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## Case-control analysis of maternal prenatal analgesic use and cardiovascular malformations: Baltimore–Washington Infant Study

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### Abstract

**OBJECTIVE**—We sought to assess maternal prenatal use of analgesics and risk of cardiovascular malformations (CVM) in the offspring.

**STUDY DESIGN**—Data from the Baltimore–Washington Infant Study, a population-based case-control investigation of CVM, were used to examine selected isolated CVM diagnoses and maternal analgesic use during the periconceptional period (3 months before and after conception). We compared case and control infants on frequency of maternal use of analgesics and estimated adjusted odds ratios (adjORs) and 95% confidence intervals (CI) with logistic regression models for specific CVM phenotypes.

**RESULTS**—Frequency of periconceptional use of any analgesic was 52% among control mothers and 53% among case mothers. Analyses by CVM diagnoses identified an association of tetralogy of Fallot with maternal acetaminophen use (adjOR, 1.6; 95% CI, 1.1–2.3) and dextrotransposition of the great arteries with intact ventricular septum with maternal nonsteroidal antiinflammatory drug use (adjOR, 3.2; 95% CI, 1.2–8.7).

**CONCLUSION**—Analgesic use during the periconceptional period was not associated with CVM in the aggregate or with most phenotypes of CVM examined. Associations with 2 phenotypes of CVM may have occurred by chance. These findings warrant corroboration and further study, including further evaluation of the observed associations, the dose of analgesic taken, more specific timing of analgesic use, and indications for use.

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## Keywords

analgesics; birth defects; cardiovascular malformations; congenital heart defects; pregnancy

Analgesic medications are commonly used during pregnancy. Estimates of the prevalence of maternal analgesic use during pregnancy have reached 70%.<sup>1,2</sup> Indications for analgesic use are varied and include pain, fever, flu, preterm labor, and certain rheumatologic conditions. Analgesics are easily accessed either through prescription or over-the-counter purchase. They freely cross the placental barrier, which theoretically could pose potential risk to the developing fetus.<sup>3</sup> However, while maternal use of analgesics is high, the safety of analgesic use during pregnancy has not been well established.

Cardiac morphogenesis is complex and dependent on the expression of multiple genes and on many molecular pathways.<sup>4</sup> Maternal use of certain medications during fetal development, such as anticonvulsants and antihypertensives, has been associated with some types of cardiovascular malformations (CVM).<sup>5,6</sup> Whether use of analgesics may pose a risk is unclear. Many nonopioid analgesics, including salicylates and some other nonsteroidal antiinflammatory drugs (NSAIDs), exert their analgesic and antiinflammatory effects through inhibition of cyclooxygenase (COX) 1 and 2. It has been hypothesized that COX inhibition during the sensitive window of cardiogenesis may be involved in the disruption of heart development.<sup>7-9</sup> However, epidemiologic studies of the possible association between maternal analgesic use and CVM have had varied results.

Given the prevalence of analgesic use during pregnancy, the limited data on the safety of analgesic use during pregnancy, and the varied results from existing studies, additional evaluation of the possible association between maternal use of the more common analgesics and CVM is needed. In this analysis, we used data from the Baltimore–Washington Infant Study (BWIS) to examine associations between maternal analgesic use during the periconceptional period and CVM phenotypes.

## Materials and Methods

The BWIS population consisted of infants born to residents of Maryland, the District of Columbia, and 6 adjacent counties of northern Virginia from April 1981 through December 1989. The methods of this study have been previously described in detail.<sup>10,11</sup> All data used in our study were deidentified and analyses were performed with an exemption from the Institutional Review Board of the Centers for Disease Control and Prevention.

## Cases

Cases were infants with any type of CVM ascertained from searches of community hospitals, 6 pediatric cardiology centers serving the study region, and the medical examiner's logbooks from Maryland. CVM noted at registration were confirmed by echocardiography, cardiac catheterization, surgery, or autopsy. CVM were coded by pediatric cardiologists. Updated information about CVM diagnoses at 1 year of age obtained for all registered cases resulted in a change in only 7.8% of the initial diagnoses. Infants of gestational age < 38 weeks with patent ductus arteriosus as the only CVM were not included.

