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Use of antihistamine medications during early pregnancy and selected birth defects: The National Birth Defects Prevention Study, 1997–2011

Craig Hansen[1], **Tania A. Desrosiers**[2], **Kathy Wisniewski**[2], **Matthew J. Strickland**[3], **Martha M. Werler**[4], **Suzanne M. Gilboa**[5]

[1]CDT Analytics, Adelaide, South Australia, Australia

[2]Department of Epidemiology, University of North Carolina, Chapel Hill, North Carolina

[3]School of Community Health Sciences, University of Nevada, Reno, Nevada

[4]Boston University School of Public Health, Boston, Massachusetts

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

Abstract

Background: It is estimated that approximately 10–15% of pregnant women report antihistamine use during pregnancy. Although antihistamines are generally considered safe during pregnancy, results from published studies are inconsistent.

Methods: Using a case–control study design we analyzed 41,148 pregnancies (30,091 cases and 11,057 controls) from the National Birth Defects Prevention Study (1997–2011). Logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals for 64 birth defect groupings in relation to early pregnancy exposure to 14 distinct antihistamines. Models were adjusted for maternal age, race, parity, education level, prenatal care, folic acid use, smoking and alcohol use, and study site.

Results: Approximately 13% of cases and controls were exposed to an antihistamine during early pregnancy. Analyses were restricted to those defects where more than five cases were exposed to the antihistamine of interest, generating 340 analyses which yielded 20 (5.9%) significant positive associations (adjusted ORs ranging from 1.21 to 4.34).

Conclusions: Only a few of our findings were consistent with previous studies. There is a lack of strong evidence to conclude that birth defects are associated with exposure to antihistamines during early pregnancy.

Correspondence Suzanne M. Gilboa, Division of Birth Defects and Infant Disorders, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA. sgilboa@cdc.gov.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

Keywords

antihistamine; birth defects; pregnancy

1 | INTRODUCTION

It is estimated that approximately 10–15% of pregnant women report antihistamine use during pregnancy (Gilboa, Ailes, Rai, Anderson, & Honein, 2014; Haas et al., 2018) with promethazine and loratadine being in the top 20 prescription medications used in the first trimester (Mitchell et al., 2011). Antihistamines are commonly used during pregnancy for various indications, such as the treatment of allergy and asthma symptoms, relief of indigestion, and nausea and vomiting during pregnancy. Promethazine is the most common antihistamine taken during pregnancy and is often used to treat nausea and vomiting during early pregnancy (Fiaschi, Nelson-Piercy, Deb, King, & Tata, 2019), which affects up to 80% of pregnant women (Bustos, Venkataramanan, & Caritis, 2017). Other common antihistamines taken during pregnancy include (but are not limited to) loratadine, diphenhydramine, and cetirizine, which are often used to treat allergy symptoms (Simons & Simons, 2008).

The association between antihistamine use during pregnancy and the risk of birth defects has been investigated over the past 30 years with studies conducted mostly in the United States (Anderka et al., 2012; Aselton, Jick, Milunsky, Hunter, & Stergachis, 1985; Gilboa et al., 2009; Li, Mitchell, Werler, Yau, & Hernandez-Diaz, 2013) and Europe (Acs, Banhidy, Puho, & Czeizel, 2009; Banhidy, Dakhlaoui, Puho, & Czeizel, 2011; Bartfai, Kocsis, Puho, & Czeizel, 2008; Czeizel, Sarkozi, & Wyszynski, 2003; Kallen & Olausson, 2006; Källén & Olausson, 2001; Smedts et al., 2014). A recent systematic literature review reported on 54 studies (through February 2014) that examined the association between antihistamines and birth defects: among the 31 cohort studies, 2 identified significant adverse associations; and, among the 23 case–control studies, 7 identified significant adverse associations (Gilboa et al., 2014). Although most findings across these studies suggest that the use of antihistamines during early pregnancy is not associated with an increased risk of birth defects, there is inconsistency in the findings regarding specific antihistamines and birth defects (selected case–control studies are presented in Table 1). The reasons for these inconsistent findings are unclear, however different study methods employed may be a factor. These could include, (a) assessment of exposure (e.g., interview/questionnaires, medical records, claims data), (b) timing of exposure, or (c) assessment of outcomes (e.g., abstraction from medical records or claims without additional review, review and recoding of birth defects, differences in classification and grouping of birth defects).

The National Birth Defects Prevention Study (NBDPS) was a large population-based multicenter case–control study of major birth defects in the United States, coordinated by the Centers for Disease Control and Prevention (CDC) (Reefhuis, Gilboa, et al., 2015). The first published outcomes study from the NBDPS investigated the association between hypospadias and exposure to loratadine during early pregnancy (CDC, 2004). Among male infants born between October 1997 and June 2001, there was no association between

loratadine and hypospadias. In 2009, Gilboa et al. (2009) analyzed 7 years (1997–2003) of data from NBDPS participants to investigate the association between 54 different antihistamine agents (categorized into 14 analytic groups) and the risk of isolated birth defects (26 categories). Results showed that exposure to antihistamines during the period 1 month prior to conception through the end of the first trimester yielded 24 positive associations across 14 defect categories.

We conducted an updated analysis of the NBDPS data using the complete study cohort of pregnancies with estimated dates of delivery from 1997 to 2011, extending the original cohort analyzed by Gilboa et al. (2009) by 8 years.

2 | METHODS

2.1 | Study population

The NBDPS methods have been described in detail elsewhere (Reefhuis, Gilboa, et al., 2015; Yoon et al., 2001). Briefly, the NBDPS is a case–control study (pregnancies with estimated dates of delivery from between 1997 and 2011) that collected information on over 30 different birth defects (excluding chromosomal or monogenic disorders) diagnosed prenatally, at birth, or during the first year of life. Cases were identified from 10 state birth defects surveillance systems and could be live bom, stillborn, or induced terminations. The 10 states that collaborated on NBDPS are Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah.

Based on the same catchment area and month of birth as the cases, liveborn infants without major birth defects were selected as controls from birth certificates or hospital records. Detailed information about various demographic and lifestyle factors (including medication use) during pregnancy was collected from the participating mothers via computer-assisted telephone interviews (in English or Spanish) conducted between 6 weeks and 24 months after the estimated date of delivery (EDD). The interview included information about maternal demographics; health and pregnancy history; lifestyle, nutritional, and occupational exposures; and over-the-counter (OTC) and prescription medication, vitamin, and supplement use. The median time to interview was 11 months for case and 9 months for control mothers. The participation rate during the study period was 67% for case and 65% for control mothers (Reefhuis, Devine, Friedman, Louik, & Honein, 2015). The NBDPS was approved by institutional review boards at all participating institutions.

2.2 | Birth defects

The NBDPS clinical data for birth defect cases were abstracted from medical records and classified by clinical experts (Rasmussen et al., 2003; Reefhuis, Gilboa, et al., 2015). All birth defects were first assessed by a clinical geneticist at each site for study eligibility into the study, and then reviewed centrally to confirm classification into specific birth defect categories and assign isolated or multiple defects status (Botto et al., 2007; Rasmussen et al., 2003; Reefhuis, Gilboa, et al., 2015). Isolated defects are those that occur in the absence of any other major defects in a different organ system, and multiple defects are those that occur in the presence of other major birth defects in a different organ system. Isolated

cardiac defects were further classified as “simple isolated”, defined as a single cardiac defect without other major cardiac defects (Botto et al., 2007).

Table 1 shows the list of birth defects analyzed in the current study. The defects are presented in major categories that comprise the overall grouping, along with the sub-classifications of individual defects. Analyses were conducted at the major category and sub-classification levels. Analyses pertaining to a major category included all defects within its sub-classifications. The main analyses for this study focused on all defects (regardless of being isolated or multiple). Additionally, to assess potential etiologic heterogeneity between cases with isolated and nonisolated defects, we conducted sub-analyses examining only those with isolated defects (cardiac and non-cardiac). The sub-analyses for isolated cardiac defects were conducted at two levels of detail: (a) isolated from other major defects in a different organ system (referred to here as isolated cardiac defects), and (b) isolated from other cardiac defects and isolated from other major defects in a different organ system (referred to here as simple isolated cardiac defects).

2.3 | Antihistamine exposure

During the interview, women were asked to report their medication usage, including the timing and frequency of medication use during the 3 months before and during pregnancy using calendar dates or pregnancy months. Pregnancy timing was based on estimated date of conception (2 weeks after the last menstrual period) to end of pregnancy, where pregnancy months were consecutive 30-day intervals during the time period immediately preceding and during pregnancy (Anderson et al., 2018; Crider et al., 2009; Reefhuis, Gilboa, et al., 2015).

For each participant, we identified the use of antihistamines by extracting medication data from the NBDPS database that were listed as having the following antihistamine components (alphabetical order): acrivastine, azatadine, brompheniramine, carbinoxamine, cetirizine, chlorpheniramine, clemastine, cyproheptadine, desloratadine, dexbrompheniramine, dimenhydrinate, diphenhydramine, doxepin, doxylamine, fexofenadine, hydroxyzine, levocabastine, loratadine, meclizine, phenindamine, pheniramine, phenyltoloxamine, promethazine, pyrilamine, terfenadine, trimethobenzamide, and triprolidine. Medication data listed as “antihistamine” where the component was unknown were also included and reported as “Antihistamine.” The components brompheniramine, chlorpheniramine, and pheniramine were grouped as “pheniramine,” and the components desloratadine and loratadine were grouped as “loratadine.” Coding of drug information in the NBDPS used the Slone Drug Dictionary under license from the Slone Epidemiology Center of Boston University.

Similar to previous NBDPS studies (Crider et al., 2009; Reefhuis, Gilboa, et al., 2015), we defined “exposure” as any use of antihistamines during the period of 1 month (30 days) prior to conception through to the end of the first trimester (90 days post conception) – this will be referred to as the “main exposure window” from this point forward. Women who did not report antihistamine use during the same period were classified as “nonexposed” (although they may have used antihistamines during the remainder of their pregnancy).

