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# Use of Antihistamine Medications During Early Pregnancy and Isolated Major Malformations

**Suzanne M. Gilboa**[*], **Matthew J. Strickland**[*], **Andrew F. Olshan**[†], **Martha M. Werler**[‡], **Adolfo Correa**[*], and **The National Birth Defects Prevention Study**

[*]National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA

[†]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC

[‡]Slone Epidemiology Center at Boston University, Boston, MA

## Abstract

**BACKGROUND—**Antihistamines are commonly used during pregnancy. There is little evidence that they have teratogenic effects, but there are knowledge gaps with respect to newer products, as well as the relationship between specific antihistamines and specific birth defects.

**METHODS—**Using the National Birth Defects Prevention Study (1997-2003), the authors examined associations between maternal use of 14 antihistamines during early pregnancy and 26 isolated major birth defects. A Bayesian analysis incorporating prior knowledge about the relationships between the antihistamines, birth defects, and measured covariates was conducted.

**RESULTS—**Of the 364 associations investigated, 24 had 95% posterior intervals excluding 1.0. All 24 associations were positive; 23 associations were of weak to moderate magnitude (posterior odds ratio [OR] < 3.0) and one was strong (OR > 6.0) but very imprecise. Of the 24 associations, 20 were with non-cardiac defects. Eight associations involved the antihistamine diphenhydramine.

**CONCLUSIONS—**The results of this study generally were consistent with no association between birth defects and antihistamine use during early pregnancy. Several of the findings might warrant further investigation, although the observed elevated associations should be interpreted in the context of the number of associations investigated and the analysis of retrospective, self-reported data.

### Keywords

antihistamine; Bayesian methods; birth defects; H1 blockers; pregnancy

## INTRODUCTION

Antihistamines, or $H_1$ receptor antagonists, are widely prescribed or taken as over-the-counter formulations during pregnancy, primarily for the treatment of nausea and vomiting or relief of cold and allergy symptoms. Antihistamines were first developed in the 1930s,

Corresponding Author: Suzanne M. Gilboa, PhD National Center on Birth Defects and Developmental Disabilities Centers for Disease Control and Prevention Mail Stop E-86 1600 Clifton Road Atlanta, GA 30333.

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and several early products are still in widespread use. The reported prevalence of antihistamine use ranges from 4–10% during the first trimester, and from 8–15% at any time during pregnancy (Kallen, 2002; Rubin and others, 1993; Werler and others, 2005).

The epidemiologic literature, which dates back over 40 years, (Heinonen and others, 1977) provides little support for the teratogenicity of first generation antihistamines, also known as "nonselective" or "sedating" antihistamines (Briggs and others, 2005). There are, however, relatively few epidemiologic studies that have examined associations between specific antihistamines taken during pregnancy and specific birth defects. The National Collaborative Perinatal Project (NCPP), the first prospective, large-scale investigation of the possible teratogenic role of medications, reported elevated associations with first trimester use of brompheniramine and chlorpheniramine and all birth defects combined. Chlorpheniramine and meclizine were both associated with eye and ear defects. All other NCPP analyses showed no association between specific antihistamines and birth defects (Heinonen and others, 1977). The Baltimore-Washington Infant Study, a retrospective case-control study, found no association between use of any antihistamine medication from 3 months before pregnancy through the end of the first trimester and risk of all congenital heart defects (Ferencz and others, 1993). Seto and colleagues' pooled analysis of 24 studies conducted during the period 1960–1991 reported a Mantel-Haenszel summary odds ratio (OR) of 0.76 (95% confidence interval [CI]: 0.60, 0.94), indicating a reduced risk of major malformations (all types of malformations combined) associated with first trimester use of any antihistamine (Seto and others, 1997). More recently, a publication from the Swedish Medical Birth Registry raised concerns regarding the possible association between use of the allergy medication loratadine (a second generation antihistamine) and hypospadias (Källén and Olausson, 2001). Several subsequent studies, including one based on more recent data from the Swedish registry, found no association between loratadine and hypospadias (Centers for Disease Control and Prevention, 2004; Diav-Citrin and others, 2003; Källén and Olausson, 2006; Moretti and others, 2003; Pedersen and others, 2006a; Pedersen and others, 2006b). The antinauseant Bendectin (which contains the antihistamine, doxylamine succinate) is one of the most thoroughly studied medications during pregnancy and is not believed to have teratogenic effects (Boneva and others, 1999; Brent, 2003; Brent, 1995; Cordero and others, 1981; Elbourne and others, 1985; McKeigue and others, 1994; Milkovich and van den Berg, 1976; Mitchell and others, 1981; Mitchell and others, 1983; Shiono and Klebanoff, 1989; Zierler and Rothman, 1985).

Although the body of epidemiologic evidence suggests little or no harmful effect of first-generation antihistamines on the risk of birth defects, there have been few investigations into the possible teratogenic effects of the second- and third-generation (also called "selective" or "non-sedating") antihistamines that have entered the market relatively recently (e.g., fexofenadine). Given the popularity of antihistamines during pregnancy and the gaps in our knowledge about specific antihistamines in relation to specific birth defects, we conducted a large-scale analysis of data from a retrospective case-control study to examine a range of antihistamine products in relation to a range of major malformations. Because there is a body of literature suggesting that antihistamines are not likely to be teratogenic, we employed Bayesian analytic methods to incorporate this prior knowledge in the analysis.

## MATERIALS AND METHODS

### National Birth Defects Prevention Study

The National Birth Defects Prevention Study (NBDPS) is an ongoing, multistate, population-based case-control study of environmental and genetic risk factors for major birth defects, incorporating data from 10 birth defects surveillance systems across the United States and coordinated by the Centers for Disease Control and Prevention (CDC). Detailed

methods for the NBDPS have been described elsewhere (Yoon and others, 2001). Each year, Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey (ending in 2002), New York, North Carolina (beginning in 2003), Texas, and Utah (beginning in 2003) contribute 300 cases from their birth defects surveillance systems and randomly select100 liveborn controls without birth defects from birth certificate files or delivery logs of birth hospitals. Medical records of potential cases were reviewed by a team of clinicians and clinical geneticists to ensure they satisfy the inclusion criteria; infants and fetuses with chromosomal abnormalities and single-gene disorders are excluded from the study. In addition, cases with heart defects were confirmed by echocardiography and/or cardiac catheterization, surgery, or autopsy. Several heart defects were excluded from NBDPS because they were rare, poorly ascertained in infancy, related to preterm delivery (isolated patent ductus arteriosus and isolated patent foramen ovale), minor defects of unclear significance, or vascular defects rather than malformations of the heart (Botto and others, 2007). Computer-assisted telephone interviews were conducted with mothers from 6 weeks to 24 months after the estimated date of delivery; interviews were conducted in English or Spanish, as applicable. Overall participation rates were 72%t among case mothers and 69% among control mothers during the study period. Women were asked to report medications, vitamins, or supplements taken for any reason during pregnancy. Estimated dates of use, and the frequency and duration of use were recorded. Medications were coded using the Slone Epidemiology Center Drug Dictionary (Kelley and others, 2003), thereby linking the reported substances to their active ingredients. The NBDPS has been approved by the institutional review boards of CDC and the participating study centers.

## Data Analysis

**Outcome Definitions—**All cases were classified as having either an isolated defect or multiple defects. An isolated defect consisted of any of the following: one major defect; one major defect and one or more minor defects; one or more major defects that affected one organ system only; or a well-described sequence of related defects without any other unrelated major defects. Multiple defects were two or more major unrelated defects affecting different organ systems (Rasmussen and others, 2003). Major defect groups were categorized by organ system and by organ subgroups when possible. Cases with cardiac defects received a second classification denoting the complexity of the cardiac defect. “Simple” cardiac defects were anatomically discrete or a well-recognized single entity (e.g., hypoplastic left heart syndrome or tetralogy of Fallot). “Associations” were common, uncomplicated combinations of cardiac defects (Botto and others, 2007).

Our study population consisted of cases with isolated birth defects and controls born without birth defects on or after October 1, 1997, with an estimated date of delivery on or before December 31, 2003. All infants whose mothers had pregestational diabetes (type 1 or type 2) were excluded. Isolated birth defects for which there were at least 200 cases were included in this analysis. We considered 11 non-cardiac defects and three aggregated groupings: neural tube defects, oral clefts and limb deficiencies. We also considered seven simple cardiac defects, one cardiac defect association, and four aggregated groupings of cardiac defects: conotruncal defects, left ventricular outflow tract obstructions, right ventricular outflow tract obstructions, and septal defects.