Also, because of improvements in diagnostic capability over the study period and the resultant rapid rise in the population prevalence among young infants, only a random sample of the infants with small ventricular septal defects (VSD) were included in BWIS. Infants with >1 cardiac defect were assigned 1 anatomic diagnosis using a hierarchical classification approach developed for BWIS based on the presumed embryonic timing of the defects. These diagnoses were then placed into categories based on their developmental mechanism.<sup>10,12</sup> Cases were further classified based on the presence of other anomalies as isolated (ie, no noncardiac defects); chromosomal disorders (eg, Down syndrome, other trisomies); recognizable syndromes (eg, Ivemark, DiGeorge, Noonan, Williams, fetal alcohol, congenital rubella); or multiple defects (ie, with noncardiac anomalies of unknown cause).

From all identified CVM cases (n = 4390), we excluded all cases with 1 of the following factors: maternal reports of pregestational diabetes since this condition is a known risk factor for CVM (n = 87); recognized syndromes or chromosomal abnormalities with the exception that we included infants with Down syndrome who had atrioventricular septal defect (AVSD) (n = 947 excluded); infants who were 1 of a set of twins, triplets, or other multiple births (n = 156); and those for whom no maternal interview was obtained (n = 1013). We then evaluated singleton infants with isolated CVM whose mothers did not have pregestational diabetes and did complete interviews (final n = 2525).

### Controls

Controls (n = 3572) were a random sample of all liveborn infants without CVM from the same birth cohort who were delivered in participating hospitals, stratified by month, year, and hospital of birth. Controls were similar to all area births during the study period by infant sex, race, birth weight, plurality, season of birth, and maternal age.<sup>13</sup> For this analysis, we included interviewed, singleton controls with no CVM, chromosomal anomalies, syndromes, or maternal reports of pregestational diabetes (final n = 3435).

### Data collection

Home interviews with the parents of case and control infants were conducted within 18 months of birth of the study subjects. A structured, standardized questionnaire was administered by trained interviewers to obtain information on sociodemographic factors, family history, maternal medical conditions, and environmental factors. The latter included reports on medication use during the periconceptional period (3 months before the last menstrual period through the first trimester of pregnancy).

### Analgesic use

For this analysis, we defined exposure as maternal use of an analgesic-containing medication at any time during the periconceptional period to ensure that all relevant exposures were included regardless of errors in recall of the last menstrual period or in recall of the exact timing of medication use. Maternal reports of use of prescription and nonprescription analgesics during the periconceptional period were grouped into pharmacologic classes: salicylates, acetaminophen, other NSAIDs, and opioids.

## Statistical analysis

First, we compared the frequency of selected maternal and infant demographic and clinical characteristics among cases and controls using the  $\chi^2$  statistic. A  $\chi^2$  statistic was not calculated if the proportion of subjects with missing values was >5% of the total. Then, because the presence of maternal fever or flu symptoms has been associated with an increased risk of CVM in the infant in previous analyses of BWIS data, we examined the frequency of maternal analgesic use among case and control infants by pharmacologic class stratified by the presence of fever or maternal flu symptoms during the periconceptual period.<sup>5,10</sup> Finally, we used multiple logistic regression models to evaluate possible associations of selected specific CVM diagnostic groups with maternal periconceptual use of analgesics by pharmacologic class using adjusted odds ratios (adjORs) and 95% confidence intervals (CIs). For this part of the analysis, we excluded infants of mothers who reported use of >1 class of analgesic drug, including use of single preparations that contained >1 class of analgesic, during the periconceptual period (28% of cases and 27% of controls). However, infants of mothers who reported use of nonanalgesic drugs only, or use of single preparations that contained both an analgesic and a nonanalgesic drug, during the periconceptual period were included. All models were adjusted for the covariates of infant sex, infant race, maternal age, family history of CVM, family history of other birth defects, maternal fever or flu symptoms during the periconceptual period, maternal prepregnancy body mass index (weight in kilograms/height in m<sup>2</sup>), and maternal smoking during the periconceptual period, with inclusion of quadratic terms for maternal age and prepregnancy body mass index because of their potential nonlinear relationship with the risk for birth defects. Only subjects with nonmissing values for all covariates were included in the models. We considered only associations based on at least 3 exposed cases to be stable.

## Results

### Characteristics of case and control infants

Compared with control infants, case infants were significantly more likely to have a family history of CVM ( $P < .001$ ). Otherwise, case and control infants were similar with respect to maternal and infant demographic and clinical characteristics (Table 1).