Because it is less likely for structural birth defects to occur due to harmful exposures during the second trimester, we conducted sensitivity analyses to assess whether birth defects are associated with antihistamine use during month four through month six of pregnancy. In these sensitivity analyses, we included only cases and controls who were exposed in the second trimester (and not exposed in the first trimester).

2.4 | Statistical analyses

The NBDPS cohort comprised 44,029 study participants (32,200 cases and 11,829 controls). In order to define the final analytic sample for the current study, we used a "complete-case" approach where each pregnancy had to have complete information for all covariates. Based on this method of inclusion, there were 41,148 pregnancies included in the final analytic cohort (30,091 cases, and 11,057 controls). Hence, 6.5% of both the original cases and controls were excluded due to missing covariate data.

We first describe the analytic cohort by examining the difference in covariates across the cases (all birth defect case groups combined) and controls by presenting the frequencies, percentages, and chi square tests for independence (Table 2). The covariates used to describe the maternal characteristics of the analytic sample in the current study include: age (<18, 18–24, 25–29, 30–34, 35+ years), race (Hispanic, Non-Hispanic black, Non-Hispanic-white, other), parity (primi, multi), education level (<high school, high school, >high school), prenatal care (entry into prenatal care <10 weeks of pregnancy), folic acid use (1 month prior to pregnancy through the first trimester), smoking status (1 month prior to pregnancy through the first trimester), alcohol use (1 month prior to pregnancy through the first trimester), and study site.

Our main analyses focused on examining all defects (regardless of being multiple or isolated), and further sub-analyses focused on cases with isolated defects (and simple isolated cardiac defects). All analyses were restricted to those where more than five cases were exposed to the antihistamine of interest. Hence, for the main analyses this generated a total of 340 analyses of birth defects and antihistamines, comprising 62 birth defect groupings and 14 distinct antihistamines (including "any antihistamine"). Due to the large volume of results, in the main text we present all results from the main analyses pertaining to the major grouping of birth defects, and within each of these major groups we present only sub-classifications of defects that yielded statistically significant positive associations. However, results from all analyses (e.g., main analyses including sub-classifications; and sub-analyses: isolated defects and simple isolated cardiac defects) are presented in Supporting Information.

For all analyses, logistic regression models were used to assess the association between each specific birth defect and the odds of being exposed to the antihistamine of interest during the main exposure window. Crude and adjusted odds ratios (and 95% confidence intervals [CIs]) were estimated from the logistic regression models. For consistency with the earlier NBDPS study (Gilboa et al., 2009), the regression models were adjusted for all covariates presented in Table 2.

For any statistically significant adverse associations from the main analyses, we further investigated: (a) if the number of days exposed to an antihistamine was different between the cases and controls; and (b) if the daily distribution (e.g., timing of exposure) of those exposed across the 120-day period was different between the cases and controls. For the number of days analysis, we calculated the crude ratio of exposed days (referred to as the exposure rate ratio [ERR]) by summing the total days of exposure, and then dividing it by the total potential-days-of-exposure (calculated by multiplying the number of pregnancies exposed by 120 [the number of days in the exposure window]). For the timing of exposure analyses, the daily proportion of pregnancies exposed was calculated by dividing the number exposed (for the day of interest) by the total exposed during the main exposure window. This provides a distribution of where the exposures occurred during the 120-day period. This daily exposure distribution was calculated for the cases and controls separately, and then the difference in the daily proportions between cases and controls was calculated.

All data manipulation and analyses were performed using the SAS Software 9.4 (Cary, NC). The PROC LOGISTIC procedure was used to calculate crude and adjusted odds ratios (aORs), and 95% CIs.

3 | RESULTS

The final analytic cohort comprised 30,091 cases and 11,057 controls. Table 2 shows the cross-tabulations of the covariates used in all analyses. All covariates except for folic acid use and alcohol use were associated with case-control status. It is important to note that the statistics presented in Table 2 refer to the distributions across the entire analytic sample.

3.1 | Exposure to antihistamines

Based on the overall number of cases and controls in the analytic cohort, 13.3% (n = 4,005) of the cases, and 13.0% (n = 1,435) of the controls, were exposed to an antihistamine during the main exposure window. Promethazine was the most common antihistamine with 3.7% of both cases and controls being exposed, followed by loratadine (2.7% of cases; 2.5% of controls), diphenhydramine (2.4% of cases; 2.2% of controls), doxylamine (1.8% of cases; 1.7% controls), pheniramine (1.6% of cases; 1.7% controls), and cetirizine (1.4% of cases; 1.4% controls). Fewer than 1% of cases/controls were exposed to each of the remaining antihistamines. Regarding exposure to multiple antihistamines, 86.0% (n = 3,436) of the exposed cases, and 87.4% (n = 1,254) of the exposed controls, used only one antihistamine during the main exposure window. Across cases and controls, approximately 12% used two different antihistamines during the main exposure, and fewer than 2% used three or more.

3.2 | Exposure to antihistamines and risk of cardiac defects

Results for the cardiac defect categories are presented in Table 3, along with results that reached statistical significance for specific cardiac defect sub-classifications (see Table SI for all results). The following exposures were associated with a birth defect: exposure to cetirizine and truncus arteriosus (aOR 3.28; 95%CI 1.40, 7.69) and tetralogy of Fallot (aOR 1.64; 95%CI 1.07, 2.50); exposure to diphenhydramine and tricuspid atresia (aOR 2.67; 95% Cl 1.28, 5.55); exposure to doxylamine and hypoplastic left heart syndrome (HLHS)

(aOR 1.73; 95%CI 1.09, 2.76); exposure to hydroxyzine and conotruncal defects (aOR 3.75; 95%CI 1.25, 11.26); and exposure to loratadine and truncus arteriosus (aOR 2.66; 95%CI 1.27, 5.56).

For results pertaining to isolated cardiac defects see Table S2. To briefly highlight consistencies with the main analyses (e.g., positive associations), isolated conotruncal defects (as a group) were associated with exposure to hydroxyzine (aOR 4.50; 95%CI 1.50, 13.55), truncus arteriosus was associated with loratadine (aOR 2.42; 95%CI 1.04, 5.64), and tricuspid atresia was associated with diphenhydramine (aOR 2.72; 95%CI 1.24, 5.94). Additionally (e.g., not significant in the main analyses), atrioventricular septal defect was associated with pheniramine (aOR 2.23; 95%CI 1.16, 4.29), ventricular septal defect plus coarctation of the aorta (VSD + COA) was associated with fexofenadine (aOR 2.88; 95%CI 1.24, 6.68), and tetralogy of Fallot was associated with any antihistamine (aOR 1.23; 95%CI 1.02, 1.49) and promethazine (aOR 1.47; 95%CI 1.07, 2.03).

When analyzing simple isolated cardiac defects (see Table S3) the only positive associations that persisted (from the overall isolated cardiac defects) were for tetralogy of Fallot and any antihistamine (aOR 1.24 95%CI 1.02, 1.50) and promethazine (aOR 1.45; 95%CI 1.05, 2.01), and atrioventricular septal defect and pheniramine (aOR 2.53; 95%CI 1.16, 5.51). Additionally, double outlet right ventricle was associated with any histamine (aOR 3.17; 95%CI 1.30, 7.72).

3.3 | Exposure to antihistamines and risk of non-cardiac defects

Results for the non-cardiac defect categories are presented in Table 4, along with results that reached statistical significance for specific defect sub-classifications (see Table S4 for all results). The following exposures were associated with an increased risk of a birth defect: exposure to any antihistamine and craniosynostosis (aOR 1.17; 95%CI 1.01, 1.36), duodenal atresia/stenosis (aOR 1.51; 95%CI 1.06, 2.15), and neural tube defects (aOR 1.22; 95%CI 1.06, 1.40), including the sub-classifications of anencephaly/craniorachischisis (aOR 1.31; 95%CI 1.04, 1.66) and spina bifida (aOR 1.22 95%CI 1.02, 1.45); exposure to diphenhydramine and craniosynostosis (aOR 1.43; 95%CI 1.04, 1.95) and anencephaly/craniorachischisis (aOR 1.70; 95%CI 1.08, 2.68); exposure to doxylamine and amniotic band sequence affecting limbs only (ABS-LBW) (aOR 2.32; 95%CI 1.05, 5.12) and omphalocele (aOR 2.02; 95%CI 1.15, 3.55); exposure to fexofenadine and bilateral renal agenesis/hypoplasia (aOR 4.34; 95%CI 1.85,10.22); exposure to loratadine and bilateral renal agenesis/hypoplasia (aOR 2.56; 95%CI 1.32, 4.96) and duodenal atresia/stenosis (aOR 2.08; 95% Cl 1.14, 3.80); exposure to pheniramine and choanal atresia (aOR 2.49; 95%CI 1.08, 5.74); and exposure to promethazine and craniosynostosis (aOR 1.37; 95%CI 1.07,1.76).

For results pertaining to isolated non-cardiac defects see Table S5. To briefly highlight consistencies with the main analyses (e.g., positive associations), exposure to any antihistamine was associated with duodenal atresia/stenosis (aOR 1.66; 95%CI 1.07, 2.57) and neural tube defects (aOR 1.19 95%CI 1.03, 1.38); exposure to loratadine and bilateral renal agenesis/hypoplasia (aOR 2.37; 95%CI 1.08, 5.21); and exposure to promethazine and craniosynostosis (aOR 1.37; 95% Cl 1.06 1.77). Additionally, exposure to doxylamine was

associated with ABS-LBW (aOR 2.09; 95%CI 1.04, 4.21); exposure to hydroxine and cleft lip (w/wo cleft palate) (aOR 3.11; 95%CI 1.03, 9.36), and exposure to loratadine and Dandy Walker malformation (aOR 2.42; 95%CI 1.04, 5.65).