**Antihistamine exposure definitions—**Study participants reported use of 54 different antihistamine agents during the period one month before pregnancy through the end of the first trimester. We collapsed these 54 components into 14 analytic groups: one group encompassed the use of any antihistamine, and the other 13 groups were based on the similarity of formulations and mechanism of action of their antihistamine components:: cetirizine, clemastine, dimenhydrinate, diphenhydramine, doxylamine, hydroxyzine,

fexofenadine, loratadine, meclizine, pheniramine, promethazine, triprolidine, and not otherwise specified antihistamine products. Cetirizine, fexofenadine, and loratadine are second-generation antihistamines. All other groups are first-generation products. Exposure was defined as any use during the period one month before pregnancy through the end of the first trimester; the reference group was comprised of infants whose mother did not report the use of an antihistamine during the same time period.

**Covariate definitions—**The following covariates were considered potential confounders of the associations of interest: maternal age (<18, 18–24, 25–29, 30–34, and >35 years), maternal race or ethnicity (non-Hispanic White, non-Hispanic Black or African American, Hispanic, and other), maternal education (less than high school, completion of high school, and more than high school), entry into prenatal care (<10 weeks gestation and >10 weeks gestation), parity (primiparous and multiparous), household income (<$40,000 and > $40,000/year), and study center. In addition, periconceptional folic acid use, smoking, and alcohol intake were dichotomized as any use during the period 1 month before pregnancy through the first 3 months of pregnancy and no use during the same time window.

**Frequentist analyses—**We first undertook frequentist analyses (Kleinbaum and Klein, 2002) using multiple logistic regression to estimate adjusted odds ratios and 95% confidence intervals for the associations between each of the 14 antihistamine groups and the 26 birth defects under study. All above-mentioned covariates were included in the final adjusted models.

**Bayesian analyses—**Following the approach recently detailed by Greenland (Greenland, 2007) we then incorporated prior knowledge about the associations between birth defects and antihistamines and between birth defects and the other covariates into our analyses. Because past research has provided little evidence to support the teratogencity of antihistamines, it seemed reasonable to specify a prior mean log OR = 0 (OR = 1.0) for the effect of antihistamines. However, because it was unclear how applicable these previous results were to specific associations between a particular antihistamine and a particular birth defect, we selected an appropriately large variance (1.125) (95% CI = 0.13, 8.0) around this prior mean to reflect our uncertainty.

We selected these same prior values (prior OR = 1.0 and 95% CI: 0.13-8.0) for all independent variables in the model, with the exception of maternal age (30-34 years and >35 years), any smoking during the first trimester, and any alcohol use during the first trimester. These factors have been associated with an elevated risk of certain birth defects, (Honein and others, 2007; Reefhuis and Honein, 2004; Romitti and others, 2007) and we specified prior values to reflect this (mean log OR = 0.693, variance = 1.125, corresponding to a prior OR = 2.0 and 95% CI: 0.25, 16.00). As described by Greenland (Greenland, 2007), we incorporated this prior information by adding observations to the dataset. Briefly, for each independent variable in the logistic regression model, approximately 200,000 observations were added to the dataset to represent the prior information about the relationship between that factor and birth defects. An additional variable was also created to denote whether the record was part of the original (actual) data or prior data. This variable was included in all regression models. Multivariable logistic regression models were used to estimate Bayesian posterior odds ratios and 95% posterior intervals based on this augmented dataset. Both the frequentist and Bayesian analyses were conducted in SAS 9.1.3 (Cary, NC).

**Secondary Analyses—**After reviewing our results, we conducted secondary analyses of selected associations to explore potential confounding by two types of conditions: a) nausea and/or vomiting of pregnancy during the first semester (Boneva and others, 1999); b)

respiratory infection accompanied by fever, because hyperthermia is a risk factor for selected birth defects (Li and others, 2007). In addition, because evidence for teratogenicity has frequently been found among infants with multiple congenital anomalies (MCA) (Khoury and others, 1994; Khoury and others, 1993), we also analyzed all cases with MCA as a single group, in relation to the 14 antihistamine exposures.

## RESULTS

The frequency of antihistamine use was similar among cases with either an isolated non-cardiac defect or an isolated cardiac defect and among controls (Tables 1 and 2). Promethazine, an antinauseant, was the most frequently used antihistamine. Pheniramines (including chlorpheniramine, brompheniramine, and their derivatives), generally used to treat cold and allergy symptoms, were the second most common antihistamine components used. Diphenhydramine, loratadine, and doxylamine were also used by more than 1% of control mothers. Out of the 364 possible antihistamine–birth defect combinations, 74 (20%) had no exposed cases.

In analyses conducted before the Bayesian augmentation of the dataset, there were 23 statistically significant associations; after Bayesian augmentation, there were 24 associations with posterior intervals that excluded 1.0 (Tables 3 and 4). Eighteen of the 24 were found in both analyses. The six associations that had Bayesian posterior intervals that excluded 1.0 but were not statistically significant before Bayesian augmentation were of “borderline” significance prior to data augmentation (any antihistamine and cleft lip with or without cleft palate and craniosynostosis; diphenhydramine and spina bifida, pheniramine and spina bifida, and promethazine and neural tube defects and ventricular septal defect with atrial septal defect). The five that were significant before Bayesian augmentation of the dataset but had posterior intervals that included 1.0 were very imprecise results based on between 3 and 6 exposed cases (meclizine and oral clefts, hydroxyzine and atrial septal defect, and antihistamine not otherwise specified and spina bifida, cleft lip with or without cleft palate and ventricular septal defect).

Of the 24 associations, 20 were with non-cardiac defects (Table 3) and four were with cardiac defects (Table 4). Twenty-three associations were of modest magnitude (OR < 3.0); the association between meclizine and cleft palate was large, but imprecise (OR = 6.16, 95% posterior interval: 1.78, 21.33). There was one positive association with a second–generation product: loratadine and transverse limb deficiencies (OR = 2.04; 95% posterior interval: 1.04, 4.03). Eight of the associations were with exposure to diphenhydramine. These were for neural tube defects, spina bifida, oral clefts, cleft lip with or without cleft palate, transverse limb deficiencies, craniosynostosis, gastroschisis, and right ventricular outflow tract obstruction defects. Risk of spina bifida was associated with five antihistamine categories: use of any antihistamine, diphenhydramine, doxylamine, pheniramine, and promethazine. Among the four associations with cardiac defects, two were between doxylamine and left ventricular outflow tract obstruction defects.

For all 24 results for which the Bayesian posterior interval excluded 1.0, we conducted secondary analyses to explore potential residual confounding. Results for doxylamine, promethazine, meclizine, and diphenhydramine were reanalyzed for potential confounding by the common indication of nausea or vomiting during the first trimester. The pheniramine and diphenhydramine results were explored for potential confounding by respiratory infection accompanied by fever during the first trimester. These analyses were largely insensitive to adjustment by these additional potential confounders in the multivariable model (data not shown). Lastly, we found no elevated associations between any of the 14

antihistamine exposure groups and odds of delivering an infant with MCA (n=1365 cases) (data not shown).

## DISCUSSION

We conducted a large-scale analysis to examine a range of antihistamine products in relation to a range of major malformations and employed Bayesian methods to incorporate our prior knowledge into the analysis. Overall, the results were consistent with a lack of association of birth defects with the use of antihistamines during early pregnancy. Our results should be interpreted with the understanding that we created many statistical models and that several associations may have resulted by chance. The Bayesian approach was not implemented as a solution to the problem of multiple comparisons. Rather, the approach was helpful in controlling estimates based on very small cell counts; five associations that were unstable, yet statistically significant before Bayesian analysis, now had 95% posterior intervals that included 1.0. This was a sign that the approach was useful for this purpose. The six associations that had posterior intervals that excluded 1.0 in the Bayesian analysis that were not statistically significant before were arguably of “borderline” significance, and can be considered hypothesis-generating findings. The 18 associations that were found in both the pre-Bayesian and the Bayesian analyses are potentially more noteworthy, having withstood the Bayesian adjustment. However these may still be chance findings. Of the 24 associations with posterior intervals excluding 1.0, 16 were of weak magnitude (OR < 2.0), seven were of moderate magnitude (OR 2.0 – < 3.0), and one association had an OR ≥3.0 (meclizine and cleft palate). Eight of the twenty-four associations were with diphenhydramine exposure. Five of the twenty-four were with spina bifida.

The observed associations with diphenhydramine were unexpected. Diphenhydramine was one of the first antihistamines sold in the United States (1946); it is still used in several prescription and over-the-counter medications (Briggs and others, 2005). There is little evidence that it is teratogenic in animals although non-teratogenic adverse effects in rats have been reported (Chiavegatto and others, 1997; Sturman and others, 2002). One epidemiologic study reported increased risk for cleft palate associated with diphenhydramine use, although this analysis did not adjust for potential confounders and was based on only 8 exposed cases (Saxen, 1974). This finding has not been replicated in the epidemiologic literature. We observed an elevated risk associated with cleft lip with or without cleft palate, but not with cleft palate alone. The modest positive associations between diphenhydramine exposure and neural tube defects, spina bifida (but not with anencephaly), transverse limb deficiencies, craniosynostosis, and gastroschisis might warrant follow-up evaluation but none of them have been reported previously.