### Maternal analgesic use

From April 1981 through December 1989, the BWIS enrolled and interviewed 2525 singleton infants with isolated CVM or with AVSD and Down syndrome and 3435 singleton infants with no CVM, chromosomal anomalies, or syndromes whose mothers did not have pregestational diabetes. The frequency of any analgesic use during the periconceptual period was 53% among case mothers and 52% among control mothers. The frequency of analgesic use by pharmacologic class among case and control mothers, respectively, was: any salicylate-containing medication, 13.5% and 12.1%; any acetaminophen-containing medication, 42.9% and 43.5%; any NSAID-containing medication, 8.8% and 8.6%; and any opioid-containing medication, 4.4% and 3.6%. Among mothers of case infants who reported fever or flu symptoms during the periconceptual period, 177 (67.3%) used an analgesic compared with 235 (70.1%) among mothers of control infants who reported fever or flu symptoms (Table 2). Among mothers of case infants who did not report fever or flu

symptoms during the periconceptional period, 1160 (51.3%) used an analgesic compared with 1560 (50.3%) among mothers of control infants who did not report fever or flu symptoms. Overall, analgesic use was similar among mothers of case and control infants for all pharmacologic categories when stratified by the presence of fever or flu symptoms.

### **CVM diagnostic groups and maternal analgesic use**

When comparing use of analgesics by pharmacologic class and case or control status, multiple logistic regression analyses showed few significant associations between analgesic use and CVM (Table 3). Mothers of infants with tetralogy of Fallot were significantly more likely to have used acetaminophen during the periconceptional period than were control mothers (adjOR, 1.57; 95% CI, 1.08–2.27); mothers of infants with dextrotransposition of the great arteries (dTGA) with intact ventricular septum were significantly more likely to have used NSAIDs during the periconceptional period (adjOR, 3.24; 95% CI, 1.19–8.77). Maternal use of salicylates or opioids during the periconceptional period was not associated with CVM in the offspring.

### **Comment**

We found that use of any analgesic during the periconceptional period was common among pregnant women enrolled in BWIS, with the most commonly used analgesic class being medications containing acetaminophen. Analgesic use did not differ by the presence of fever or flu symptoms. Consistent with prior knowledge of congenital cardiac defects,<sup>14</sup> we found that family history of cardiac malformation was associated with increased prevalence of CVM in the offspring. Although analgesic use in the periconceptional period was not associated with CVM in the aggregate, we found associations of specific CVM phenotypes with maternal periconceptional use of acetaminophen and NSAID.

An association of CVM with periconceptional NSAID or acetaminophen use is consistent with the hypothesis that COX inhibition during fetal heart development might increase the risk of CVM in the infant. However, if COX inhibition were the underlying cause, one would expect that fetal exposure to irreversible inhibition of COX isoforms by salicylate during the critical period would also result in CVM. We did not observe an association between salicylate use and CVM.

Prior studies examining the association between exposure to COX inhibitors during the critical period of heart development and CVM have had mixed findings. In animal studies, use of high-dose aspirin and NSAIDs has been associated with cardiac septal defects.<sup>15,16</sup> In human beings, data from the Collaborative Perinatal Project, a prospective cohort study, showed no association of aspirin use early in pregnancy with CVM in the aggregate.<sup>17</sup> Similarly, findings from a case-control study by Werler et al<sup>18</sup> showed no association of aspirin use with CVM in the aggregate (relative risk, 0.9; 95% CI, 0.8–1.1). However, a slight association between maternal NSAID use during gestational weeks 5–8 and atrial septal defects was seen in a prospective cohort study from Norway, although the findings were not statistically significant (adjOR, 1.6; 95% CI, 0.7–3.9).<sup>19</sup> Data based on the Swedish Birth Registry suggested an association between NSAID use and CVM in the aggregate (OR, 1.86; 95% CI, 1.32–2.62).<sup>20</sup> A Canadian Registry-based study also found an

association between maternal NSAID use in the first trimester and cardiac septal defects (OR, 3.34; 95% CI, 1.87–5.98).<sup>21</sup>