3.4 | Differences in the number of days exposed between cases and controls

Among the statistically significant positive associations reported in Tables 3 and 4, we assessed if there was a difference in the number of days the cases and controls were exposed during the main exposure window. As shown in Table S6, among cardiac defects the only association where cases had significantly more days of exposure was among cases with truncus arteriosus and exposure to loratadine where cases had on average 29% more exposed days (ERR 1.29; 95%CI 1.19, 1.41). Among non-cardiac defects, only the associations of bilateral renal agenesis/hypoplasia and exposure to loratadine (ERR 1.20; 95%CI 1.11, 1.29); and craniosynostosis and exposure to any antihistamine (ERR 1.12; 95%CI 1.10, 1.14), diphenhydramine (ERR 1.19; 95%CI 1.14, 1.24), and promethazine (ERR 1.06; 95%CI 1.02,1.10) indicated that cases had significantly more days of exposure. However, for most non-cardiac defect associations cases had significantly fewer days of exposure than controls.

Figure SI shows the daily distribution of exposure among the same statistically significant positive associations. Overall, the daily distribution of exposure was the same for cases and controls for all birth defect/antihistamine combinations, indicating that the pattern of antihistamine use across the main exposure window was similar for cases and controls. Based on calculation of the difference in the daily exposure rate (and where the 95% confidence interval did not include unity), the only difference was for anencephaly/craniorachischisis cases, where the daily rate of those exposed to diphenhydramine toward the end of the first trimester was less than exposed controls. A similar result was found for conotruncal defects and hydroxyzine exposures; however, this result was based on only seven exposed controls and six exposed cases.

3.5 | Exposure to antihistamines during months four to six of pregnancy and risk of defects

We performed sensitivity analyses comparing antihistamine exposures during month four to six of pregnancy (among those not exposed to the antihistamine of interest during the main exposure window). These analyses were performed to observe if exposures later in pregnancy, a period where the formation of birth defects is less likely, were associated with any birth defects. As shown in Table S7, there were 10 statistically significant positive associations, all of which were not found within the main analyses that focused on exposures during 1 month prior to conception through to the end of the first trimester.

4 | DISCUSSION

Using data from the NBDPS, we examined potential associations between exposures 1 month prior to pregnancy through the first trimester of 14 distinct antihistamines and 64 birth defect categories. Given the overlap with the data analyzed in the earlier research conducted on the NBDPS cohort by Gilboa et al. (2009), we found consistent statistically

significant positive associations for NTDs (any) and exposure to any antihistamine, spina bifida and exposure to any antihistamine, and craniosynostosis and exposure to diphenhydramine. Among the cardiac defects the main consistent finding was an association between hypoplastic left heart syndrome and exposure to doxylamine.

For the main analyses, we performed 340 analyses and based on 95% confidence intervals to ascertain statistical significance it would be expected that 5% of the results reach statistical significance purely by chance (assuming the true effect is null). Of the 340 analyses performed in the main analyses, there were 20 (5.9%) significant positive associations (as well as a small number of significant negative results). When applying a strict Bonferroni correction to the p values (α = .05/340 = 0.000147), none of the 20 significant results remained significant, although this would be expected in studies of rare events. When applying a less strict adjustment of α= <.01, six of the 20 significant associations persisted. However, of these six associations, only the association between exposure to any antihistamine and NTDs (aOR 1.22; 95%CI 1.06, 1.40) had more than 10 cases exposed (exposed NTD cases = 301; p value = .005). Most of the statistically significant positive associations found in our study are weak (odds ratios smaller than two) suggesting that the associations could be driven by other factors unaccounted for in the analyses. Almost all the statistically significant ORs that were greater than two had only 11 or fewer exposed cases, therefore generating less precise estimates. Only three associations had odds ratios greater than three, and these analyses had only between 6 and 8 exposed cases.

Hence, there is the possibility that some of our findings occurred by chance and interpretation within the context of the current literature is warranted. Since Gilboa et al. (2009) published their findings there have been five case–control studies published investigating the association between antihistamine exposure and birth defects. One from the NBDPS (using births from 1997 to 2004) (Anderka et al., 2012), one from the HAVEN Study/EUROCAT in the Netherlands (Smedts et al., 2014), one from the Slone Epidemiology Center Birth Defects Study (Li et al., 2013), and two from the Hungarian Case–Control Surveillance of Congenital Anomalies Study (Acs et al., 2009; Banhidy et al., 2011). Furthermore, only two cohort studies have been published after 2009, with both studies conducted in Israel (Ashkenazi-Hoffnung, Merlob, Stahl, & Klinger, 2013; Matok et al., 2010).

The most recent of the case–control studies investigated 16 a priori previously reported associations between specific antihistamines (diphenhydramine, loratadine, chlorpheniramine, doxylamine) and 11 birth defects using data from the Slone Epidemiology Center's Birth Defect Study (Li et al., 2013). Of the 44 a priori analyses, no statistically significant associations were found. The study also explored other potential associations with 30 birth defects and the four antihistamine exposures. Results showed significant positive associations for D-Transposition of the great arteries and exposure to diphenhydramine (aOR 2.3; 95% Cl 1.1, 5.0); and exposure to chlorpheniramine associated with tetralogy of Fallot (aOR 3.1; 95%CI 1.2, 8.4), hypoplastic left heart syndrome (aOR 4.9; 95% Cl 1.6, 14.9), and NTDs (aOR 2.6; 95% Cl 1.1, 6.1). Our study did not find any of these associations (when analyzing both nonisolated and isolated defects); however, we did

detect positive associations between tetralogy of Fallot and cetirizine; hypoplastic left heart syndrome and doxylamine; and NTDs with any antihistamine.

Two case–control studies analyzed data from the Hungarian Case–Control Surveillance of Congenital Abnormalities. Using pregnancies from 1980 to 1996, Bartfai et al. (2008) analyzed a cohort of 22,843 cases and 38,151 matched population controls, and reported a higher rate of cleft lip ± cleft palate (aOR 1.5; 95% Cl 1.1, 2.0) among women exposed to promethazine during the second and third months of pregnancy. Using a cohort derived from the same data source, Czeizel et al. (2003) investigated the potential association between antihistamines and the risk of oral clefts among women with hyperemesis gravidarum (severe vomiting). Results showed that the use of dimenhydrinate was more common among mothers of subjects with isolated cleft palate (aOR 2.47; 95% Cl 1.11, 5.49). Our study did not find any significant associations (including among isolated defects) between oral clefts and promethazine and dimenhydrinate.

Other Hungarian studies investigated antihistamine treatments during pregnancy (as secondary exposures of interest) for peptic ulcer (Banhidy et al., 2011) and dyspepsia (Acs et al., 2009) and found no associations with birth defects. In contrast, a study in the Netherlands (which was much smaller in size) investigated antihistamine use during early pregnancy and the risk of congenital heart defects and reported a significant association between antihistamines and overall cardiac defects, which was strongly driven by the association with atrioventricular septal defects (Smedts et al., 2014).

Of the other case–control studies that reported positive associations, all were published more than 10 years ago (Aselton et al., 1984; Bartfai et al., 2008; Czeizel et al., 2003; Eskenazi & Bracken, 1985; Saxen, 1974). The oldest of these studies suggested associations between exposure to diphenhydramine and oral clefts (Saxen, 1974), and antihistamines and pyloric stenosis (Aselton et al., 1984; Eskenazi & Bracken, 1985). Our study did not find any significant associations between oral clefts and any of the antihistamines analyzed.

Of the 31 cohort studies reviewed by Gilboa et al. (2014), only two studies reported an increased risk of birth defects. The first of these two studies was published in 1976 and reported that promethazine use during pregnancy was positively associated with congenital dislocation of the hip (Kullander & Kallen, 1976). The second of these studies analyzed data in the Swedish Medical Birth Register 1995–2001 and reported an association between loratadine and hypospadias; however, the study was based on only 15 infants with hypospadias among 2,780 loratadine-exposed infants (Källén & Olausson, 2001). The same researchers later conducted further analyses using data for the period 2001–2004 and found no association between loratadine and hypospadias (Kallen & Olausson, 2006). For comparison, our study yielded no significant associations (including among isolated defects) between hypospadias and antihistamines; however, the association with loratadine was of borderline significance (aOR 1.32; 95%CI 1.00,1.73).

Our sensitivity analyses investigated exposures during the second trimester and yielded 11 significant positive associations, none of which were found in the main analyses that focused on exposure during 1 month prior to pregnancy through the first trimester. This finding

may suggest that: (1) significant positive associations may occur regardless of the timing of exposure and therefore all findings should be interpreted with caution; (b) exposure to antihistamines during the second trimester is correlated with exposure to an unknown risk factor during the first trimester; or (c) the associations found with exposure to antihistamines during the first trimester are most likely not fully explained by residual confounding because the same results (e.g., defect and antihistamine) were not found for exposures during the second trimester.

Among the significant positive associations from the main analyses, we investigated the number of exposed days between the cases and controls. For most of the non-cardiac defects the cases had fewer days of exposure, while only a few associations showed that cases had more days of exposure. However, these differences in exposed days were relatively small (~15%) and if there is any suggestion that any of the 20 positive associations found in our study are true, the number of exposed days may not influence those associations. Based on the methods employed in previous studies where exposures are focused over several months of pregnancy, and with no calculation of the length of exposures, it is unclear if acute or chronic exposures to antihistamines are associated with birth defects. Therefore, more detailed analyses regarding the duration and timing of medication exposures during pregnancy are warranted in future studies.

4.1 | Strengths and limitations

Our study has several strengths and limitations. A major strength of the NBDPS is the large geographically diverse sample size of cases and controls, which allows for investigation of a broad spectrum of defects. Furthermore, cases within the NBDPS are reviewed and classified through a rigorous process (Rasmussen et al., 2003; Reefhuis, Gilboa, et al., 2015). Based on participant recall, the NBDPS collects information on all medications used during pregnancy, including OTC medications. Whereas, many medication-birth defect studies analyze administrative data, which does not include OTC medications. Our study investigated exposures during the second trimester and found that positive associations can be detected outside of the critical period of pregnancy, suggesting that positive associations need to be interpreted within the context of previous findings. We also investigated the timing of exposures across the main window of exposure, showing that the patterns of medication use were the same for cases and controls.

