

	Non-heart defects								Heart defects							
	Gastroschisis	Hypospadias	Cleft palate	Cleft lip with cleft palate	Cleft lip without cleft palate	Anencephaly and craniorachischisis	Encephalocele	Spina bifida	atrioventricular septal defect	dextro-Transposition of the great arteries	Hypoplastic left heart syndrome	Pulmonary valve stenosis	Tetralogy of Fallot	Perimembranous ventricular septal defect	Muscular ventricular septal defect, not simple	Ventricular septal defect with atrial septal defect
Sensitivity Analysis (n of cases/controls)																
NSAIDs analysis (15,791 ca./5,748 co.)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
No surgery* (15,525 ca./5,676 co.)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
No injury* (15,318 ca./5,602 co.)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
No fever* (13,735 ca./5,010 co.)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
No chronic conditions† (15,484 ca./5,644 co.)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
No family history (15,328 ca./5,631 co.)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
No non-analgesics‡ (7,355 ca./2,820 co.)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Isolated defects only (14,392 ca./5,748 co.)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Planned pregnancy only (7,621 ca./2,735 co.)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Interview at 6–42 weeks (6,830 ca./3,679 co.)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Opioids analysis (8,275 ca./3,340 co.)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
No surgery* (8,078 ca./3,271 co.)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
No injury* (7,991 ca./3,242 co.)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
No fever* (7,064 ca./2,852 co.)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
No chronic conditions† (8,126 ca./3,279 co.)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
No family history (8,012 ca./3,275 co.)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
No non-analgesics‡ (3,918 ca./1,685 co.)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Isolated defects only (7,528 ca./3,340 co.)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Planned pregnancy only (4,081 ca./1,631 co.)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Interview at 6–42 weeks (3,585 ca./2,148 co.)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Opioids and NSAIDs analysis (8,246 ca./3,316 co.)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
No surgery* (8,051 ca./3,255 co.)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
No injury* (7,960 ca./3,222 co.)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
No fever* (7,040 ca./2,839 co.)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
No chronic conditions† (8,097 ca./3,251 co.)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
No family history (7,984 ca./3,252 co.)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
No non-analgesics‡ (3,886 ca./1,678 co.)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Isolated defects only (7,486 ca./3,316 co.)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Planned pregnancy only (4,073 ca./1,624 co.)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Interview at 6–42 weeks (3,553 ca./2,134 co.)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○

Supplemental Figure. Sensitivity analyses for the degree of association between NSAIDs and/or opioids and selected birth defects, National Birth Defects Prevention Study 1997–2011. Bubble plot showing the size and statistical significance of the association between NSAIDs and/or opioids and selected birth defects. Odds ratios plots (adjusted for maternal age at delivery, race/ethnicity, parity, maternal education, periconceptional alcohol, periconceptional smoking, periconceptional antibiotic use, study location, and estimated date of delivery) are presented for birth defect categories with at least four exposed cases. Circle size is relative to the significance of the estimate (small circle = elevated estimate with $P \geq .05$; large circle = elevated estimate with $P < .05$); circle shading is relative to the strength of the association (no circle = aOR < 1.0; white = aORs between 1.0 and 1.4; light purple = aORs between 1.5 and 1.9; medium purple = aORs between 2.0 and 2.4; and dark purple = aORs 2.5 and greater). aOR = adjusted odds ratio; NSAIDs = nonsteroidal anti-inflammatory drugs; Ca. = cases; Co. = controls; NC = not calculated; *From 1 month before conception through third month of pregnancy; †Selected chronic conditions include asthma, digestive diseases (e.g., celiac disease, colitis and ulcerative colitis, Crohn's disease, and irritable bowel syndrome), fibromyalgia, hepatitis, systemic lupus erythematosus, multiple sclerosis, nephritis, psoriasis, rheumatoid arthritis, and thyroid diseases (e.g., Hashimoto's disease and Graves' disease); ‡From 1 month before conception through third month of pregnancy; nonanalgesic medications include antihistamines, anti-infectives, antineoplastics, autonomic drugs, cardiovascular drugs, contraceptives, gastrointestinal drugs, gold compounds, hormones, local anesthetics, miscellaneous therapeutics and classifications, oxytocics, radioactive agents, respiratory tract agents, serums, toxoids, vaccines, allergens, skin and mucous membrane agents, smooth muscle relaxants, and other central nervous system agents.