Prospective data from the Danish National Birth Cohort and case-control data from the National Birth Defects Prevention Study (NBDPS) showed no increased risk of CVM with acetaminophen use.<sup>22,23</sup> In addition, no significant associations were noted between muscular VSD and maternal use of either NSAIDs or acetaminophen, adjusting for maternal fever, in NBDPS data.<sup>24</sup> However, more recent reports from this study have shown associations of maternal use of opioid analgesics with all CVM in the aggregate as well as with specific cardiac defects (ie, AVSD without Down syndrome, tetralogy of Fallot, conoventricular septal defect, hypoplastic left heart syndrome, pulmonary valve stenosis, and atrial septal defect + VSD and pulmonary valve stenosis + VSD associations), and of maternal use of naproxen with isolated pulmonary valve stenosis among full-term infants.<sup>25,26</sup> A recent study from The Norwegian Mother and Child Cohort Study found no association between maternal codeine use in the first trimester and congenital anomalies in the offspring.<sup>27</sup>

Previous analyses of BWIS data focusing on possible risk factors for each cardiac phenotype found associations of maternal periconceptional use of ibuprofen (1 type of NSAID) with dTGA with intact ventricular septum and with AVSD among infants with Down syndrome, and use of aspirin with interrupted aortic arch.<sup>10,28</sup> We did not include interrupted aortic arch in our study due to its strong association with DiGeorge syndrome. Our analysis, which excluded infants with chromosomal anomalies and any noncardiac birth defects, also showed an association between dTGA with intact ventricular septum and maternal NSAID use.

Among the cardiac phenotypes common to the recent report on opioid exposure from NBDPS and ours (ie, AVSD without Down syndrome, tetralogy of Fallot, hypoplastic left heart syndrome, and pulmonary valve stenosis), we found no associations with opioid analgesics. Possible reasons for the difference in findings between the 2 studies include a smaller sample size for each specific cardiac phenotype in our study; possible differences in composition between the opioid analgesics used during the different time periods (ie, 1981 through 1989 vs 1997 through 2005), the amount of opioid used, concomitant use of other medications, or the indication for use; and possible sampling variation.

Our findings need to be viewed in light of the limitations and strengths of the study. Limitations include potential maternal recall bias due to self-reported exposure status. However, >90% of the home interviews for both cases and controls were completed within 12 months of the infant's birth and the interview questions related drug use to specific medical indications.<sup>10,29</sup> A low likelihood of recall bias is also suggested by a previous analysis of reported drug use within the BWIS data, which showed no significant differences between the number of drugs reported by the time elapsed between delivery and interview.<sup>13</sup> As the time period of exposure spans up to 3 months before the last menstrual period, there may be a bias towards the null, as the half-life of most analgesics is <30 hours.<sup>30</sup> Another limitation pertains to the lack of information regarding the maternal dose of analgesic used, which prevented us from examining dose-response for any of the

pharmacologic classes of analgesics. There were also a small number of women using isolated opioid medications during the preconceptional period in our study, which prohibited us from assessing associations of many CVM types with maternal opioid use. We did not have information on some of the newer analgesic classes, such as COX-2 inhibitors, which were not widely used during the period of the BWIS. In addition, we included mothers who used nonanalgesic medications and could not control for possible differential exposure to these drugs between case and control infants. We were not able to assess any potential joint effects of these preparations because of the small number of mothers who reported taking individual multicomponent preparations. Confounding by indication is another potential limitation.

There were also some nonspecific categories of medication use reported in the BWIS data, such as miscellaneous cold medicines, and some reports of medication use for which the drug name was not known; these were not included in our exposure definition but might have contained analgesics and could have resulted in exposure misclassification. To assess the impact of maternal illness, we performed analyses controlling for the presence of maternal fever or flu symptoms as proxies for hyperthermia and influenza. However, some maternal infections might have been subclinical or underreported resulting in residual confounding. Also, we made no statistical corrections for multiple comparisons, which may have resulted in our finding of 2 significant associations due to chance alone. With the number of statistical comparisons made, approximately 4 significant findings would be expected due to chance and not to truly significant associations. Finally, the BWIS data are >20 years old, and the pattern of analgesic use may have changed over that time. However, use of analgesics is still common and indications for use have not changed significantly during the intervening period.