Our results for doxylamine were also unanticipated. Doxylamine succinate was an active ingredient in the antinauseant Bendectin, and is still found in several over-the-counter products that are used frequently during pregnancy. In 1983, Bendectin was voluntarily taken out of production following the filing of several hundred lawsuits alleging its teratogenicity and the adverse media attention associated with the litigation. The vast majority of epidemiologic studies of Bendectin and birth defects, including all prospective analyses, as well as several reviews and meta-analyses of the literature have reported null results or inverse associations (Boneva and others, 1999; Brent, 2003; Brent, 1995; Cordero and others, 1981; Elbourne and others, 1985; McKeigue and others, 1994; Milkovich and van den Berg, 1976; Mitchell and others, 1981; Mitchell and others, 1983; Shiono and Klebanoff, 1989; Zierler and Rothman, 1985). There have been only a few exceptions (Aselton and others, 1984; Eskenazi and Bracken, 1982; Golding and others, 1983; Rothman and others, 1979) based on restrospective studies. The elevated risks that we observed for doxylamine in relation to hypoplastic left heart syndrome, left ventricular outflow tract

obstruction defects, spina bifida, and neural tube defects were therefore not anticipated given the extensive epidemiologic data suggesting the safety of doxylamine in relation to birth defects overall, as well as several specific birth defect phenotypes, including neural tube defects. Regarding left ventricular outflow tract obstructions, one study reported no association with hypoplastic left heart syndrome in the context of a primary analysis of nausea during pregnancy (Boneva and others, 1999).

The associations observed between pheniramine (which included medications containing either brompheniramine or chlorpheniramine) and spina bifida and cleft lip with or without cleft palate have not been previously reported and there is no evidence in the literature to suggest its teratogenicity. The NCPP reported associations between brompheniramine and chlorpheniramine and all birth defects, but not specifically with clefts (Heinonen and others, 1977). Meclizine, which is teratogenic in rats and is known to induce cleft palate at 25–50 times the human doses, (King, 1963) has not been reported to cause human birth defects (Källén and Mottet, 2003). The observed association between meclizine and cleft palate was based on five exposed cases and was our most imprecise result. Promethazine, the most commonly used antihistamine among NBDPS participants, was nearly always prescribed for morning sickness (82% of users). The associations with spina bifida, all neural tube defects as a group, and ventricular septal defects with atrial septal defects have never been reported in the literature and may be chance results. Our analyses corroborated the lack of association between loratadine and hypospadias that had been reported recently in the literature (Centers for Disease Control and Prevention, 2004; Diav-Citrin and others, 2003; Källén and Olausson, 2006; Moretti and others, 2003; Pedersen and others, 2006a; Pedersen and others, 2006b).

We stabilized imprecise effect estimates by using a Bayesian analysis with a dataset augmented with additional observations to represent prior data. Because our prior estimates for the mean and variance for the effect of antihistamine exposure (OR = 1.0; 95% CI: 0.13, 8.0) and the other independent variables in the multivariable models were conservative (i.e. very wide confidence interval around the prior mean), the overall effect of the Bayesian adjustment was small. The Bayesian adjustment, however, had a more pronounced effect on initially unstable effect estimates with very large confidence intervals because of few exposed cases. These estimates were stabilized substantially after data augmentation. For example, the association between meclizine use and isolated cleft palate (five exposed cases) before data augmentation was large and imprecise (frequentist OR = 12.69; 95% CI: 2.89, 55.66). After data augmentation, these results were more precise and pulled toward the null (posterior OR = 6.16; 95% posterior interval: 1.78, 21.33).

The NBDPS provided an opportunity to look at more birth defect phenotypes in relation to more types of antihistamines than ever previously reported in the literature. A strength of our study was the detailed classification of birth defects by clinical geneticists, which allowed for analyses of etiologically similar outcome groups. In addition, our focus on isolated phenotypes was intended to add to this homogeneity within outcome groupings and reduced the “double counting” of cases. Yet despite these strengths, there were several limitations that pertain specifically to the medication data. First, we were unable to consider over-the-counter versus prescription status in our analyses. It is possible that over-the-counter medication use was perceived as more casual than prescription drug use and recollection of use might have varied between these two types or over time. This would be particularly true if a medication became available over-the-counter during the course of the study. Loratadine is one example of this. In November 2002, the FDA approved loratadine for marketing over the counter. In NBDPS data, the first pregnancies potentially affected by this transition were delivered in late 2003; we saw no evidence of increased use from 2002 to 2003. Second, some mothers reported the use of an antihistamine on an “as needed” basis.

"As needed" use was more common for some antihistamine types than for others, but sensitivity analyses excluding "as needed" exposures did not show differences in the associations with birth defects. Third, antihistamine products can have more than one active ingredient, such as a fever reducer, decongestant, or cough suppressant. Our analyses did not distinguish between use of products that contained only the antihistamine and those that contained the antihistamine in combination with other drugs. Fourth, although we conducted several secondary analyses to evaluate the sensitivity of our results to potential confounding by indication, these analyses were not comprehensive. Antihistamines have several primary uses; in our data, approximately 40% of episodes were indicated for a reported respiratory illness and about 20% for nausea or vomiting, or both, during pregnancy. Because an additional 30% of women did not report an indication for their antihistamine medication use and the remaining 10% reported a wide range of medical indications, a substantial number of observations were excluded from these analyses because of no or uncommon indications. Some indications, such as for seasonal allergies, could not be explicitly reported in these data, and might (or might not) have been captured by the "respiratory illness" indication.

We were also unable to evaluate potential exposure misclassification due to biased or incorrect recall. Even though all interviews were conducted within 24 months of delivery, the time lag, or perhaps an intervening pregnancy, might have led to inaccurate recall of maternal antihistamine use. The average time between delivery and interview was longer for case mothers than for control mothers (11 months versus 9 months); however, analyses stratifying by time between expected date of delivery and date of interview (<12 months, 12–<18 months, and >18 months) did not suggest that the associations observed were due to recall bias. In addition, we could not preclude the possibility of residual confounding in these data by either unmeasured or poorly measured covariates. Finally, it is possible that some antihistamines are associated with birth defects that are not included in the NBDPS.

Even though our study included more exposed case and control infants than most previous studies, the data were sparse for some antihistamine exposures, especially the second-generation products. Our analytic approach mitigated this problem because it allowed us to shrink and stabilize several large, but very imprecise estimates in multivariable models. However, our approach did not eliminate the possibility of type 1 errors (false positives). The results of our study were consistent with no large increased risk for birth defects associated with antihistamine use during early pregnancy. The observed elevated associations should be interpreted in the context of the number of associations investigated and the analysis of retrospective, self-reported data.

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## Table 1

Number and Percentage of Cases with Isolated Non-Cardiac Birth Defects and Healthy Controls Exposed to Antihistamines From the Month Before Pregnancy Through the First Trimester, National Birth Defects Prevention Study, 1997–2003

