, 7.39)** |
| Cleft lip only e | 14 | 49 | | 1.25 (0.65, 2.41) |
| Cleft lip with cleft palate e | 12 | 65 | | **2.02 (1.03, 3.94)** |
| Esophageal atresia c | 5 | 27 | | 1.86 (0.68, 6.34) |
| Duodenal atresia/stenosis | 6 | 9 | | 0.46 (0.15, 1.36) |
| Small intestinal atresia/stenosis | 3 | 15 | | 1.86 (0.51, 10.2) |
| Colonic atresia/stenosis | 0 | 1 | | NC |
| Anorectal atresia/stenosis | 10 | 23 | | 0.78 (0.34, 1.77) |
| Biliary atresia | 3 | 9 | | 1.11 (0.27, 6.49) |
| Hypospadias f | 29 | 82 | | 1.17 (0.69, 2.00) |
| Renal agenesis/hypoplasia | 2 | 6 | | NC |
| Bladder exstrophy | 2 | 5 | | NC |
| Cloacal exstrophy | 2 | 2 | | NC |
| Longitudinal limb deficiency g | 4 | 34 | | **3.06 (1.06, 12.1)** |
| Transverse limb deficiency | 5 | 24 | | 1.68 (0.62, 4.59) |
| Craniosynostosis | 18 | 51 | | 0.98 (0.55, 1.78) |
| Diaphragmatic hernia | 12 | 17 | | 0.49 (0.22, 1.07) |
| Omphalocele | 5 | 17 | | 1.13 (0.40, 3.18) |
| Gastroschisis | 10 | 61 | | **2.24 (1.04, 4.83)** |
| Sacral agenesis | 3 | 3 | | 0.37 (0.05, 2.81) |
| *Congenital Heart Defects* |  |  | |  |
| Truncus arteriosus c | 5 | 9 | | 0.67 (0.20, 2.59) |
| Tetralogy of Fallot | 11 | 35 | | 1.08 (0.52, 2.27) |
| D-TGA | 6 | 23 | | 1.26 (0.49, 3.22) |
| DORV-TGA | 1 | 2 | | NC |
| Conoventricular VSD h | 1 | 5 | | NC |
| Atrioventricular septal defect | 1 | 15 | | NC |
| TAPVR | 1 | 11 | | NC |
| Hypoplastic heart syndrome | 9 | 22 | | 0.88 (0.39, 2.00) |
| Coarctation of the aorta | 12 | 33 | | 1.00 (0.50, 2.03) |
| Aortic valve stenosis | 0 | 18 | | NC |
| Pulmonary atresia | 2 | 13 | | NC |
| Pulmonary valve stenosis i | 19 | 55 | | 1.15 (0.63, 2.07) |
| Tricuspid atresia | 1 | 10 | | NC |
| Ebstein anomaly | 2 | 6 | | NC |
| Perimembranous VSD c,h | 8 | 46 | | 1.97 (0.87, 5.07) |
| Muscular VSD | 2 | 4 | | NC |
| Secundum ASD | 21 | 107 | | **1.85 (1.09, 3.14)** |
| Single ventricle | 1 | 3 | | NC |
| Heterotaxy | 1 | 15 | | NC |
| OR = odds ratio, CI = confidence interval, NC = not calculated, TGA = transposition of the great arteries, DORV = double outlet right ventricle, VSD = ventricular septal defect, TAPVR = total anomalous pulmonary venous return, ASD = atrial septal defect. Bold font indicates a statistically significant finding.  a The number of exposed in early pregnancy is different than in Table 3 and 4, as we removed from this analysis those case and controls only exposed to terbutaline in both time periods (16 exposed in early pregnancy and 417 exposed in late pregnancy).  b For defects with 5+ exposed cases, estimates were adjusted for maternal age (continuous), race/ethnicity, BMI, smoking, folic acid-containing supplement use, and parity. Counts in the adjusted analysis were slightly lower than presented due to missing values for some covariates. Crude ORs and exact 95% CIs are presented for defects groups with 3–4 exposed cases. Estimates are not presented for analyses based on either < 3 exposed cases or <3 unexposed cases.  c Adjusted logistic model did not converge; estimates presented are crude OR and exact 95% CIs.  d 117 unexposed controls, 306 exposed controls.  e 132 unexposed controls, 355 exposed controls.  f 74 unexposed controls, 185 exposed controls.  g Includes longitudinal and intercalary limb deficiencies.  h 71 unexposed controls, 207 exposed controls.  i 126 unexposed controls, 347 exposed controls. | | | | |