Within the NBDPS, information on medication use was self-reported and interviews were conducted between 6 weeks and 24 months after the EDD. Therefore, the recall of the exact medication and timing may have been inaccurately reported by some women (Reefhuis, Gilboa, et al., 2015; Rockenbauer et al., 2001). It also may be more challenging for participants to recall OTC medications as opposed to prescription medications, and many antihistamines are sold as OTC medications. The NBDPS implemented a standardized algorithm to calculate the dates of medication exposure based on self-reported approximations of the timing of medication use recalled by the study participants. Hence, there is the possibility that timing of the exposures may be slightly inaccurate, however this estimation would need to be inconsistent between both the cases and controls for there to be potential exposure bias. As with many studies investigating the risk of birth defects in

association with medication use, it is often unknown if the birth defect is associated with the illness the medication was administered for, or the medication itself. Hence, within these data it is difficult to tease apart the potential effect of confounding by indication. The final analytic sample was based on those who had nonmissing data for all covariates, therefore there may be some bias if the missingness of covariates is associated with the outcome analyzed. However, given the large volume of defects and antihistamines examined it was appropriate to have consistency in the analytic sample across all analyses. Lastly, given the exploratory nature of our analyses we did not adjust for multiple comparisons, even though we did perform a large number of analyses. It is therefore difficult to conclude if the positive associations found occurred purely by chance.

5 | CONCLUSION

Our main analyses identified 20 significant positive associations, and only a few of these findings were consistent with previous studies. Due to many inconsistent findings across multiple studies, and the high probability that several positive associations in our findings are Type 1 errors, there is lack of strong evidence to conclude that birth defects are associated with exposure to antihistamines during early pregnancy. However, for NTDs, hypoplastic left heart syndrome, and tetralogy of Fallot there is slight consistency in positive findings with previous studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY STATEMENT

Author elects to not share data.

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TABLE 1

Birth defects and antihistamines analyzed in this study, in relation to results from five previous case-control studies

Birth defects analyzed in the current study	Specific defects	Antihistamines associated with the birth defect	Antihistamines not associated with the birth defect
Cardiac defects (alphabetical order)			
Any heart defect		Any antihistamine[d]	Dimenhydrinate[c], Promethazine[e]
Anomalous pulmonary venous return	Total APVR Partial APVR	*Not previously studied*	*Not previously studied*
Atrioventricular septal defect (AVSD)		Any antihistamine[d]	
Conotruncal defects	Truncus arteriosus Interrupted aortic arch (type B) Interrupted aortic arch (NOS) Tetralogy of Fallot D-Transposition of the great arteries (TGA) Double outlet right ventricle (DORV)—TGA DORV—NOS VSD—Conoventricular	*D-Transposition of the great arteries:* Diphenhydramine[b] *Tetralogy of Fallot:* Chlorpheniramine[b]	Cetirizine[a], Clemastine[a], Dimenhydrinate[a], Diphenhydramine[a,b], Doxylamine[a,b], Fexofenadine[a], Hydroxyzine[a], Loratadine[a,b], Pheniramine[a], Promethazine[a]
Left ventricular outflow tract obstruction	Interrupted aortic arch (type A) Hypoplastic left heart syndrome (HLHS) Coarctation of the aorta Aortic stenosis	*LVOTO:* Doxylamine[a] *HLHS:* Chlorpheniramine[b], Doxylamine[a]	Cetirizine[a], Clemastine[a], Dimenhydrinate[a], Diphenhydramine[a,b], Doxylamine[b], Fexofenadine[a], Loratadine[a,b], Pheniramine[a], Promethazine[a], Triprolidine[a]
Right ventricular outflow tract obstruction	Pulmonary atresia Pulmonary valve stenosis (PVS) Ebstein anomaly Tricuspid atresia	*RVOTO:* Diphenhydramine[a]	Cetirizine[a], Clemastine[a], Diphenhydramine[b], Doxylamine[a,b], Fexofenadine[a], Hydroxyzine[a], Loratadine[a,b], Pheniramine[a], Promethazine[a], Triprolidine[a]
Septal defect (VSD/ASD)	VSD perimembranous ASD secundum ASD NOS ASD secundum or ASD NOS VSD + COA, VSD + PVS ASD + PVS, ASD + VSD	*VSD perimembraneous:* Any antihistamine[d]	Cetirizine[a], Clemastine[a], Chlorpheniramine[b], Dimenhydrinate[a], Diphenhydramine[a,b], Doxylamine[a], Fexofenadine[a], Hydroxyzine[a], Loratadine[a,b], Meclizine[a], Pheniramine[a], Promethazine[a], Triprolidine[a]
Non-cardiac defects			
Amniotic band syndrome/limb body wall	Limb anomalies only Craniofacial disruptions ± limb anomalies BWC ± Limb anomalies and craniofacial disruptions	*Not previously studied*	*Not previously studied*
Anorectal atresia/stenosis			Dimenhydrinate[c], Diphenhydramine[a,b], Doxylamine[a,b], Fexofenadine[a], Loratadine[a,b], Pheniramine[a], Promethazine[a,e]

Birth defects analyzed in the current study	Specific defects	Antihistamines associated with the birth defect	Antihistamines not associated with the birth defect
Anotia/microtia			Chlorpheniramine[b], Dimenhydrinate[a,c], Diphenhydramine[a], Doxylamine[a], Loratadine[a], Meclizine[a], Pheniramine[a], Promethazine[a,e]
Biliary atresia		*Not previously studied*	*Not previously studied*
Bilateral renal agenesis or hypoplasia			
Bladder exstrophy			
Cerebellar hypoplasia			
Choanal atresia/stenosis			
Craniosynostosis		Diphenhydramine[a]	Cetirizine[a], Clemastine[a], Doxylamine[a], Fexofenadine[a], Loratadine[a], Pheniramine[a], Promethazine[a], Triprolidine[a]
Dandy-Walker malformation		*Not previously studied*	*Not previously studied*
Diaphragmatic hernia			Cetirizine[a], Dimenhydrinate[c], Diphenhydramine[a], Doxylamine[a], Fexofenadine[a], Hydroxyzine[a], Loratadine[a], Meclizine[a], Pheniramine[a], Promethazine[a,e]
Duodenal atresia/stenosis		*Not previously studied*	*Not previously studied*
Esophageal atresia			Dimenhydrinate[c], Promethazine[e]
Gastroschisis		Diphenhydramine[a]	Cetirizine[a], Dimenhydrinate[a,c], Diphenhydramine[b], Doxylamine[a], Fexofenadine[a], Loratadine[a], Pheniramine[a], Promethazine[a,e]
Holoprosencephaly		*Not previously studied*	*Not previously studied*
Hypospadias (second/third degree)			Cetirizine[a], Clemastine[a], Chlorpheniramine[b], Dimenhydrinate[c], Diphenhydramine[a,b], Doxylamine[a], Fexofenadine[a], Loratadine[a,b], Meclizine[a], Pheniramine[a], Promethazine[a,e], Triprolidine[a]
Intestinal atresia/stenosis			Dimenhydrinate[c]
Limb deficiency	Longitudinal limb deficiency Transverse limb deficiency Intercalary limb deficiency NOS limb deficiency	*Transverse limb deficiency:* Any antihistamine[a], Diphenhydramine[a], Loratadine[a]	Cetirizine[a], Dimenhydrinate[a,c], Diphenhydramine[b], Doxylamine[a], Fexofenadine[a], Hydroxyzine[a], Loratadine[b], Pheniramine[a], Promethazine[a,e], Triprolidine[a]
Neural tube defects (NTDs)	Anencephaly and craniorachischisis Spina bifida Encephalocele	*NTDs:* Any antihistamine[a], Chlorpheniramine[b], Diphenhydramine[a],	Cetirizine[a], Clemastine[a], Dimenhydrinate[c], Diphenhydramine[b], Doxylamine[b], Fexofenadine[a],

Birth defects analyzed in the current study	Specific defects	Antihistamines associated with the birth defect	Antihistamines not associated with the birth defect
		Doxylamine[a], Promethazine[a], *Spina bifida:* Any antihistamine[a], Diphenhydramine[a], Doxylamine[a], Promethazine[a]	Loratadine[a,b], Meclizine[a], Pheniramine[a], Promethazine[e], Triprolidine[a]
Omphalocele		*Not previously studied*	*Not previously studied*
Oral clefts	Cleft palate (CP) Cleft lip (CL) w/wo CP • CL with CP • CL without CP	*Oral clefts:* Diphenhydramine[a] CL w/wo CP: Diphenhydramine[a], Pheniramine[a], Promethazine[e] CP: Meclizine[a]	Cetirizine[a], Clemastine[a], Chlorpheniramine[b], Dimenhydrinate[a,c], Diphenhydramine[b], Doxylamine[a,b], Fexofenadine[a], Hydroxyzine[a], Loratadine[a,b], Pheniramine[a], Promethazine[a], Triprolidine[a]
Sacral agenesis or caudal dysplasia		*Not previously studied*	*Not previously studied*
Antihistamines analyzed in current study			
Antihistamine (NOS), Acrivastine, Carbinoxamine, Cetirizine, Clemastine, Dexbrompheniramine, Dimenhydrinate, Diphenhydramine, Doxepin, Doxylamine, Fexofenadine, Hydroxyzine, Loratadine (incl. Desloratadine), Meclizine, Pheniramine (incl. Brompheniramine, Chlorpheniramine), Promethazine, Pyrilamine, Terfenadine, Trimethobenzamide, Triprolidine			

[a]Previous case-control study (Gilboa, 2009).

[b]Previous case-control study (Li et al., 2013).

[c]Previous case-control study (Czeizel, 2005).

[d]Previous case-control study (Smedts et al., 2014).

[e]Previous case-control study (Bartfai et al., 2008).