| Birth Defect | None* | | Any Antihistamine | | Cetirizine | | Clemastine | | Dimenhydrinate | | Diphenhydramine | | Doxylamine | | Fexofenadine | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| **Controls (n = 4982)** | **4445** | **89.2** | **518** | **10.4** | **28** | **0.6** | **6** | **0.1** | **9** | **0.2** | **93** | **1.9** | **64** | **1.3** | **30** | **0.6** |
| **Cases** | | | | | | | | | | | | | | | | |
| All non-cardiac defects (n = 5491)† | 4826 | 87.9 | 643 | 11.7 | 28 | 0.5 | 8 | 0.1 | 7 | 0.1 | 151 | 2.7 | 97 | 1.8 | 39 | 0.7 |
| Neural tube defects (n = 802) | 686 | 85.5 | 114 | 14.2 | 2 | 0.2 | 2 | 0.2 | 0 | 0 | 27 | 3.4 | 21 | 2.6 | 6 | 0.7 |
| Anencephalus (n = 234) | 195 | 83.3 | 38 | 16.2 | 1 | 0.4 | 0 | 0 | 0 | 0 | 11 | 4.7 | 5 | 2.1 | 2 | 0.9 |
| Spina bifida (n = 489) | 420 | 85.9 | 68 | 13.9 | 0 | 0 | 2 | 0.4 | 0 | 0 | 14 | 2.9 | 14 | 2.9 | 4 | 0.8 |
| Anotia / Microtia (n = 218) | 198 | 90.8 | 19 | 8.7 | 0 | 0 | 0 | 0 | 1 | 0.5 | 4 | 1.8 | 4 | 1.8 | 0 | 0 |
| Oral clefts (n = 1725) | 1527 | 88.5 | 191 | 11.1 | 13 | 0.8 | 4 | 0.2 | 4 | 0.2 | 45 | 2.6 | 26 | 1.5 | 13 | 0.8 |
| Cleft palate (n= 575) | 518 | 90.1 | 55 | 9.6 | 5 | 0.9 | 1 | 0.2 | 2 | 0.3 | 11 | 1.9 | 9 | 1.6 | 4 | 0.7 |
| Cleft lip with or without cleft palate (n = 1150) | 1009 | 87.7 | 136 | 11.8 | 8 | 0.7 | 3 | 0.3 | 2 | 0.2 | 34 | 3 | 17 | 1.5 | 9 | 0.8 |
| Anorectal atresia (n = 223) | 205 | 91.9 | 17 | 7.6 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 1.3 | 2 | 0.9 | 2 | 0.9 |
| Hypospadias (n = 864) | 760 | 88 | 101 | 11.7 | 7 | 0.8 | 1 | 0.1 | 0 | 0 | 15 | 1.7 | 15 | 1.7 | 10 | 1.2 |
| Limb deficiency defects (n = 415) | 367 | 88.4 | 45 | 10.8 | 1 | 0.2 | 0 | 0 | 1 | 0.2 | 11 | 2.7 | 5 | 1.2 | 2 | 0.5 |
| Transverse limb deficiency defects (n = 283) | 245 | 86.6 | 35 | 8.4 | 0 | 0 | 0 | 0 | 0 | 0 | 9 | 3.2 | 3 | 1.1 | 2 | 0.7 |
| Craniosynostosis (n = 477) | 407 | 85.3 | 68 | 14.3 | 2 | 0.4 | 1 | 0.2 | 0 | 0 | 23 | 4.8 | 7 | 1.5 | 3 | 0.6 |
| Diaphragmatic hernia (n = 298) | 261 | 87.6 | 37 | 12.4 | 1 | 0.3 | 0 | 0 | 0 | 0 | 7 | 2.3 | 6 | 2 | 1 | 0.3 |
| Gastroschisis (n = 473) | 418 | 88.4 | 51 | 10.8 | 2 | 0.4 | 0 | 0 | 1 | 0.2 | 16 | 3.4 | 12 | 2.5 | 2 | 0.4 |

| Birth Defect | Hydroxyzine | | Loratadine | | Meclizine | | Antihistamine Not Otherwise Specified | | Pheniramine‡ | | Promethazine | | Triprolidine | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| **Controls (n = 4982)** | **5** | **0.1** | **79** | **1.6** | **4** | **0.1** | **15** | **0.3** | **108** | **2.2** | **127** | **2.5** | **13** | **0.3** |
| **Cases** | | | | | | | | | | | | | | |
| All non-cardiac defects (n = 5491) † | 6 | 0.1 | 99 | 1.8 | 13 | 0.2 | 17 | 0.3 | 125 | 2.3 | 132 | 2.4 | 10 | 0.2 |
| Neural tube defects (n = 802) | 0 | 0 | 15 | 1.9 | 3 | 0.4 | 6 | 0.7 | 19 | 2.4 | 30 | 3.7 | 3 | 0.4 |
| Anencephalus (n = 234) | 0 | 0 | 7 | 3 | 0 | 0 | 1 | 0.4 | 4 | 1.7 | 9 | 3.8 | 2 | 0.9 |

| Birth Defect | Hydroxyzine | | Loratadine | | Meclizine | | Antihistamine Not Otherwise Specified | | Pheniramine‡ | | Promethazine | | Triprolidine | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| **Controls (n = 4982)** | **5** | **0.1** | **79** | **1.6** | **4** | **0.1** | **15** | **0.3** | **108** | **2.2** | **127** | **2.5** | **13** | **0.3** |
| Spina bifida (n = 489) | 0 | 0 | 6 | 1.2 | 3 | 0.6 | 5 | 1 | 15 | 3.1 | 20 | 4.1 | 1 | 0.2 |
| Anotia / Microtia (n = 218) | 0 | 0 | 3 | 1.4 | 1 | 0.5 | 1 | 0.5 | 1 | 0.5 | 4 | 1.8 | 0 | 0 |
| Oral clefts (N = 1725) | 3 | 0.2 | 19 | 1.1 | 6 | 0.3 | 5 | 0.3 | 46 | 2.7 | 34 | 2 | 3 | 0.2 |
| Cleft palate (N = 575) | 0 | 0 | 5 | 0.9 | 5 | 0.9 | 0 | 0 | 9 | 1.6 | 8 | 1.4 | 0 | 0 |
| Cleft lip with or without cleft palate (n = 1150) | 3 | 0.3 | 14 | 1.2 | 1 | 0.1 | 5 | 0.4 | 37 | 3.2 | 26 | 2.3 | 3 | 0.3 |
| Anorectal atresia (n = 223) | 0 | 0 | 7 | 3.1 | 0 | 0 | 0 | 0 | 2 | 0.9 | 3 | 1.3 | 0 | 0 |
| Hypospadias (n = 864) | 0 | 0 | 22 | 2.5 | 1 | 0.1 | 3 | 0.3 | 24 | 2.8 | 13 | 1.5 | 1 | 0.1 |
| Limb deficiency defects (n = 415) | 2 | 0.5 | 11 | 2.7 | 0 | 0 | 1 | 0.2 | 8 | 1.9 | 7 | 1.7 | 1 | 0.2 |
| Transverse limb deficiency defects (n = 283) | 1 | 0.4 | 10 | 3.5 | 0 | 0 | 1 | 0.4 | 5 | 1.8 | 7 | 2.5 | 1 | 0.4 |
| Craniosynostosis (n = 477) | 0 | 0 | 10 | 2.1 | 0 | 0 | 0 | 0 | 15 | 3.1 | 15 | 3.1 | 2 | 0.4 |
| Diaphragmatic hernia (n = 298) | 1 | 0.3 | 6 | 2 | 2 | 0.7 | 1 | 0.3 | 5 | 1.7 | 10 | 3.4 | 0 | 0 |
| Gastroschisis (n = 473) | 0 | 0 | 6 | 1.3 | 0 | 0 | 0 | 0 | 5 | 1.1 | 16 | 3.4 | 0 | 0 |

*None = No exposure to any antihistamines between the month before pregnancy and the end of the first trimester.

†Groupings of all non-cardiac defects and all cardiac defects were not analyzed. Overall frequencies in these groupings are provided to facilitate comparison with control group.

‡Brompheniramine + chlorpheniramine

*None = No exposure to any antihistamines between the month before pregnancy and the end of the first trimester.

†Groupings of all non-cardiac defects and all cardiac defects were not analyzed. Overall frequencies in these groupings are provided to facilitate comparison with control group.

‡Brompheniramine + chlorpheniramine

## Table 2

Number and Percentage of Cases with Isolated Cardiac Birth Defects and Healthy Controls Exposed to Antihistamines From the Month Before Pregnancy Through the First Trimester, National Birth Defects Prevention Study, 1997–2003

| Birth Defect | None * | | Any Antihistamine | | Cetirizine | | Clemastine | | Dimenhydrinate | | Diphenhydramine | | Doxylamine | | Fexofenadine | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| **Controls (n = 4982)** | **4445** | **89.2** | **518** | **10.4** | **28** | **0.6** | **6** | **0.1** | **9** | **0.2** | **93** | **1.9** | **64** | **1.3** | **30** | **0.6** |
| **Cases** | | | | | | | | | | | | | | | | |
| All cardiac defects (n = 3587) † | 3149 | 87.8 | 421 | 11.7 | 15 | 0.4 | 5 | 0.1 | 8 | 0.2 | 73 | 2.0 | 61 | 1.7 | 25 | 0.7 |
| Conotruncal defects (n = 778) | 688 | 88.4 | 87 | 11.2 | 3 | 0.4 | 1 | 0.1 | 3 | 0.4 | 13 | 1.7 | 14 | 1.8 | 7 | 0.9 |
| Tetralogy of Fallot (n = 391) | 340 | 87 | 49 | 12.5 | 1 | 0.3 | 0 | 0 | 1 | 0.3 | 8 | 2 | 8 | 2 | 2 | 0.5 |
| D-transposition of the great arteries (n = 278) | 250 | 89.9 | 27 | 9.7 | 1 | 0.4 | 1 | 0.4 | 2 | 0.7 | 3 | 1.1 | 6 | 2.2 | 2 | 0.7 |
| Left ventricular outflow tract obstruction defects (n = 575) | 503 | 87.5 | 68 | 11.8 | 2 | 0.3 | 1 | 0.2 | 2 | 0.3 | 9 | 1.6 | 15 | 2.6 | 4 | 0.7 |
| Hypoplastic left heart syndrome (n = 229) | 201 | 87.8 | 27 | 11.8 | 0 | 0 | 1 | 0.4 | 0 | 0 | 5 | 2.2 | 8 | 3.5 | 0 | 0 |
| Coarctation of the aorta (n = 218) | 190 | 87.2 | 25 | 11.5 | 0 | 0 | 0 | 0 | 1 | 0.5 | 3 | 1.4 | 5 | 2.3 | 3 | 1.4 |
| Right ventricular outflow tract obstruction defects (n = 569) | 502 | 88.2 | 67 | 11.8 | 4 | 0.7 | 1 | 0.2 | 0 | 0 | 20 | 3.5 | 6 | 1.1 | 1 | 0.2 |
| Pulmonary valve stenosis (n = 413) | 366 | 88.6 | 47 | 11.4 | 4 | 1 | 1 | 0.2 | 0 | 0 | 12 | 2.9 | 3 | 0.7 | 1 | 0.2 |
| Septal defects (n = 1396) | 1223 | 87.6 | 165 | 11.8 | 5 | 0.4 | 1 | 0.1 | 2 | 0.1 | 26 | 1.9 | 21 | 1.5 | 11 | 0.8 |
| Ventricular septal defect − Perimembranous (n = 616) | 537 | 87.2 | 76 | 12.3 | 1 | 0.2 | 1 | 0.2 | 0 | 0 | 17 | 2.8 | 8 | 1.3 | 5 | 0.8 |
| Atrial septal defect − Ostium secundum (n = 475) | 418 | 88 | 56 | 11.8 | 3 | 0.6 | 0 | 0 | 2 | 0.4 | 6 | 1.3 | 6 | 1.3 | 6 | 1.3 |
| Ventricular septal defect + Atrial septal defect (n = 269) | 233 | 86.6 | 34 | 12.6 | 1 | 0.4 | 1 | 0.4 | 1 | 0.4 | 5 | 1.9 | 5 | 1.9 | 2 | 0.7 |