Strengths of our study include the population-based design of BWIS, which can minimize the potential for selection bias. Also, cases were identified from multiple sources, which maximized ascertainment. Other strengths are the classification of CVM in this study that took embryonic origin into account and was reviewed by pediatric cardiologists, and the verification of CVM diagnoses by echocardiogram, catheterization, or surgery for all case infants, which allowed evaluation of possible associations of analgesic use with specific phenotypes. In addition, we classified all analgesics by their pharmacologic mechanism, which allowed evaluation of biologically plausible associations between maternal analgesic use and CVM. Finally, we examined maternal analgesic use during the periconceptional period of organogenesis when potential teratogens would be expected to affect cardiac development.

Our findings provide reassurance that maternal analgesic use during pregnancy does not result in major teratogenic effects relative to congenital heart defects. We did find suggestion of a possible association of maternal use of NSAIDs and acetaminophen during the periconceptional period with dTGA with intact ventricular septum and tetralogy of Fallot in the offspring, respectively. Further studies are warranted to replicate these findings. Future studies regarding the potential teratogenicity of analgesics also should include information on dose and the specific timing of use; evaluate the use of newer analgesic classes such as COX-2 inhibitors; and attempt to limit exposure to the period of cardiac

development while taking into account the half-life of the drugs, their excretion, and their indication for use.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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TABLE 1

Case and control infants<sup>a</sup> by selected maternal and fetal characteristics

Characteristic	Cases (n = 2525)	% <sup>b</sup>	Controls (n = 3435)	% <sup>b</sup>	$\chi^2$ P value <sup>c</sup>
Family history of					
Cardiovascular malformation					
Yes	98	3.9	40	1.2	< .001
No	2427	96.1	3395	98.8	
Noncardiac malformation					
Yes	120	4.8	155	4.5	.66
No	2405	95.2	3280	95.5	
Maternal characteristics during periconceptional period					
Treated hypertension					
Yes	16	0.6	23	0.7	–
No	1743	69.0	2672	77.8	
Pregnancy BMI <sup>d</sup>					
<30	2346	92.9	3180	92.6	
30	174	6.9	248	7.2	.62
<35	2444	96.8	3351	97.6	
35	76	3.0	77	2.2	.06
Smoking <sup>e</sup>					
Yes	921	36.5	1222	35.6	.47
No	1604	63.5	2213	64.4	
Alcohol use <sup>e</sup>					
Yes	1508	59.7	2011	58.5	.34
No	1015	40.2	1424	41.5	
Education, y					
<12	461	18.3	637	18.5	.25
12	949	37.6	1221	35.5	
>12	1112	44.0	1575	45.9	

Characteristic	Cases (n = 2525)	% <sup>b</sup>	Controls (n = 3435)	% <sup>b</sup>	$\chi^2$	P value <sup>c</sup>
Fever <sup>d</sup>						
Yes	132	5.2	155	4.5		.20
No	2393	94.8	3280	95.5		
Flu symptoms <sup>e</sup>						
Yes	208	8.2	261	7.6		.37
No	2317	91.8	3174	92.4		
Age, y						
<20	339	13.4	485	14.1		.29
20–24	629	24.9	852	24.8		
25–29	748	29.6	1083	31.5		
30–34	576	22.8	730	21.3		
35	224	8.9	277	8.1		
Gravidity						
Primiparous	767	30.4	1119	32.6		.07
Multiparous	1758	69.6	2316	67.4		
Infant characteristics:						
Race						
White	1624	64.3	2279	66.3		.10
Other	901	35.7	1156	33.7		
Sex						
Male	1265	50.1	1741	50.7		.66
Female	1260	49.9	1694	49.3		

BMI, body mass index.

<sup>a</sup> Singleton infants of mothers without pregestational diabetes who completed interviews—infants with major noncardiac organ system anomalies, recognized syndromes, or chromosomal abnormalities other than Down syndrome with atrioventricular septal defect were excluded;

<sup>b</sup> Percents may not add up to 100 because of missing values;

<sup>c</sup> Calculations include only subjects with nonmissing values—P values were not calculated if proportion of subjects with missing values was >5% of total;

<sup>d</sup> Weight in kilograms/height in m<sup>2</sup>;

Exposure refers to periconceptional period.