TABLE 2

Distribution of covariates by case-control status, National Birth Defects Prevention Study, 1997–2011

	Cases		Controls		
	n **= 30,091**		***n*** **= 11,057**		**Chi-square**
Covariate	***n***	**%**	***n***	**%**	***p*** **value**
Maternal age					
<18 years	969	3.2	350	3.2	.0001
18–24 years	9,031	30.0	3,160	28.6	
25–29 years	8,131	27.0	3,088	27.9	
30–34 years	7,372	24.5	2,890	26.1	
35+ years	4,588	15.3	1,569	14.2	
Maternal race-ethnicity					
Hispanic	7,173	23.8	2,602	23.5	.0275
Non-Hispanic Black	2,966	9.9	1,201	10.9	
Non-Hispanic White	17,945	59.6	6,536	59.1	
Other	2,007	6.7	718	6.5	
Maternal education level					
<High school	5,123	17.0	1,769	16.0	<.0001
High school	7,683	25.5	2,611	23.6	
>High school	17,285	57.4	6,677	60.4	
Smoking (1 month before pregnancy through the first 3 months of pregnancy)					
No	24,068	80.0	9,064	82.0	<.0001
Yes	6,023	20.0	1,993	18.0	
Alcohol use (1 month before pregnancy through the first 3 months of pregnancy)					
No	19,065	63.4	6,893	62.3	.0580
Yes	11,026	36.6	4,164	37.7	
Folic Acid use (1 month before pregnancy through the first 3 months of pregnancy)					
No	4,166	13.8	1,492	13.5	.3595
Yes	25,925	86.2	9,565	86.5	
Parity					
Primiparity	9,279	30.8	3,260	29.5	.0082

	Cases		Controls		
	n **= 30,091**		***n*** **= 11,057**		**Chi-square**
Covariate	***n***	**%**	***n***	**%**	***p*** **value**
Multiparity	20,812	69.2	7,797	70.5	
Entry into prenatal care <10 weeks of pregnancy					
No	6,725	22.4	2,591	23.4	.0198
Yes	23,366	77.7	8,466	76.6	
Study site					
Arkansas	3,986	13.3	1,365	12.4	<.0001
California	3,673	12.2	1,136	10.3	
Iowa	2,861	9.5	1,260	11.4	
Massachusetts	3,821	12.7	1,350	12.2	
New Jersey	1,578	5.2	559	5.1	
New York	2,056	6.8	938	8.5	
Texas	3,211	10.7	1,232	11.1	
CDC/Atlanta	3,379	11.2	1,203	10.9	
North Carolina	2,291	7.6	938	8.5	
Utah	3,235	10.8	1,076	9.7	

TABLE 3

Cardiac defects and exposure to antihistamines during 1 month prior to pregnancy through first trimester. Results presented have more than five exposed cases. National Birth Defects Prevention Study, 1997–2011

Antihistamine	Controls		Cases		Odds ratios (95% CI)	
Birth defect—Defect sub-classification[a]	**Not exposed**	**Exposed**	**Not exposed**	**Exposed**	**Crude**	**Adjusted**
Any Antihistamine						
Heart defect (any)	9,622 (87.02)	1,435 (12.98)	10,294 (87.33)	1,493 (12.67)	0.97 (0.90,1.05)	0.96 (0.89,1.04)
Conotruncal defect	9,622 (87.02)	1,435 (12.98)	2,161 (86.61)	334 (13.39)	1.04 (0.91,1.18)	1.07 (0.94,1.22)
Atrioventricular septal defect	9,622 (87.02)	1,435 (12.98)	309 (86.55)	48 (13.45)	1.04 (0.77,1.42)	0.97 (0.71,1.33)
Anomalous pulmonary venous return	9,622 (87.02)	1,435 (12.98)	327 (89.59)	38 (10.41)	0.78 (0.55,1.10)	0.84 (0.60,1.19)
LVOTO	9,622 (87.02)	1,435 (12.98)	1,863 (87.14)	275 (12.86)	0.99 (0.86,1.14)	0.92 (0.80,1.06)
RVOTO	9,622 (87.02)	1,435 (12.98)	1,759 (88.04)	239 (11.96)	0.91 (0.79,1.05)	0.87 (0.75,1.01)
Septal defect	9,622 (87.02)	1,435 (12.98)	3,977 (87.75)	555 (12.25)	0.94 (0.84,1.04)	0.92 (0.83,1.03)
Antihistamine (nos)						
Heart defect (any)	11,049 (99.93)	8 (0.07)	11,778 (99.92)	9 (0.08)	1.06 (0.41,2.74)	0.97 (0.37,2.54)
Cetirizine						
Heart defect (any)	10,897 (98.55)	160 (1.45)	11,649 (98.83)	138 (1.17)	0.81 (0.64,1.02)	0.82 (0.65,1.03)
Conotruncal defect	10,897 (98.55)	160 (1.45)	2,450 (98.20)	45 (1.80)	1.25 (0.90,1.75)	1.32 (0.94,1.85)
• Truncus Arteriosus	**10,897 (98.55)**	**160 (1.45)**	**123 (95.35)**	**6 (4.65)**	**3.32 (1.44,7.65)**	**3.28 (1.40,7.69)**
• Tetralogy of Fallot	**10,897 (98.55)**	**160 (1.45)**	**1,129 (97.75)**	**26 (2.25)**	**1.57 (1.03,2.39)**	**1.64 (1.07,2.50)**
Anomalous pulmonary venous return	10,897 (98.55)	160 (1.45)	359 (98.36)	6 (1.64)	1.14 (0.50,2.59)	1.34 (0.59,3.08)
LVOTO	10,897 (98.55)	160 (1.45)	2,116 (98.97)	22 (1.03)	0.71 (0.45,1.11)	0.63 (0.40,0.98)
RVOTO	10,897 (98.55)	160 (1.45)	1,969 (98.55)	29 (1.45)	1.00 (0.67,1.49)	0.97 (0.65,1.45)
Septal defect	10,897 (98.55)	160 (1.45)	4,496 (99.21)	36 (0.79)	0.55 (0.38,0.78)	0.55 (0.38,0.79)
Clemastine						
Heart defect (any)	11,051 (99.95)	6 (0.05)	11,780 (99.94)	7 (0.06)	1.09 (0.37,3.26)	1.04 (0.35,3.12)
Dimenhydrinate						
Heart defect (any)	11,037 (99.82)	20 (0.18)	11,758 (99.75)	29 (0.25)	1.36 (0.77,2.41)	1.33 (0.75,2.35)
Conotruncal defect	11,037 (99.82)	20 (0.18)	2,488 (99.72)	7 (0.28)	1.55 (0.66,3.68)	1.56 (0.66,3.71)
Septal defect	11,037 (99.82)	20 (0.18)	4,521 (99.76)	11 (0.24)	1.34 (0.64,2.81)	1.37 (0.65,2.90)
Diphenhydramine						

Antihistamine	Controls		Cases		Odds ratios (95% CI)	
Birth defect—Defect sub-classification[a]	**Not exposed**	**Exposed**	**Not exposed**	**Exposed**	**Crude**	**Adjusted**
Heart defect (any)	10,814 (97.80)	243 (2.20)	11,513 (97.68)	274 (2.32)	1.06 (0.89,1.26)	1.04 (0.88,1.25)
Conotruncal defect	10,814 (97.80)	243 (2.20)	2,441 (97.84)	54 (2.16)	0.99 (0.73,1.33)	0.97 (0.72,1.31)
Atrioventricular septal defect	10,814 (97.80)	243 (2.20)	347 (97.20)	10 (2.80)	1.28 (0.68,2.43)	1.18 (0.62,2.25)
Anomalous pulmonary venous return	10,814 (97.80)	243 (2.20)	355 (97.26)	10 (2.74)	1.25 (0.66,2.38)	1.30 (0.68,2.49)
LVOTO	10,814 (97.80)	243 (2.20)	2,092 (97.85)	46 (2.15)	0.98 (0.71,1.35)	0.93 (0.68,1.29)
RVOTO	10,814 (97.80)	243 (2.20)	1,952 (97.70)	46 (2.30)	1.05 (0.76,1.44)	1.02 (0.74,1.41)
• Tricuspid atresia	**10,814 (97.80)**	**243 (2.20)**	**156 (95.12)**	**8 (4.88)**	**2.28 (1.11,4.70)**	**2.67 (1.28,5.55)**
Septal defect	10,814 (97.80)	243 (2.20)	4,430 (97.75)	102 (2.25)	1.03 (0.81,1.30)	1.01 (0.80,1.29)
Doxylamine						
Heart defect (any)	10,870 (98.31)	187 (1.69)	11,576 (98.21)	211 (1.79)	1.06 (0.87,1.29)	1.06 (0.87,1.30)
Conotruncal defect	10,870 (98.31)	187 (1.69)	2,449 (98.16)	46 (1.84)	1.09 (0.79,1.51)	1.20 (0.86,1.67)
LVOTO	10,870 (98.31)	187 (1.69)	2,091 (97.80)	47 (2.20)	1.31 (0.95,1.81)	1.07 (0.77,1.48)
• HLHS	**10,870 (98.31)**	**187 (1.69)**	**611 (96.68)**	**21 (3.32)**	**2.00 (1.26,3.16)**	**1.73 (1.09,2.76)**
RVOTO	10,870 (98.31)	187 (1.69)	1,969 (98.55)	29 (1.45)	0.86 (0.58,1.27)	0.78 (0.52,1.16)
Septal defect	10,870 (98.31)	187 (1.69)	4,454 (98.28)	78 (1.72)	1.02 (0.78,1.33)	1.089 (0.83,1.43)
Fexofenadine						
Heart defect (any)	10,964 (99.16)	93 (0.84)	11,699 (99.25)	88 (0.75)	0.89 (0.66,1.19)	0.90 (0.67,1.21)
Conotruncal defect	10,964 (99.16)	93 (0.84)	2,475 (99.20)	20 (0.80)	0.95 (0.59,1.55)	0.97 (0.60,1.58)
LVOTO	10,964 (99.16)	93 (0.84)	2,119 (99.11)	19 (0.89)	1.06 (0.64,1.74)	1.01 (0.61,1.66)
RVOTO	10,964 (99.16)	93 (0.84)	1,986 (99.40)	12 (0.60)	0.71 (0.39,1.30)	0.70 (0.38,1.29)
Septal defect	10,964 (99.16)	93 (0.84)	4,498 (99.25)	34 (0.75)	0.89 (0.60,1.32)	0.94 (0.63,1.40)
Hydroxyzine						
Heart defect (any)	11,050 (99.94)	7 (0.06)	11,770 (99.86)	17 (0.14)	2.28 (0.95,5.50)	2.17 (0.90,5.25)
Conotruncal defect	**11,050 (99.94)**	**7 (0.06)**	**2,489 (99.76)**	**6 (0.24)**	**3.81 (1.28,11.33)**	**3.75 (1.25,11.26)**
Septal defect	11,050 (99.94)	7 (0.06)	4,524 (99.82)	8 (0.18)	2.79 (1.01,7.69)	2.73 (0.98,7.61)
Loratadine						
Heart defect (any)	10,775 (97.45)	282 (2.55)	11,503 (97.59)	284 (2.41)	0.94 (0.80,1.12)	0.97 (0.82,1.15)
Conotruncal defect	10,775 (97.45)	282 (2.55)	2,415 (96.79)	80 (3.21)	1.27 (0.98,1.63)	1.25 (0.97,1.61)
• Truncus Arteriosus	**10,775 (97.45)**	**282 (2.55)**	**121 (93.80)**	**8 (6.20)**	**2.53 (1.22,5.22)**	**2.66 (1.27,5.56)**
Atrioventricular septal defect	10,775 (97.45)	282 (2.55)	349 (97.76)	8 (2.24)	0.88 (0.43,1.78)	0.82 (0.40,1.68)