| Birth Defect | Hydroxyzine | | Loratadine | | Meclizine | | Antihistamine Not Otherwise Specified | | Pheniramine‡ | | Promethazine | | Triprolidine | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| **Controls (n = 4982)** | **5** | **0.1** | **79** | **1.6** | **4** | **0.1** | **15** | **0.3** | **108** | **2.2** | **127** | **2.5** | **13** | **0.3** |
| **Cases** | | | | | | | | | | | | | | |
| All cardiac defects (n = 3587) † | 6 | 0.2 | 64 | 1.8 | 1 | 0.0 | 10 | 0.3 | 82 | 2.3 | 117 | 3.3 | 9 | 0.3 |



*Birth Defects Res A Clin Mol Teratol*. Author manuscript; available in PMC 2013 April 08.

| Birth Defect | Hydroxyzine | | Loratadine | | Meclizine | | Antihistamine Not Otherwise Specified | | Pheniramine‡ | | Promethazine | | Triprolidine | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| **Controls (n = 4982)** | **5** | **0.1** | **79** | **1.6** | **4** | **0.1** | **15** | **0.3** | **108** | **2.2** | **127** | **2.5** | **13** | **0.3** |
| Conotruncal defects (n = 778) | 1 | 0.1 | 19 | 2.4 | 0 | 0 | 2 | 0.3 | 16 | 2.1 | 19 | 2.4 | 0 | 0 |
| Tetralogy of Fallot (n = 391) | 0 | 0 | 10 | 2.6 | 0 | 0 | 1 | 0.3 | 9 | 2.3 | 15 | 3.8 | 0 | 0 |
| D-transposition of the great arteries (n = 278) | 1 | 0.4 | 6 | 2.2 | 0 | 0 | 1 | 0.4 | 4 | 1.4 | 4 | 1.4 | 0 | 0 |
| Left ventricular outflow tract obstruction defects (n = 575) | 0 | 0 | 12 | 2.1 | 0 | 0 | 2 | 0.3 | 12 | 2.1 | 14 | 2.4 | 3 | 0.5 |
| Hypoplastic left heart syndrome (n = 229) | 0 | 0 | 2 | 0.9 | 0 | 0 | 1 | 0.4 | 5 | 2.2 | 5 | 2.2 | 2 | 0.9 |
| Coarctation of the aorta (n = 218) | 0 | 0 | 6 | 2.8 | 0 | 0 | 1 | 0.5 | 3 | 1.4 | 6 | 2.8 | 1 | 0.5 |
| Right ventricular outflow tract obstruction defects (n = 569) | 1 | 0.2 | 5 | 0.9 | 0 | 0 | 1 | 0.2 | 14 | 2.5 | 21 | 3.7 | 2 | 0.4 |
| Pulmonary valve stenosis (n = 413) | 1 | 0.2 | 3 | 0.7 | 0 | 0 | 1 | 0.2 | 9 | 2.2 | 17 | 4.1 | 2 | 0.5 |
| Septal defects (n = 1396) | 4 | 0.3 | 25 | 1.8 | 1 | 0.1 | 5 | 0.4 | 36 | 2.6 | 50 | 3.6 | 2 | 0.1 |
| Ventricular septal defect − Perimembranous (n = 616) | 1 | 0.2 | 9 | 1.5 | 1 | 0.2 | 3 | 0.5 | 15 | 2.4 | 23 | 3.7 | 2 | 0.3 |
| Atrial septal defect − Ostium secundum (n = 475) | 3 | 0.6 | 8 | 1.7 | 0 | 0 | 1 | 0.2 | 11 | 2.3 | 21 | 4.4 | 0 | 0 |
| Ventricular septal defect + Atrial septal defect (n = 269) | 0 | 0 | 3 | 1.1 | 0 | 0 | 0 | 0 | 4 | 1.5 | 13 | 4.8 | 2 | 0.7 |

*None=No exposure to any antihistamines between the month before pregnancy and the end of the first trimester

†Groupings of all non-cardiac defects and all cardiac defects were not analyzed. Overall frequencies in these groupings are provided to facilitate comparison with control group.

‡Brompheniramine + chlorpheniramine

*None=No exposure to any antihistamines between the month before pregnancy and the end of the first trimester

†Groupings of all non-cardiac defects and all cardiac defects were not analyzed. Overall frequencies in these groupings are provided to facilitate comparison with control group.

‡Brompheniramine + chlorpheniramine

## Table 3

Adjusted Odds Ratios and 95% Confidence Intervals and Adjusted Posterior Odds Ratios and 95% Posterior Intervals For Associations Between Antihistamine Use and Isolated Non-Cardiac Birth Defects, Before and After Bayesian Data Augmentation, National Birth Defects Prevention Study, 1997-2003