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TABLE 2

Maternal analgesic use by analgesic class during periconceptional period<sup>a</sup>

Analgesic class	Cases (n = 2525)	%	Controls (n = 3435)	%
No fever or flu symptoms	2262	100	3100	100
No analgesic drugs	1102	48.7	1540	49.7
Any analgesic drug	1160	51.3	1560	50.3
Any aspirin-containing drug	295	13.0	359	11.6
Aspirin only	127	5.6	171	5.5
Any acetaminophen-containing drug	935	41.3	1296	41.8
Acetaminophen only	649	28.7	905	29.2
Any NSAID	190	8.4	257	8.3
NSAID only	51	2.3	60	1.9
Any opioid-containing drug	94	4.2	100	3.2
Opioid drug only	8	0.4	7	0.2
With fever and/or flu symptoms	263	100	335	100
No analgesic drugs	86	32.7	100	29.9
Any analgesic drug	177	67.3	235	70.1
Any aspirin-containing drug	46	17.5	57	17.0
Aspirin only	16	6.1	23	6.9
Any acetaminophen-containing drug	149	56.7	199	59.4
Acetaminophen only	100	38.0	136	40.6
Any NSAID	33	12.5	37	11.0
NSAID only	9	3.4	7	2.1
Any opioid-containing drug	16	6.1	23	6.9
Opioid drug only	1	0.4	4	1.2

NSAID, nonsteroidal antiinflammatory drug.

<sup>a</sup> Singleton infants of mothers without pregestational diabetes who completed interviews—infants with major noncardiac organ system anomalies, recognized syndromes, or chromosomal abnormalities other than Down syndrome with atrioventricular septal defects were excluded.

**TABLE 3**

Association<sup>a</sup> of cardiac malformations and maternal periconceptional analgesic use<sup>b,c</sup>

Cardiac malformation	Salicylates			Acetaminophen			Other NSAIDs			Opioids		
	Total no.	Exposed/ nonexposed <sup>d</sup>	AdjOR (95% CI)	Exposed/ nonexposed <sup>d</sup>	AdjOR (95% CI)	Exposed/ nonexposed <sup>d</sup>	AdjOR (95% CI)	Exposed/ nonexposed <sup>d</sup>	AdjOR (95% CI)	Exposed/ nonexposed <sup>d</sup>	AdjOR (95% CI)	
No malformation	2953	194/1640		1041/1640		67/1640		11/1640				
Any cardiac malformation	2149	143/1188	1.02 (0.81–1.28)	749/1188	0.99 (0.88–1.12)	60/1188	1.23 (0.86–1.77)	9/1188	1.02 (0.41–2.57)			
Lateral/looping	36	3/20	1.47 (0.42–5.13)	12/20	1.00 (0.48–2.08)	0/20	N/A	1/20	25.57 (2.42–270.25) <sup>e</sup>			
Conotruncal	321	18/173	0.85 (0.51–1.43)	119/173	1.08 (0.84–1.39)	10/173	1.45 (0.72–2.89)	1/173	0.92 (0.11–7.31)			
dTGA	154	9/85	0.81 (0.39–1.66)	53/85	0.89 (0.62–1.29)	6/85	1.74 (0.72–4.21)	1/85	1.63 (0.20–13.38)			
dTGA with IVS	78	5/40	0.98 (0.37–2.57)	28/40	0.96 (0.58–1.59)	5/40	3.24 (1.19–8.77) <sup>e</sup>	0/40	N/C			
dTGA with VSD	47	2/26	0.65 (0.15–2.83)	18/26	1.00 (0.54–1.87)	0/26	N/A	1/26	8.09 (0.90–72.42)			
dTGA with DORV	14	1/7	0.82 (0.10–7.12)	5/7	0.91 (0.28–2.98)	1/7	2.92 (0.34–25.16)	0/7	N/C			
Truncus arteriosus	14	1/10	0.78 (0.10–6.36)	3/10	0.47 (0.13–1.76)	0/10	N/A	0/10	N/C			
Tetralogy of Fallot	135	8/64	1.10 (0.51–2.36)	59/64	1.57 (1.08–2.27) <sup>e</sup>	4/64	1.61 (0.56–4.61)	0/64	N/C			
Any AVSD	213	16/107	1.19 (0.68–2.09)	81/107	1.14 (0.83–1.55)	9/107	1.97 (0.94–4.13)	0/107	N/C			
AVSD with Down syndrome	162	13/81	1.24 (0.66–2.32)	62/81	1.15 (0.81–1.63)	6/81	1.68 (0.69–4.10)	0/81	N/C			
AVSD without Down syndrome	51	3/26	1.07 (0.31–3.66)	19/26	1.10 (0.59–2.03)	3/26	3.37 (0.95–11.93)	0/26	N/C			
Membranous VSD	410	27/236	1.01 (0.66–1.56)	133/236	0.92 (0.73–1.16)	11/236	1.13 (0.58–2.18)	3/236	2.08 (0.56–7.67)			
Atrial septal defect secundum	162	14/89	1.48 (0.81–2.70)	55/89	1.01 (0.70–1.45)	3/89	0.95 (0.29–3.11)	1/89	N/C			
Left-sided obstruction	210	17/116	1.11 (0.64–1.92)	70/116	0.87 (0.64–1.20)	7/116	1.42 (0.63–3.21)	0/116	N/C			
Hypoplastic left heart	95	10/53	1.62 (0.79–3.30)	30/53	0.89 (0.56–1.42)	2/53	0.95 (0.22–4.03)	0/53	N/C			