Antihistamine	Controls		Cases		Odds ratios (95% CI)	
Birth defect—Defect sub-classification[a]	**Not exposed**	**Exposed**	**Not exposed**	**Exposed**	**Crude**	**Adjusted**
Anomalous pulmonary venous return	10,775 (97.45)	282 (2.55)	354 (96.99)	11 (3.01)	1.19 (0.64,2.19)	1.32 (0.71,2.44)
LVOTO	10,775 (97.45)	282 (2.55)	2,083 (97.43)	55 (2.57)	1.01 (0.75,1.35)	0.99 (0.74,1.33)
RVOTO	10,775 (97.45)	282 (2.55)	1,955 (97.85)	43 (2.15)	0.84 (0.61,1.16)	0.88 (0.63,1.22)
Septal defect	10,775 (97.45)	282 (2.55)	4,454 (98.28)	78 (1.72)	0.67 (0.52,0.86)	0.71 (0.55,0.92)
Meclizine						
Heart defect (any)	11,050 (99.94)	7 (0.06)	11,777 (99.92)	10 (0.08)	1.34 (0.51,3.51)	1.30 (0.49,3.41)
Pkeniramine						
Heart defect (any)	10,871 (98.32)	186 (1.68)	11,586 (98.29)	201 (1.71)	1.01 (0.83,1.24)	1.02 (0.83,1.25)
Conotruncal defect	10,871 (98.32)	186 (1.68)	2,455 (98.40)	40 (1.60)	0.95 (0.68,1.35)	1.00 (0.71,1.41)
Atrioventricular septal defect	10,871 (98.32)	186 (1.68)	346 (96.92)	11 (3.08)	1.86 (1.00,3.45)	1.80 (0.97,3.35)
LVOTO	10,871 (98.32)	186 (1.68)	2,105 (98.46)	33 (1.54)	0.91 (0.63,1.33)	0.96 (0.66,1.39)
RVOTO	10,871 (98.32)	186 (1.68)	1,969 (98.55)	29 (1.45)	0.86 (0.58,1.28)	0.88 (0.59,1.31)
Septal defect	10,871 (98.32)	186 (1.68)	4,455 (98.30)	77 (1.70)	1.01 (0.77,1.32)	0.98 (0.75,1.29)
Promethazine						
Heart defect (any)	10,652 (96.34)	405 (3.66)	11,348 (96.28)	439 (3.72)	1.02 (0.89,1.17)	0.96 (0.83,1.10)
Conotruncal defect	10,652 (96.34)	405 (3.66)	2,412 (96.67)	83 (3.33)	0.91 (0.71,1.15)	0.97 (0.76,1.24)
Atrioventricular septal defect	10,652 (96.34)	405 (3.66)	345 (96.64)	12 (3.36)	0.92 (0.51,1.64)	0.82 (0.45,1.48)
Anomalous pulmonary venous return	10,652 (96.34)	405 (3.66)	357 (97.81)	8 (2.19)	0.59 (0.29,1.20)	0.60 (0.29,1.23)
LVOTO	10,652 (96.34)	405 (3.66)	2,060 (96.35)	78 (3.65)	1.00 (0.78,1.28)	0.93 (0.72,1.20)
RVOTO	10,652 (96.34)	405 (3.66)	1,920 (96.10)	78 (3.90)	1.07 (0.83,1.37)	0.92 (0.72,1.19)
Septal defect	10,652 (96.34)	405 (3.66)	4,350 (95.98)	182 (4.02)	1.10 (0.92,1.32)	0.98 (0.81,1.18)
Triprolidine						
Heart defect (any)	11,042 (99.86)	15 (0.14)	11,770 (99.86)	17 (0.14)	1.06 (0.53,2.13)	1.05 (0.52,2.11)
Septal defect	11,042 (99.86)	15 (0.14)	4,526 (99.87)	6 (0.13)	0.98 (0.38,2.52)	1.02 (0.39,2.64)

Abbreviations: HLHS = hypoplastic left heart syndrome; LVOTO = left ventricular outflow tract obstruction; RVOTO = right ventricular outflow tract obstruction; VSD = ventricular septal defect.

Note. Logistic regression models adjusted for: maternal age, maternal race, maternal education, parity, folic acid use, prenatal care (time of entry), smoking and alcohol status, and study site (see Table 2 for categorizations). The results marked in bold reached statistical significance where the lower confidence interval does not include unity.

[a]The defect sub-classification is only included if it reached statistical significance. See Table SI for all results (including all sub-classifications).

TABLE 4

Non-cardiac defects and exposure to antihistamines during 1 month prior to pregnancy through first trimester. Results presented have more than five exposed cases. National Birth Defects Prevention Study, 1997–2011

Antihistamine	Controls		Cases		Odds ratios (95% CI)	
Birth defect—Defect sub-classification[a]	**Not exposed**	**Exposed**	**Not exposed**	**Exposed**	**Crude**	**Adjusted**
Any Antihistamine						
ABS-LBW	9,622 (87.02)	1,435 (12.98)	261 (86.14)	42 (13.86)	1.08 (0.78,1.50)	1.18 (0.84,1.66)
Anorectal atresia/stenosis	9,622 (87.02)	1,435 (12.98)	911 (89.84)	103 (10.16)	0.76 (0.61,0.94)	0.81 (0.66,1.01)
Anotia/microtia	9,622 (87.02)	1,435 (12.98)	606 (91.82)	54 (8.18)	0.60 (0.45,0.80)	0.78 (0.58,1.04)
Bilateral renal agenesis or hypoplasia	9,622 (87.02)	1,435 (12.98)	149 (84.18)	28 (15.82)	1.26 (0.84,1.90)	1.32 (0.86,2.01)
Biliary atresia	9,622 (87.02)	1,435 (12.98)	167 (87.89)	23 (12.11)	0.92 (0.60,1.43)	0.94 (0.60,1.47)
Bladder exstrophy	9,622 (87.02)	1,435 (12.98)	63 (85.14)	11 (14.86)	1.17 (0.62,2.23)	1.23 (0.64,2.38)
Cerebellar hypoplasia	9,622 (87.02)	1,435 (12.98)	53 (88.33)	7 (11.67)	0.89 (0.40,1.95)	0.76 (0.34,1.69)
Choanal atresia	9,622 (87.02)	1,435 (12.98)	132 (85.16)	23 (14.84)	1.17 (0.75,1.83)	1.15 (0.73,1.81)
Colonic atresia/stenosis	9,622 (87.02)	1,435 (12.98)	43 (84.31)	8 (15.69)	1.25 (0.59,2.66)	1.58 (0.72,3.48)
Craniosynostosis	**9,622 (87.02)**	**1,435 (12.98)**	**1,282 (83.46)**	**254 (16.54)**	**1.33 (1.15,1.54)**	**1.17 (1.01,1.36)**
Dandy Walker Malformation	9,622 (87.02)	1,435 (12.98)	149 (85.63)	25 (14.37)	1.13 (0.73,1.73)	1.24 (0.80,1.93)
Diaphragmatic hernia	9,622 (87.02)	1,435 (12.98)	706 (85.27)	122 (14.73)	1.16 (0.95,1.42)	1.16 (0.95,1.43)
Duodenal atresia/stenosis	**9,622 (87.02)**	**1,435 (12.98)**	**190 (82.61)**	**40 (17.39)**	**1.41 (1.00,1.99)**	**1.51 (1.06,2.15)**
Esophageal atresia	9,622 (87.02)	1,435 (12.98)	644 (88.10)	87 (11.90)	0.91 (0.72,1.14)	0.89 (0.71,1.13)
Gastroschisis	9,622 (87.02)	1,435 (12.98)	1,150 (87.32)	167 (12.68)	0.97 (0.82,1.16)	1.13 (0.93,1.36)
Holoprosencephaly	9,622 (87.02)	1,435 (12.98)	142 (88.75)	18 (11.25)	0.85 (0.52,1.39)	1.05 (0.63,1.74)
Hypospadias	4,907 (87.44)	705 (12.56)	2,097 (85.17)	365 (14.83)	1.21 (1.06,1.39)	1.10 (0.95,1.27)
Intestinal atresia/stenosis	9,622 (87.02)	1,435 (12.98)	390 (86.67)	60 (13.33)	1.03 (0.78,1.36)	1.24 (0.93,1.64)
Limb deficiencies	9,622 (87.02)	1,435 (12.98)	1,040 (87.25)	152 (12.75)	0.98 (0.82,1.17)	1.22 (0.86,1.23)
Neural tube defects	**9,622 (87.02)**	**1,435 (12.98)**	**1,711 (85.04)**	**301 (14.96)**	**1.18 (1.03,1.35)**	**1.22 (1.06,1.40)**
• Anencephaly and craniorachischisis	**9,622 (87.02)**	**1,435 (12.98)**	**498 (83.70)**	**97 (16.30)**	**1.31 (1.04,1.64)**	**1.31 (1.04,1.66)**
• Spina bifida	**9,622 (87.02)**	**1,435 (12.98)**	**1,025 (85.13)**	**179 (14.87)**	**1.17 (1.00,1.39)**	**1.22 (1.02,1.45)**
Omphalocele	9,622 (87.02)	1,435 (12.98)	359 (85.07)	63 (14.93)	1.18 (0.90,1.55)	1.16 (0.88,1.54)
Oral clefts	9,505 (87.00)	1,420 (13.00)	3,915 (87.29)	570 (12.71)	0.98 (0.88,1.08)	0.99 (0.89,1.10)
Sacral agenesis or caudal dysplasia	9,622 (87.02)	1,435 (12.98)	91 (90.10)	10 (9.90)	0.74 (0.38,1.50)	0.83 (0.42,1.62)
Cetirvdne						
Anorectal atresia/stenosis	10,897 (98.55)	160 (1.45)	1,008 (99.41)	6 (0.59)	0.41 (0.18,0.92)	0.46 (0.20,1.05)
Craniosynostosis	10,897 (98.55)	160 (1.45)	1,505 (97.98)	31 (2.02)	1.40 (0.95,2.07)	1.08 (0.73,1.60)
Diaphragmatic hernia	10,897 (98.55)	160 (1.45)	818 (98.79)	10 (1.21)	0.84 (0.44,1.58)	0.84 (0.44,1.60)
Esophageal atresia	10,897 (98.55)	160 (1.45)	717 (98.08)	14 (1.92)	1.33 (0.77,2.31)	1.27 (0.73,2.22)
Gastroschisis	10,897 (98.55)	160 (1.45)	1,304 (99.01)	13 (0.99)	0.68 (0.39,1.20)	1.03 (0.56,1.90)
Hypospadias	5,535 (98.63)	77 (1.37)	2,408 (97.81)	54 (2.19)	1.61 (1.14,2.29)	1.40 (0.97,2.02)
Limb deficiencies	10,897 (98.55)	160 (1.45)	1,175 (98.57)	17 (1.43)	0.99 (0.60,1.63)	1.07 (0.65,1.79)
Neural tube defects	10,897 (98.55)	160 (1.45)	1,982 (98.51)	30 (1.49)	1.03 (0.60,1.53)	1.07 (0.72,1.60)