| Birth Defect | Analysis* | Any Antihistamine | Cetirizine | Clemastine | Dimenhydrinate | Diphenhydramine | Doxylamine | Fexofenadine |
|---|---|---|---|---|---|---|---|---|
| Neural tube defects | Non-Bayesian | **1.35 (1.06,1.73)** | 0.50 (0.12,2.11) | 0.96 (0.11,8.15) | -- | **1.72 (1.03,2.87)** | **2.09 (1.20,3.62)** | 1.28 (0.52,3.14) |
| | Bayesian | **1.54 (1.20,1.98)** | 0.64 (0.21,1.96) | 1.03 (0.23,4.68) | -- | **1.95 (1.16,3.27)** | **2.32 (1.33,4.03)** | 1.29 (0.55,3.05) |
| Anencephalus | Non-Bayesian | 1.18 (0.77,1.81) | 0.71 (0.09,5.39) | -- | -- | 1.49 (0.63,3.55) | 1.73 (0.67,4.47) | 1.23 (0.28,5.29) |
| | Bayesian | 1.29 (0.85,1.97) | 0.85 (0.21,3.49) | -- | -- | 1.50 (0.66,3.41) | 1.68 (0.69,4.13) | 1.14 (0.33,3.88) |
| Spina bifida | Non-Bayesian | **1.45 (1.07,1.97)** | -- | 1.86 (0.22,16.10) | -- | 1.83 (0.97,3.44) | **2.21 (1.12,4.33)** | 1.49 (0.51,4.33) |
| | Bayesian | **1.61 (1.18,2.18)** | -- | 1.38 (0.28,6.82) | -- | **1.94 (1.04,3.63)** | **2.27 (1.17,4.42)** | 1.52 (0.56,4.11) |
| Anotia / Microtia | Non-Bayesian | 1.21 (0.73,2.01) | -- | -- | 3.10 (0.37,26.29) | 1.48 (0.52,4.26) | 1.67 (0.56,4.96) | -- |
| | Bayesian | 1.30 (0.79,2.15) | -- | -- | 1.81 (0.33,10.04) | 1.45 (0.54,3.87) | 1.60 (0.58,4.43) | -- |
| Oral clefts | Non-Bayesian | 1.07 (0.89,1.30) | 1.23 (0.59,2.54) | 1.29 (0.32,5.23) | 1.08 (0.27,4.22) | **1.58 (1.07,2.34)** | 1.21 (0.73,1.99) | 1.23 (0.62,2.46) |
| | Bayesian | 1.23 (1.00,1.50) | 1.17 (0.58,2.36) | 1.31 (0.40,4.32) | 1.28 (0.39,4.22) | **1.77 (1.18,2.65)** | 1.43 (0.85,2.38) | 1.51 (0.76,3.00) |
| Cleft palate | Non-Bayesian | 0.95 (0.69,1.29) | 1.60 (0.60,4.30) | Not estimable | 2.16 (0.44,10.60) | 1.26 (0.66,2.43) | 1.44 (0.70,2.99) | 1.27 (0.44,3.70) |
| | Bayesian | 1.03 (0.75,1.41) | 1.46 (0.58,3.64) | 0.61 (0.11,3.41) | 1.85 (0.47,7.31) | 1.34 (0.71,2.54) | 1.47 (0.73,2.98) | 1.34 (0.50,3.56) |
| Cleft lip w/wo cleft palate | Non-Bayesian | 1.14 (0.91,1.42) | 1.02 (0.41,2.54) | 2.09 (0.52,8.52) | 0.52 (0.06,4.26) | **1.73 (1.12,2.68)** | 1.12 (0.62,2.02) | 1.24 (0.56,2.77) |
| | Bayesian | 1.30 (1.03,1.63) | 1.02 (0.44,2.38) | 1.85 (0.55,6.23) | 0.77 (0.18,3.23) | **1.91 (1.23,2.98)** | 1.30 (0.72,2.36) | 1.47 (0.68,3.21) |
| Anorectal atresia | Non-Bayesian | 0.63 (0.36,1.11) | -- | -- | -- | 0.57 (0.14,2.35) | 0.75 (0.18,3.13) | 1.56 (0.36,6.68) |
| | Bayesian | 0.68 (0.40,1.17) | -- | -- | -- | 0.68 (0.22,2.06) | 0.80 (0.25,2.54) | 1.38 (0.39,4.84) |
| Hypospadias | Non-Bayesian | 1.07 (0.81,1.41) | 0.85 (0.33,2.20) | 0.48 (0.05,4.68) | -- | 1.23 (0.63,2.42) | 1.65 (0.81,3.34) | 1.60 (0.67,3.83) |
| | Bayesian | 1.09 (0.82,1.45) | 0.86 (0.36,2.05) | 0.73 (0.16,3.29) | -- | 1.28 (0.66,2.49) | 1.63 (0.81,3.27) | 1.50 (0.67,3.39) |
| Limb deficiencies | Non-Bayesian | 1.22 (0.87,1.71) | 0.52 (0.07,3.88) | -- | Not estimable | 1.74 (0.90,3.34) | 1.06 (0.42,2.69) | 0.91 (0.21,3.86) |
| | Bayesian | 1.30 (0.93,1.82) | 0.71 (0.18,2.75) | -- | 0.67 (0.11,3.92) | 1.77 (0.93,3.35) | 1.12 (0.47,2.65) | 0.98 (0.30,3.23) |
| Transverse limb deficiencies | Non-Bayesian | **1.62 (1.11,2.38)** | -- | -- | -- | **2.30 (1.11,4.73)** | 1.04 (0.32,3.39) | 1.50 (0.35,6.48) |
| | Bayesian | **1.71 (1.17,2.50)** | -- | -- | -- | **2.23 (1.10,4.53)** | 1.07 (0.38,3.03) | 1.34 (0.38,4.67) |
| Craniosynostosis | Non-Bayesian | 1.31 (0.98,1.75) | 0.65 (0.15,2.79) | 1.23 (0.14,10.57) | -- | **2.48 (1.48,4.13)** | 1.05 (0.47,2.36) | 0.99 (0.30,3.33) |
| | Bayesian | **1.38 (1.03,1.85)** | 0.72 (0.23,2.29) | 1.15 (0.25,5.30) | -- | **2.47 (1.48,4.10)** | 1.05 (0.49,2.23) | 1.02 (0.36,2.92) |
| Diaphragmatic hernia | Non-Bayesian | 1.05 (0.71,1.56) | 0.55 (0.07,4.10) | -- | -- | 1.35 (0.57,3.16) | 1.10 (0.39,3.10) | 0.54 (0.07,4.02) |
| | Bayesian | 1.11 (0.75,1.65) | 0.74 (0.19,2.87) | -- | -- | 1.33 (0.60,2.99) | 1.13 (0.44,2.88) | 0.75 (0.19,2.94) |
| Gastroschisis | Non-Bayesian | 1.17 (0.82,1.68) | 1.18 (0.25,5.59) | -- | 1.07 (0.12,9.34) | **2.02 (1.04,3.92)** | 1.57 (0.72,3.42) | 1.11 (0.25,5.00) |
| | Bayesian | 1.26 (0.87,1.82) | 1.03 (0.29,3.66) | -- | 1.28 (0.26,6.21) | **1.99 (1.03,3.83)** | 1.61 (0.75,3.43) | 1.16 (0.33,4.08) |

| Birth Defect | Analysis* | Hydroxyzine | Loratadine | Meclizine | Antihistamine Not Otherwise Specified | Pheniramine† | Promethazine | Triprolidine |
|---|---|---|---|---|---|---|---|---|
| Neural tube defects | Non-Bayesian | -- | 1.13 (0.63,2.03) | 3.48 (0.57,21.27) | 3.14 (0.80,12.28) | 1.21 (0.71,2.06) | 1.41 (0.90,2.20) | 1.08 (0.24,4.90) |
| | Bayesian | -- | 1.19 (0.67,2.13) | 1.68 (0.39,7.27) | 2.08 (0.61,7.10) | 1.36 (0.80,2.32) | **1.63 (1.04,2.54)** | 0.99 (0.29,3.44) |
| Anencephalus | Non-Bayesian | -- | 1.60 (0.67,3.79) | -- | Not estimable | 0.67 (0.21,2.16) | 1.01 (0.45,2.26) | 1.54 (0.19,12.42) |
| | Bayesian | -- | 1.56 (0.68,3.54) | -- | 0.73 (0.12,4.56) | 0.79 (0.29,2.16) | 1.17 (0.55,2.50) | 1.21 (0.26,5.61) |
| Spina bifida | Non-Bayesian | -- | 0.80 (0.34,1.87) | 5.64 (0.91,35.09) | **5.52 (1.42,21.47)** | 1.68 (0.94,3.01) | **1.81 (1.07,3.05)** | 0.95 (0.12,7.48) |