Supplemental Table 1

Association between birth defects and maternal report of periconceptional use of acetaminophen compared to mothers not reporting analgesics from B1–P9, National Birth Defects Prevention Study 1997–2011

Birth defect type (n)	Unexposed (n = 7473)		Acetaminophen with or without NSAIDs and opioids* (n = 18,678)		Acetaminophen without NSAIDs or opioids* (n = 13,228)			
	n		n	cOR (95% CI)	aOR [†] (95% CI)	n	cOR (95% CI)	aOR [‡] (95% CI)
Controls (7124)	2137		4987	Referent	Referent	3834	Referent	Referent
Gastroschisis (863)	263		600	1.0 (0.8–1.1)	1.0 (0.8–1.2)	349	0.7 (0.6–0.9)	0.8 (0.7–1.0)
Hypospadias [‡] (1545)	424		1121	1.1 (1.0–1.3)	1.0 (0.9–1.2)	783	1.0 (0.9–1.2)	1.0 (0.8–1.2)
Orofacial clefts [§]								
Cleft palate (1004)	246		758	1.3 (1.1–1.5)	1.2 (1.1–1.5)	488	1.1 (0.9–1.3)	1.1 (0.9–1.3)
Cleft lip with cleft palate (1208)	336		872	1.1 (1.0–1.3)	1.1 (1.0–1.3)	571	1.0 (0.8–1.1)	1.0 (0.8–1.1)
Cleft lip without cleft palate (704)	173		531	1.3 (1.1–1.6)	1.2 (1.0–1.5)	335	1.1 (0.9–1.3)	1.0 (0.9–1.3)
Neural tube defects								
Anencephaly and craniorachischisis (411)	114		297	1.1 (0.9–1.4)	1.3 (1.0–1.6)	197	1.0 (0.8–1.2)	1.1 (0.9–1.5)
Encephalocele (135)	41		94	1.0 (0.7–1.4)	1.2 (0.8–1.8)	71	1.0 (0.7–1.4)	1.2 (0.8–1.8)
Spina bifida (765)	225		540	1.0 (0.9–1.2)	1.1 (0.9–1.3)	356	0.9 (0.7–1.1)	0.9 (0.8–1.1)
Heart defects								
AVSD (231)	51		180	1.5 (1.1–2.1)	1.4 (1.0–1.9)	116	1.3 (0.9–1.8)	1.1 (0.8–1.6)
d-TGA (471)	127		344	1.2 (0.9–1.4)	1.1 (0.9–1.3)	249	1.1 (0.9–1.4)	1.0 (0.8–1.3)
HLHS (398)	130		268	0.9 (0.7–1.1)	0.8 (0.6–1.0)	181	0.8 (0.6–1.0)	0.7 (0.6–0.9)
PVS [¶] (958)	234		724	1.3 (1.1–1.5)	1.3 (1.1–1.5)	469	1.1 (0.9–1.3)	1.1 (0.9–1.3)
TOF (735)	231		504	0.9 (0.8–1.1)	1.0 (0.8–1.2)	337	0.8 (0.7–1.0)	0.9 (0.7–1.0)
Perimembranous VSD (968)	275		693	1.1 (0.9–1.3)	1.1 (0.9–1.3)	545	1.1 (0.9–1.3)	1.0 (0.9–1.2)
VSD muscular, not simple [¶] (389)	100		289	1.2 (1.0–1.6)	1.2 (0.9–1.5)	215	1.2 (0.9–1.5)	1.2 (0.9–1.5)
VSD with ASD (450)	113		337	1.3 (1.0–1.6)	1.2 (1.0–1.5)	250	1.2 (1.0–1.5)	1.2 (1.0–1.6)

aOR = adjusted odds ratio; ASD = atrial septal defect; AVSD = atrioventricular septal defect; B1 = one month before conception; CI = confidence interval; cOR = crude odds ratio; d-TGA = dextro-Transposition of the great arteries; HLHS = hypoplastic left heart syndrome; NSAIDs = nonsteroidal anti-inflammatory drugs; P9 = end of pregnancy; PVS = pulmonary valve stenosis; TOF = tetralogy of Fallot; VSD = ventricular septal defect.

Odds ratios are presented for birth defect categories with at least four exposed cases; all values shown exclude cases and controls with missing values for covariates.

* From 1 month before conception through the third month of pregnancy.

[†] Adjusted for maternal age at delivery, race/ethnicity, parity, maternal education, periconceptional alcohol, periconceptional smoking, periconceptional antibiotic use, study location, and estimated date of delivery.

[‡] Exposed controls: unexposed (n = 1082); any acetaminophen (n = 2518); acetaminophen only (n = 1921).

[§] Exposed controls: unexposed (n = 2120); any acetaminophen (n = 4924); acetaminophen only (n = 3781).

[¶] Exposed controls: unexposed (n = 2013); any acetaminophen (n = 4803); acetaminophen only (n = 3702).

[¶] Not simple denotes presence of other heart defects.

Supplemental Table 2

Frequency of analgesic use among mothers of cases and controls included in descriptive analysis, National Birth Defects Prevention Study 1997–2011

Analgesic type	Acetaminophen (n = 23,548) n (%)	NSAIDs (n = 12,716) n (%)	Opioids (n = 1021) n (%)
Acetaminophen	13,665 (58.0)	8950 (70.4)	461 (45.2)
NSAIDs		3267 (25.7)	27 (2.6)
Opioids			61 (6.0)
All three analgesics			472 (46.2)

NSAIDs, nonsteroidal anti-inflammatory drugs.

This table shows a cross-tabulation of self-reported analgesic use during pregnancy to document the prevalence and patterns of analgesic use during pregnancy. The shaded cells represent duplicated values in an adjacent column.