Antihistamine	Controls		Cases		Odds ratios (95% CI)	
Birth defect—Defect sub-classification[a]	**Not exposed**	**Exposed**	**Not exposed**	**Exposed**	**Crude**	**Adjusted**
Oral clefts	10,766 (98.54)	159 (1.46)	4,425 (98.66)	60 (1.34)	0.92 (0.68,1.24)	0.96 (0.71,1.29)
Dimenhydrinate						
Oral clefts	10,906 (99.83)	19 (0.17)	4,475 (99.78)	10 (0.22)	1.28 (0.60,2.76)	1.26 (0.58,2.73)
Diphenhydramine						
ABS-LBW	10,814 (97.80)	243 (2.20)	295 (97.36)	8 (2.64)	1.21 (0.59,2.46)	1.20 (0.58,2.48)
Anorectal atresia/stenosis	10,814 (97.80)	243 (2.20)	992 (97.83)	22 (2.17)	0.99 (0.63,1.53)	1.04 (0.67,1.62)
Anotia/microtia	10,814 (97.80)	243 (2.20)	645 (97.73)	15 (2.27)	1.04 (0.61,1.76)	1.35 (0.79,2.31)
Craniosynostosis	**10,814 (97.80)**	**243 (2.20)**	**1,485 (96.68)**	**51 (3.32)**	**1.53 (1.13,2.08)**	**1.43 (1.04,1.95)**
Diaphragmatic hernia	10,814 (97.80)	243 (2.20)	801 (96.74)	27 (3.26)	1.50 (1.00,2.25)	1.48 (0.99,2.23)
Duodenal atresia/stenosis	10,814 (97.80)	243 (2.20)	222 (96.52)	8 (3.48)	1.60 (0.78,3.28)	1.73 (0.84,3.56)
Esophageal atresia	10,814 (97.80)	243 (2.20)	717 (98.08)	14 (1.92)	0.87 (0.50,1.50)	0.84 (0.48,1.45)
Gastroschisis	10,814 (97.80)	243 (2.20)	1,282 (97.34)	35 (2.66)	1.22 (0.85,1.74)	1.33 (0.90,1.98)
Hypospadias	5,491 (97.84)	121 (2.16)	2,399 (97.44)	63 (2.56)	1.19 (0.88,1.62)	1.09 (0.79,1.51)
Intestinal atresia/stenosis	10,814 (97.80)	243 (2.20)	440 (97.78)	10 (2.22)	1.01 (0.53,1.92)	1.17 (0.61,2.23)
Limb deficiencies	10,814 (97.80)	243 (2.20)	1,159 (97.23)	33 (2.77)	1.27 (0.88,1.83)	1.33 (0.92,1.93)
Neural tube defects	10,814 (97.80)	243 (2.20)	1,959 (97.37)	53 (2.63)	1.20 (0.89,1.63)	1.23 (0.91,1.67)
• Anencephaly and craniorachischisis	**10,814 (97.80)**	**243 (2.20)**	**573 (96.30)**	**22 (3.70)**	**1.71 (1.10,2.67)**	**1.70 (1.08,2.68)**
Omphalocele	10,814 (97.80)	243 (2.20)	410 (97.16)	12 (2.84)	1.30 (0.72,2.35)	1.22 (0.68,2.21)
Oral clefts	10,685 (97.80)	240 (2.20)	4,384(97.75)	101 (2.25)	1.03 (0.81,1.30)	1.04 (0.82,1.32)
Doxylamine						
ABS-LBW	10,870 (98.31)	187 (1.69)	293 (96.70)	10 (3.30)	1.98 (1.04,3.79)	1.94 (1.00,3.77)
• Limb anomalies only	**10,870 (98.31)**	**187 (1.69)**	**186 (96.37)**	**7 (3.63)**	**2.19 (1.01,4.72)**	**2.32 (1.05,5.12)**
Anorectal atresia/stenosis	10,870 (98.31)	187 (1.69)	1,001 (98.72)	13 (1.28)	0.76 (0.43,1.33)	0.86 (0.49,1.52)
Anotia/microtia	10,870 (98.31)	187 (1.69)	650 (98.48)	10 (1.52)	0.89 (0.47,1.70)	1.02 (0.53,1.96)
Craniosynostosis	10,870 (98.31)	187 (1.69)	1,506 (98.05)	30 (1.95)	1.16 (0.78,1.71)	0.83 (0.56,1.24)
Diaphragmatic hernia	10,870 (98.31)	187 (1.69)	810 (97.83)	18 (2.17)	1.29 (0.79,2.11)	1.23 (0.75,2.03)
Esophageal atresia	10,870 (98.31)	187 (1.69)	720 (98.50)	11 (1.50)	0.89 (0.48,1.64)	0.89 (0.48,1.66)
Gastroschisis	10,870 (98.31)	187 (1.69)	1,295 (98.33)	22 (1.67)	0.99 (0.63,1.54)	1.04 (0.64,1.68)
Hypospadias	5,523 (98.41)	89 (1.59)	2,419 (98.25)	43 (1.75)	1.10 (0.76,1.59)	1.04 (0.71,1.51)
Intestinal atresia/stenosis	10,870 (98.31)	187 (1.69)	439 (97.56)	11 (2.44)	1.46 (0.79,2.70)	1.71 (0.92,3.21)
Limb deficiencies	10,870 (98.31)	187 (1.69)	1,169 (98.07)	23 (1.93)	1.14 (0.74,1.77)	1.08 (0.69,1.68)
Neural tube defects	10,870 (98.31)	187 (1.69)	1,968 (97.81)	44 (2.19)	1.30 (0.93,1.81)	1.28 (0.91,1.80)
Omphalocele	**10,870 (98.31)**	**187 (1.69)**	**408 (96.68)**	**14 (3.32)**	**2.00 (1.15,3.46)**	**2.02 (1.15,3.55)**
Oral clefts	10,745 (98.35)	180 (1.65)	4,412 (98.37)	73 (1.63)	0.99 (0.75,1.30)	0.95 (0.72,1.25)
Fexofenadine						
Anorectal atresia/stenosis	10,964 (99.16)	93 (0.84)	1,008 (99.41)	6 (0.59)	0.70 (0.31,1.61)	0.75 (0.33,1.72)
Bilateral renal agenesis or hypoplasia	**10,964 (99.16)**	**93 (0.84)**	**171 (96.61)**	**6 (3.39)**	**4.14 (1.79,9.58)**	**4.34 (1.85,10.22)**
Craniosynostosis	10,964 (99.16)	93 (0.84)	1,517 (98.76)	19 (1.24)	1.48 (0.90,2.43)	1.27 (0.77,2.11)
Gastroschisis	10,964 (99.16)	93 (0.84)	1,309 (99.39)	8 (0.61)	0.72 (0.35,1.49)	0.86 (0.40,1.84)