| Birth Defect | Analysis* | Hydroxyzine | Loratadine | Meclizine | Antihistamine Not Otherwise Specified | Pheniramine† | Promethazine | Triprolidine |
|---|---|---|---|---|---|---|---|---|
| | Bayesian | -- | 0.85 (0.39,1.87) | 2.21 (0.50,9.75) | 3.04 (0.86,10.74) | **1.86 (1.04,3.33)** | **1.99 (1.18,3.35)** | 0.96 (0.22,4.12) |
| Anotia / Microtia | Non-Bayesian | -- | 0.87 (0.26,2.87) | 4.81 (0.46,50.54) | 3.93 (0.45,34.50) | 0.28 (0.04,2.08) | 1.80 (0.62,5.23) | -- |
| | Bayesian | -- | 0.90 (0.32,2.55) | 1.65 (0.30,9.00) | 1.74 (0.32,9.51) | 0.50 (0.14,1.76) | 1.84 (0.67,5.04) | -- |
| Oral clefts | Non-Bayesian | 1.31 (0.31,5.56) | 0.56 (0.32,0.97) | **4.62 (1.15,18.67)** | 2.00 (0.65,6.20) | 1.26 (0.87,1.82) | 0.73 (0.48,1.11) | 0.69 (0.19,2.47) |
| | Bayesian | 1.20 (0.35,4.17) | 0.59 (0.34,1.02) | 3.14 (0.93,10.54) | 1.53 (0.54,4.34) | 1.47 (1.00,2.16) | 0.85 (0.56,1.30) | 0.79 (0.27,2.35) |
| Cleft palate | Non-Bayesian | -- | 0.41 (0.15,1.12) | **12.69 (2.89,55.66)** | -- | 0.73 (0.36,1.47) | 0.51 (0.23,1.11) | -- |
| | Bayesian | -- | 0.48 (0.20,1.14) | **6.16 (1.78,21.33)** | -- | 0.80 (0.41,1.55) | 0.63 (0.31,1.30) | -- |
| Cleft lip w/wo cleft palate | Non-Bayesian | 1.94 (0.46,8.29) | 0.64 (0.34,1.19) | 1.11 (0.11,10.93) | **3.15 (1.01,9.81)** | **1.54 (1.04,2.30)** | 0.84 (0.53,1.34) | 1.13 (0.31,4.03) |
| | Bayesian | 1.57 (0.45,5.54) | 0.68 (0.37,1.25) | 0.78 (0.17,3.63) | 2.20 (0.77,6.31) | **1.83 (1.21,2.76)** | 0.97 (0.61,1.55) | 1.17 (0.38,3.58) |
| Anorectal atresia | Non-Bayesian | -- | 1.93 (0.87,4.30) | -- | -- | 0.22 (0.03,1.60) | 0.32 (0.08,1.31) | -- |
| | Bayesian | -- | 1.76 (0.81,3.82) | -- | -- | 0.43 (0.13,1.48) | 0.48 (0.16,1.39) | -- |
| Hypospadias | Non-Bayesian | -- | 1.25 (0.69,2.27) | 1.09 (0.07,16.47) | 0.70 (0.17,2.97) | 1.34 (0.76,2.36) | 0.58 (0.30,1.16) | 0.21 (0.02,1.76) |
| | Bayesian | -- | 1.24 (0.69,2.23) | 0.98 (0.19,5.06) | 0.78 (0.24,2.52) | 1.37 (0.78,2.42) | 0.63 (0.33,1.20) | 0.43 (0.11,1.64) |
| Limb deficiencies | Non-Bayesian | 5.02 (0.95,26.42) | 1.58 (0.82,3.03) | -- | 1.15 (0.14,9.47) | 1.03 (0.49,2.15) | 0.90 (0.41,1.98) | 0.94 (0.12,7.31) |
| | Bayesian | 2.47 (0.58,10.54) | 1.56 (0.82,2.95) | -- | 1.04 (0.23,4.63) | 1.08 (0.53,2.18) | 1.03 (0.49,2.16) | 0.98 (0.23,4.23) |
| Transverse limb deficiencies | Non-Bayesian | 3.97 (0.45,35.35) | **2.16 (1.08,4.30)** | -- | 1.62 (0.19,13.58) | 1.04 (0.42,2.61) | 1.70 (0.76,3.80) | 1.53 (0.20,11.98) |
| | Bayesian | 1.75 (0.32,9.57) | **2.04 (1.04,4.03)** | -- | 1.24 (0.26,5.82) | 1.10 (0.47,2.57) | 1.75 (0.81,3.81) | 1.26 (0.27,5.85) |
| Craniosynostosis | Non-Bayesian | -- | 1.18 (0.60,2.33) | -- | -- | 1.42 (0.79,2.54) | 1.15 (0.65,2.03) | 1.46 (0.32,6.64) |
| | Bayesian | -- | 1.16 (0.60,2.23) | -- | -- | 1.50 (0.85,2.67) | 1.24 (0.71,2.17) | 1.28 (0.36,4.56) |
| Diaphragmatic hernia | Non-Bayesian | Not estimable | 0.95 (0.38,2.39) | 5.18 (0.51,52.09) | 1.91 (0.23,15.60) | 0.80 (0.32,2.00) | 1.20 (0.59,2.45) | -- |
| | Bayesian | 0.79 (0.12,5.15) | 0.95 (0.41,2.21) | 1.82 (0.32,10.22) | 1.31 (0.27,6.24) | 0.88 (0.38,2.02) | 1.32 (0.66,2.62) | -- |
| Gastroschisis | Non-Bayesian | -- | 0.98 (0.40,2.41) | -- | -- | 0.40 (0.12,1.30) | 1.66 (0.91,3.05) | -- |
| | Bayesian | -- | 1.02 (0.43,2.41) | -- | -- | 0.52 (0.20,1.41) | 1.73 (0.94,3.19) | -- |

--Zero exposed cases

*Non-Bayesian results show adjusted odds ratios and 95% confidence intervals. Bayesian results show adjusted posterior odds ratios and 95% posterior intervals.

†Brompheniramine + Chlorpheniramine

--Zero exposed cases

*Non-Bayesian results show adjusted odds ratios and 95% confidence intervals. Bayesian results show adjusted posterior odds ratios and 95% posterior intervals.

†Brompheniramine + Chlorpheniramine

## Table 4

Adjusted Odds Ratios and 95% Confidence Intervals and Adjusted Posterior Odds Ratios and 95% Posterior Intervals For Associations Between Antihistamine Use and Isolated Cardiac Birth Defects, Before and After Bayesian Data Augmentation, National Birth Defects Prevention Study, 1997-2003

| Birth Defect | Analysis* | Any Antihistamine | Cetirizine | Clemastine | Dimenhydrinate | Diphenhydramine | Doxylamine | Fexofenadine |
|---|---|---|---|---|---|---|---|---|
| Conotruncal defects | Non-Bayesian | 1.08 (0.83,1.40) | 0.80 (0.24,2.71) | 0.90 (0.11,7.58) | 1.47 (0.30,7.11) | 0.98 (0.53,1.83) | 1.45 (0.76,2.75) | 1.53 (0.66,3.56) |
| | Bayesian | 1.15 (0.89,1.51) | 0.85 (0.30,2.39) | 0.99 (0.22,4.43) | 1.35 (0.36,5.05) | 1.02 (0.56,1.86) | 1.54 (0.82,2.89) | 1.62 (0.72,3.66) |
| Tetralogy of Fallot | Non-Bayesian | 1.16 (0.83,1.63) | 0.50 (0.07,3.76) | -- | Not estimable | 1.11 (0.50,2.46) | 1.65 (0.73,3.71) | 0.83 (0.19,3.53) |
| | Bayesian | 1.22 (0.87,1.71) | 0.69 (0.18,2.63) | -- | 0.69 (0.12,4.12) | 1.14 (0.54,2.41) | 1.65 (0.76,3.59) | 0.93 (0.28,3.02) |
| D-Transposition of the great arteries | Non-Bayesian | 1.01 (0.65,1.56) | 0.83 (0.11,6.35) | 3.39 (0.39,29.17) | 4.01 (0.80,19.99) | 0.72 (0.22,2.32) | 1.66 (0.65,4.26) | 1.35 (0.31,5.81) |
| | Bayesian | 1.07 (0.70,1.65) | 0.90 (0.22,3.73) | 1.73 (0.32,9.32) | 2.35 (0.56,9.82) | 0.80 (0.30,2.19) | 1.62 (0.66,3.93) | 1.22 (0.36,4.21) |
| Left ventricular outflow tract obstruction defects | Non-Bayesian | 1.07 (0.80,1.43) | 0.30 (0.04,2.22) | 1.07 (0.13,9.03) | 1.68 (0.35,8.17) | 0.94 (0.46,1.91) | **1.94 (1.06,3.56)** | 1.14 (0.39,3.29) |
| | Bayesian | 1.15 (0.86,1.54) | 0.49 (0.14,1.74) | 1.11 (0.24,5.09) | 1.45 (0.39,5.43) | 1.01 (0.51,1.98) | **1.99 (1.10,3.61)** | 1.10 (0.42,2.89) |
| Hypoplastic left heart syndrome | Non-Bayesian | 1.10 (0.71,1.69) | -- | 2.62 (0.30,22.47) | -- | 1.29 (0.51,3.26) | **3.05 (1.40,6.61)** | -- |
| | Bayesian | 1.16 (0.76,1.78) | -- | 1.60 (0.31,8.36) | -- | 1.28 (0.54,3.04) | **2.78 (1.30,5.94)** | -- |
| Coarctation of the aorta | Non-Bayesian | 1.10 (0.69,1.73) | -- | -- | 2.01 (0.23,17.30) | 0.85 (0.26,2.77) | 1.86 (0.72,4.79) | 2.04 (0.60,6.90) |
| | Bayesian | 1.15 (0.73,1.81) | -- | -- | 1.41 (0.28,7.00) | 0.90 (0.33,2.49) | 1.76 (0.72,4.31) | 1.66 (0.54,5.07) |
| Right ventricular outflow tract obstruction defects | Non-Bayesian | 1.00 (0.74,1.34) | 0.86 (0.25,2.87) | 1.38 (0.16,11.75) | -- | **1.94 (1.14,3.32)** | 0.71 (0.28,1.81) | 0.29 (0.04,2.19) |
| | Bayesian | 1.06 (0.79,1.43) | 0.92 (0.32,2.60) | 1.22 (0.26,5.75) | -- | **1.94 (1.14,3.29)** | 0.76 (0.33,1.77) | 0.50 (0.14,1.80) |
| Pulmonary valve stenosis | Non-Bayesian | 0.95 (0.68,1.34) | 1.03 (0.30,3.47) | 1.98 (0.22,17.40) | -- | 1.54 (0.79,2.98) | 0.54 (0.17,1.77) | 0.39 (0.05,2.94) |
| | Bayesian | 1.01 (0.72,1.41) | 1.05 (0.36,3.02) | 1.39 (0.28,6.86) | -- | 1.48 (0.78,2.82) | 0.64 (0.24,1.73) | 0.59 (0.16,2.20) |
| Septal defects | Non-Bayesian | 1.09 (0.88,1.33) | 0.47 (0.16,1.39) | 0.49 (0.06,4.24) | 0.80 (0.16,3.96) | 0.99 (0.61,1.61) | 1.31 (0.76,2.26) | 1.03 (0.46,2.31) |
| | Bayesian | 1.15 (0.94,1.42) | 0.53 (0.21,1.35) | 0.74 (0.17,3.14) | 0.88 (0.25,3.14) | 0.99 (0.61,1.61) | 1.37 (0.79,2.39) | 1.06 (0.49,2.30) |
| Ventricular septal defect − Perimembranous | Non-Bayesian | 1.15 (0.87,1.53) | Not estimable | 1.25 (0.14,10.77) | -- | 1.61 (0.90,2.88) | 1.22 (0.56,2.62) | 0.91 (0.27,3.07) |
| | Bayesian | 1.21 (0.91,1.60) | 0.30 (0.07,1.26) | 1.17 (0.25,5.50) | -- | 1.56 (0.88,2.78) | 1.21 (0.58,2.53) | 1.00 (0.35,2.85) |
| Atrial septal defect − Ostium secundum | Non-Bayesian | 1.00 (0.73,1.37) | 1.11 (0.32,3.89) | -- | 2.00 (0.39,10.20) | 0.59 (0.25,1.39) | 1.01 (0.42,2.44) | 1.70 (0.63,4.58) |
| | Bayesian | 1.05 (0.77,1.44) | 1.02 (0.35,3.01) | -- | 1.56 (0.40,6.03) | 0.61 (0.28,1.33) | 1.03 (0.45,2.35) | 1.57 (0.62,3.97) |
| Ventricular septal defect + Atrial septal defect | Non-Bayesian | 1.23 (0.82,1.83) | 0.63 (0.08,4.81) | 2.31 (0.26,20.29) | 2.15 (0.26,17.96) | 1.34 (0.52,3.41) | 1.81 (0.70,4.68) | 0.63 (0.08,4.78) |
| | Bayesian | 1.30 (0.88,1.94) | 0.80 (0.20,3.20) | 1.54 (0.30,7.97) | 1.48 (0.29,7.46) | 1.24 (0.52,2.96) | 1.65 (0.67,4.06) | 0.80 (0.20,3.21) |