Cardiac malformation	Total no.	Salicylates		Acetaminophen		Other NSAIDs		Opioids	
		Exposed/ nonexposed <sup>d</sup>	AdjO (95% CI)	Exposed/ nonexposed <sup>d</sup>	AdjOR (95% CI)	Exposed/ nonexposed <sup>d</sup>	AdjOR (95% CI)	Exposed/ nonexposed <sup>d</sup>	AdjOR (95% CI)
Coarctation of aorta	66	6/37	1.30 (0.52–3.21)	20/37	0.81 (0.46–1.42)	3/37	1.99 (0.58–6.82)	0/37	N/C
Aortic valve stenosis	49	1/26	0.24 (0.03–1.82)	20/26	0.88 (0.48–1.62)	2/26	1.62 (0.37–7.16)	0/26	N/C
Right-sided obstruction	231	16/135	1.05 (0.60–1.85)	74/135	0.90 (0.66–1.22)	5/135	0.92 (0.36–2.36)	1/135	1.11 (0.14–8.94)
Pulmonary valve stenosis	175	13/103	1.11 (0.59–2.10)	54/103	0.87 (0.62–1.24)	4/103	0.97 (0.34–2.76)	1/103	1.43 (0.17–11.80)
Pulmonary atresia with IVS	35	2/18	0.94 (0.21–4.17)	14/18	1.17 (0.57–2.40)	1/18	1.23 (0.16–9.51)	0/18	N/C
Ebstein anomaly	27	3/12	2.26 (0.60–8.45)	11/12	1.36 (0.59–3.14)	1/12	1.55 (0.18–13.59)	0/12	N/C
Patent ductus arteriosus <sup>f</sup>	42	5/21	2.63 (0.94–7.36)	15/21	1.11 (0.56–3.14)	1/21	1.22 (0.15–9.71)	0/21	N/C
Total anomalous pulmonary venous return	37	1/20	0.44 (0.06–3.33)	14/20	1.07 (0.53–2.17)	2/20	2.74 (0.61–12.34)	0/20	N/C

*adjOR*, adjusted odds ratios; *AVSD*, atrioventricular septal defect; *CI*, confidence interval; *DORV*, double outlet right ventricle; *dTGA*, dextrotransposition of great arteries; *IVS*, intact ventricular septum; *N/A*, not applicable; *N/C*, not calculated (because there were too few exposed cases for logistic model to converge); *NSAID*, nonsteroidal antiinflammatory drug; *VSD*, ventricular septal defect.

<sup>a</sup> Adjusted for infant sex, infant race, maternal age, family history of cardiovascular and noncardiovascular malformation, maternal fever and/or flu symptoms during periconceptual period, maternal prepregnancy body mass index, and maternal smoking during periconceptual period;

<sup>b</sup> Use of only 1 analgesic type at any time from 3 mo before last menstrual period through first trimester of pregnancy—all categories of analgesic class use are mutually exclusive;

<sup>c</sup> Singleton infants of mothers without pregestational diabetes who completed interviews—infants with major noncardiac organ system anomalies, recognized syndromes, or chromosomal abnormalities other than Down syndrome with AVSD were excluded;

<sup>d</sup> Ratio of number of case or control infants whose mothers used analgesic medication during periconceptual period to number of case or control infants whose mothers did not use analgesic medication during periconceptual period;

<sup>e</sup>  $P = .05$ ;

<sup>f</sup> Excludes infants of gestational age <38 wk.