Antihistamine	Controls		Cases		Odds ratios (95% CI)	
Birth defect—Defect sub-classification[a]	**Not exposed**	**Exposed**	**Not exposed**	**Exposed**	**Crude**	**Adjusted**
Hypospadias	5,569 (99.23)	43 (0.77)	2,427 (98.58)	35 (1.42)	1.87 (1.19,2.93)	1.47 (0.93,2.34)
Limb deficiencies	10,964 (99.16)	93 (0.84)	1,186 (99.50)	6 (0.50)	0.60 (0.26,1.36)	0.63 (0.27,1.44)
Neural tube defects	10,964 (99.16)	93 (0.84)	1,989 (98.86)	23 (1.14)	1.36 (0.86,2.16)	1.43 (0.90,2.28)
Oral clefts	10,833 (99.16)	92 (0.84)	4,448 (99.18)	37 (0.82)	0.98 (0.67,1.44)	0.98 (0.67,1.44)
Hydroxyzine						
Oral clefts	10,918 (99.94)	7 (0.06)	4,479 (99.87)	6 (0.13)	2.09 (0.70,6.22)	1.77 (0.59,5.31)
Loratadine						
ABS-LBW	10,775 (97.45)	282 (2.55)	294 (97.03)	9 (2.97)	1.17 (0.60,2.29)	1.29 (0.65,2.55)
Anorectal atresia/stenosis	10,775 (97.45)	282 (2.55)	985 (97.14)	29 (2.86)	1.12 (0.76,1.66)	1.18 (0.80,1.75)
Anotia/microtia	10,775 (97.45)	282 (2.55)	649 (98.33)	11 (1.67)	0.65 (0.35,1.19)	0.78 (0.42,1.44)
Bilateral renal agenesis or hypoplasia	**10,775 (97.45)**	**282 (2.55)**	**167 (94.35)**	**10 (5.65)**	**2.29 (1.20,4.38)**	**2.56 (1.32,4.96)**
Craniosynostosis	10,775 (97.45)	282 (2.55)	1,496 (97.40)	40 (2.60)	1.02 (0.73,1.43)	0.96 (0.68,1.34)
Dandy Walker Malformation	10,775 (97.45)	282 (2.55)	167 (95.98)	7 (4.02)	1.60 (0.75,3.44)	1.69 (0.78,3.66)
Diaphragmatic hernia	10,775 (97.45)	282 (2.55)	799 (96.50)	29 (3.50)	1.39 (0.94,2.05)	1.38 (0.93,2.04)
Duodenal atresia/stenosis	**10,775 (97.45)**	**282 (2.55)**	**218 (94.78)**	**12 (5.22)**	**2.10 (1.16,3.81)**	**2.08 (1.14,3.80)**
Esophageal atresia	10,775 (97.45)	282 (2.55)	713 (97.54)	18 (2.46)	0.97 (0.60,1.56)	0.88 (0.54,1.43)
Gastroschisis	10,775 (97.45)	282 (2.55)	1,286 (97.65)	31 (2.35)	0.92 (0.63,1.34)	1.23 (0.82,1.85)
Hypospadias	5,466 (97.40)	146 (2.60)	2,366 (96.10)	96 (3.90)	1.52 (1.17,1.97)	1.32 (1.00,1.73)
Intestinal atresia/stenosis	10,775 (97.45)	282 (2.55)	438 (97.33)	12 (2.67)	1.05 (0.58,1.88)	1.18 (0.66,2.14)
Limb deficiencies	10,775 (97.45)	282 (2.55)	1,159 (97.23)	33 (2.77)	1.09 (0.75,1.57)	1.14 (0.79,1.65)
Neural tube defects	10,775 (97.45)	282 (2.55)	1,949 (96.87)	63 (3.13)	1.24 (0.94,1.63)	1.30 (0.98,1.73)
Omphalocele	10,775 (97.45)	282 (2.55)	409 (96.92)	13 (3.08)	1.21 (0.69,2.14)	1.15 (0.65,2.03)
Oral clefts	10,644 (97.43)	281 (2.57)	4,366 (97.35)	119 (2.65)	1.03 (0.83,1.28)	1.04 (0.84,1.30)
Meclizine						
Oral clefts	10,918 (99.94)	7 (0.06)	4,478 (99.84)	7 (0.16)	2.44 (0.85,6.95)	2.30 (0.80,6.62)
Pkeniramine						
Anorectal atresia/stenosis	10,871 (98.32)	186 (1.68)	1,002 (98.82)	12 (1.18)	0.70 (0.39,1.26)	0.74 (0.41,1.33)
Choanal atresia	**10,871 (98.32)**	**186 (1.68)**	**149 (96.13)**	**6 (3.87)**	**2.35 (1.03,5.39)**	**2.49 (1.08,5.74)**
Craniosynostosis	10,871 (98.32)	186 (1.68)	1,511 (98.37)	25 (1.63)	0.97 (0.64,1.47)	1.00 (0.65,1.53)
Diaphragmatic hernia	10,871 (98.32)	186 (1.68)	819 (98.91)	9 (1.09)	0.64 (0.33,1.26)	0.68 (0.35,1.33)
Esophageal atresia	10,871 (98.32)	186 (1.68)	720 (98.50)	11 (1.50)	0.89 (0.48,1.65)	0.92 (0.50,1.71)
Gastroschisis	10,871 (98.32)	186 (1.68)	1,296 (98.41)	21 (1.59)	0.95 (0.60,1.49)	1.14 (0.70,1.85)
Hypospadias	5,527 (98.49)	85 (1.51)	2,421 (98.33)	41 (1.67)	1.10 (0.76,1.60)	1.10 (0.74,1.64)
Intestinal atresia/stenosis	10,871 (98.32)	186 (1.68)	443 (98.44)	7 (1.56)	0.92 (0.43,1.98)	1.05 (0.49,2.26)
Limb deficiencies	10,871 (98.32)	186 (1.68)	1,173 (98.41)	19 (1.59)	0.95 (0.59,1.53)	1.01 (0.63,1.63)
Neural tube defects	10,871 (98.32)	186 (1.68)	1,976 (98.21)	36 (1.79)	1.07 (0.74,1.53)	1.16 (0.81,1.67)
Omphalocele	10,871 (98.32)	186 (1.68)	416 (98.58)	6 (1.42)	0.84 (0.37,1.91)	0.88 (0.38,1.99)
Oral clefts	10,740 (98.31)	185 (1.69)	4,401 (98.13)	84 (1.87)	1.11 (0.85,1.44)	1.20 (0.92,1.56)
Promethazine						
ABS-LBW	10,652 (96.34)	405 (3.66)	292 (96.37)	11 (3.63)	0.99 (0.54,1.82)	1.08 (0.58,2.02)

Antihistamine	Controls		Cases		Odds ratios (95% CI)	
Birth defect—Defect sub-classification[a]	**Not exposed**	**Exposed**	**Not exposed**	**Exposed**	**Crude**	**Adjusted**
Anorectal atresia/stenosis	10,652 (96.34)	405 (3.66)	992 (97.83)	22 (2.17)	0.58 (0.38,0.90)	0.61 (0.39,0.95)
Anotia/microtia	10,652 (96.34)	405 (3.66)	649 (98.33)	11 (1.67)	0.45 (0.24,0.82)	0.67 (0.36,1.23)
Bilateral renal agenesis or hypoplasia	10,652 (96.34)	405 (3.66)	167 (94.35)	10 (5.65)	1.57 (0.83,3.00)	1.51 (0.77,2.93)
Biliary atresia	10,652 (96.34)	405 (3.66)	184(96.84)	6 (3.16)	0.86 (0.38,1.95)	0.90 (0.39,2.07)
Craniosynostosis	**10,652 (96.34)**	**405 (3.66)**	**1,451 (94.47)**	**85 (5.53)**	**1.54 (1.21,1.96)**	**1.37 (1.07,1.76)**
Dandy Walker Malformation	10,652 (96.34)	405 (3.66)	168 (96.55)	6 (3.45)	0.94 (0.41,2.13)	0.96 (0.41,2.22)
Diaphragmatic hernia	10,652 (96.34)	405 (3.66)	798 (96.38)	30 (3.62)	0.99 (0.68,1.44)	1.00 (0.68,1.48)
Duodenal atresia/stenosis	10,652 (96.34)	405 (3.66)	219 (95.22)	11 (4.78)	1.32 (0.72,2.44)	1.47 (0.78,2.76)
Esophageal atresia	10,652 (96.34)	405 (3.66)	709 (96.99)	22 (3.01)	0.82 (0.53,1.26)	0.90 (0.58,1.40)
Gastroschisis	10,652 (96.34)	405 (3.66)	1,263 (95.90)	54 (4.10)	1.12 (0.84,1.50)	1.08 (0.79,1.49)
Hypospadias	5,418 (96.54)	194 (3.46)	2,382 (96.75)	80 (3.25)	0.94 (0.72,1.22)	0.93 (0.70,1.22)
Intestinal atresia/stenosis	10,652 (96.34)	405 (3.66)	435 (96.67)	15 (3.33)	0.91 (0.54,1.53)	1.09 (0.64,1.86)
Limb deficiencies	10,652 (96.34)	405 (3.66)	1,157 (97.06)	35 (2.94)	0.80 (0.56,1.13)	0.83 (0.58,1.19)
Neural tube defects	10,652 (96.34)	405 (3.66)	1,937 (96.27)	75 (3.73)	1.02 (0.79,1.31)	0.98 (0.76,1.27)
Omphalocele	10,652 (96.34)	405 (3.66)	409 (96.92)	13 (3.08)	0.84 (0.48,1.47)	0.83 (0.47,1.47)
Oral clefts	10,521 (96.30)	404 (3.70)	4,339 (96.74)	146 (3.26)	0.88 (0.72,1.06)	0.88 (0.72,1.07)

Abbreviation: ABS-LBW = amniotic band syndrome and limb body wall complex.

Note. Inconsistencies in the number of controls due to (1) hypospadias—males only, (2) no controls for clefts from Utah in 2003. Logistic regression models adjusted for: maternal age, maternal race, maternal education, parity, folic acid use, prenatal care (time of entry), smoking and alcohol status, and study site (see Table 2 for categorizations). The results marked in bold reached statistical significance where the lower confidence interval does not include unity.

[a]The defect sub-classification is only included if it reached statistical significance. See Table S2 for all results (including all sub-classifications).