| Birth Defect | Analysis* | Hydroxyzine | Loratadine | Meclizine | Antihistamine Not Otherwise Specified | Pheniramine† | Promethazine | Triprolidine |
|---|---|---|---|---|---|---|---|---|
| Conotruncal defects | Non-Bayesian | 1.11 (0.13,9.73) | 1.32 (0.77,2.27) | -- | 1.59 (0.33,7.61) | 0.89 (0.50,1.58) | 0.95 (0.56,1.61) | -- |
| | Bayesian | 0.91 (0.20,4.08) | 1.35 (0.79,2.31) | -- | 1.26 (0.35,4.56) | 0.94 (0.54,1.65) | 1.09 (0.64,1.84) | -- |
| Tetralogy of Fallot | Non-Bayesian | -- | 1.34 (0.66,2.72) | -- | 1.60 (0.20,13.09) | 1.05 (0.52,2.12) | 1.52 (0.84,2.74) | -- |
| | Bayesian | -- | 1.31 (0.66,2.60) | -- | 1.21 (0.26,5.64) | 1.10 (0.56,2.16) | 1.65 (0.92,2.94) | -- |
| D-Transposition of the great arteries | Non-Bayesian | 3.20 (0.36,28.13) | 1.31 (0.56,3.08) | -- | 2.30 (0.28,18.96) | 0.56 (0.18,1.81) | 0.50 (0.15,1.61) | -- |
| | Bayesian | 1.47 (0.29,7.51) | 1.30 (0.58,2.92) | -- | 1.37 (0.28,6.69) | 0.66 (0.25,1.77) | 0.66 (0.25,1.75) | -- |
| Left ventricular outflow tract obstruction defects | Non-Bayesian | -- | 1.08 (0.55,2.12) | -- | 2.18 (0.45,10.56) | 0.99 (0.53,1.83) | 0.86 (0.47,1.57) | 1.10 (0.24,4.96) |
| | Bayesian | -- | 1.11 (0.58,2.13) | -- | 1.60 (0.42,6.12) | 1.04 (0.57,1.88) | 0.97 (0.54,1.73) | 1.04 (0.30,3.56) |

| Birth Defect | Analysis * | Hydroxyzine | Loratadine | Meclizine | Antihistamine Not Otherwise Specified | Pheniramine † | Promethazine | Triprolidine |
|---|---|---|---|---|---|---|---|---|
| Hypoplastic left heart syndrome | Non-Bayesian | -- | 0.54 (0.13,2.22) | -- | 2.89 (0.35,24.19) | 1.01 (0.40,2.54) | 0.68 (0.27,1.72) | 1.23 (0.16,9.67) |
| | Bayesian | -- | 0.66 (0.22,2.01) | -- | 1.53 (0.30,7.78) | 1.08 (0.46,2.52) | 0.80 (0.35,1.85) | 1.07 (0.24,4.74) |
| Coarctation of the aorta | Non-Bayesian | -- | 1.41 (0.56,3.59) | -- | 2.97 (0.35,25.36) | 0.67 (0.21,2.15) | 1.09 (0.43,2.77) | 1.39 (0.18,10.94) |
| | Bayesian | -- | 1.37 (0.57,3.27) | -- | 1.56 (0.30,8.05) | 0.75 (0.28,2.04) | 1.15 (0.49,2.73) | 1.15 (0.25,5.20) |
| Right ventricular outflow tract obstruction defects | Non-Bayesian | 1.71 (0.19,15.11) | 0.44 (0.16,1.21) | -- | 1.01 (0.12,8.22) | 0.86 (0.46,1.63) | 1.23 (0.75,2.02) | 1.08 (0.24,4.89) |
| | Bayesian | 1.30 (0.27,6.37) | 0.51 (0.21,1.21) | -- | 0.98 (0.22,4.25) | 0.93 (0.50,1.71) | 1.38 (0.85,2.25) | 1.01 (0.30,3.46) |
| Pulmonary valve stenosis | Non-Bayesian | 2.62 (0.28,24.29) | 0.30 (0.07,1.25) | -- | 1.34 (0.16,11.08) | 0.93 (0.46,1.88) | 1.22 (0.71,2.10) | 1.41 (0.31,6.47) |
| | Bayesian | 1.50 (0.29,7.70) | 0.42 (0.15,1.20) | -- | 1.12 (0.25,5.09) | 0.99 (0.51,1.94) | 1.35 (0.80,2.31) | 1.17 (0.33,4.13) |
| Septal defects | Non-Bayesian | 3.13 (0.79,12.33) | 1.15 (0.71,1.86) | 0.87 (0.09,8.51) | 3.00 (0.94,9.53) | 1.04 (0.69,1.58) | 1.15 (0.81,1.65) | 0.53 (0.12,2.42) |
| | Bayesian | 2.33 (0.70,7.79) | 1.20 (0.74,1.93) | 0.80 (0.18,3.61) | 2.38 (0.83,6.83) | 1.11 (0.73,1.67) | 1.27 (0.89,1.82) | 0.62 (0.19,2.01) |
| Ventricular septal defect − Perimembranous | Non-Bayesian | 1.74 (0.19,15.92) | 0.94 (0.46,1.91) | 2.83 (0.28,28.09) | **3.96 (1.01,15.57)** | 1.03 (0.58,1.85) | 1.28 (0.79,2.08) | 1.12 (0.24,5.24) |
| | Bayesian | 1.30 (0.27,6.35) | 0.95 (0.48,1.88) | 1.41 (0.28,7.19) | 2.55 (0.74,8.76) | 1.09 (0.62,1.92) | 1.38 (0.86,2.24) | 1.02 (0.29,3.57) |
| Atrial septal defect − Ostium secundum | Non-Bayesian | **5.13 (1.15,22.84)** | 1.10 (0.51,2.35) | -- | 1.78 (0.20,15.47) | 0.93 (0.49,1.79) | 1.21 (0.73,2.00) | -- |
| | Bayesian | 2.93 (0.78,11.03) | 1.12 (0.54,2.33) | -- | 1.28 (0.26,6.19) | 1.01 (0.54,1.89) | 1.30 (0.79,2.15) | -- |
| Ventricular septal defect + Atrial septal defect | Non-Bayesian | -- | 0.71 (0.22,2.29) | -- | -- | 0.52 (0.16,1.68) | 1.85 (0.99,3.45) | 2.52 (0.55,11.63) |
| | Bayesian | -- | 0.76 (0.28,2.07) | -- | -- | 0.65 (0.24,1.72) | **2.07 (1.12,3.81)** | 1.74 (0.46,6.61) |

--Zero exposed cases

*Non-Bayesian results show adjusted odds ratios and 95% confidence intervals. Bayesian results show adjusted posterior odds ratios and 95% posterior intervals.

†Brompheniramine + Chlorpheniramine

--Zero exposed cases

*Non-Bayesian results show adjusted odds ratios and 95% confidence intervals. Bayesian results show adjusted posterior odds ratios and 95% posterior intervals.

†Brompheniramine + Chlorpheniramine