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Asthma Medication Use and Risk of Birth Defects: National Birth Defects Prevention Study, 1997–2011

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Abstract

Background: Evidence regarding associations between maternal asthma medication use and birth defects is mixed.

Objective: Using National Birth Defects Prevention Study (NBDPS) data from 1997–2011, we estimated associations between asthma medication use and 52 specific birth defects.

Methods: We compared self-reported maternal asthma medication use for 28,481 birth defect cases and 10,894 non-malformed controls. We calculated adjusted odds ratios [95% confidence intervals] to estimate the risk of birth defects associated with early pregnancy asthma medication use (the month before through the third month of pregnancy), controlling for maternal age, race/ethnicity, body mass index, smoking, folic acid-containing supplement use, and parity. We calculated risks by medication groupings: bronchodilators, anti-inflammatories, and both.

Results: Overall, 1,304 (5%) case and 449 (4%) control women reported early pregnancy asthma medication use. We observed an association between asthma medication use and longitudinal limb deficiency (1.81 [1.27–2.58]). Early pregnancy bronchodilator only use was associated with

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cleft palate (1.50 [1.11–2.02]), cleft lip (1.58 [1.12–2.23]), longitudinal limb deficiency (2.35 [1.55–3.54]), and truncus arteriosus (2.48 [1.13–5.42]). While early pregnancy anti-inflammatory only use was not associated with the birth defects studied, use of both medications was associated with biliary atresia (3.60 [1.55–8.35]) and pulmonary atresia (2.50 [1.09–5.78]).

Conclusion: Consistent with previous NBDPS analyses, asthma medication use was not associated with most birth defects examined, but we observed modest risks for bronchodilator use and several birth defects. Our findings support maintaining adequate asthma treatment during pregnancy, as early pregnancy asthma exacerbations have been associated with adverse birth outcomes, including birth defects.

Keywords

asthma medications; birth defects; pregnancy; congenital malformations

Introduction

Asthma affects 4–8% of pregnant women in the United States, and its prevalence is increasing.[1–7] Asthma during pregnancy can be harmful to the mother, lead to fetal hypoxia, and is associated with adverse perinatal outcomes.[6,8,9] Current guidelines recommend women with asthma who become pregnant maintain their treatment as it is considered safer to be treated with medication than to experience exacerbations during pregnancy.[10,11] Asthma medications fall into two main groups: bronchodilator medications that relieve symptoms and anti-inflammatory medications that prevent chronic airway inflammation.[10,11]

Studies evaluating maternal asthma medication use and birth defects overall have ranged from finding no association to moderate, positive associations.[12–21] Studies examining specific birth defects have been inconsistent, with some observing associations with spina bifida, orofacial clefts, gastroschisis, renal dysplasia, and various congenital heart defects (CHD).[22–31] Comparing existing findings is challenging, as studies have different exposure definitions and include different birth defects or groupings. Additionally, many studies lack the information needed to consider confounding by indication, making it difficult to disentangle the effects of the medications from the disease.

Prior National Birth Defect Prevention Study (NBDPS) analyses examined associations between asthma medication use and birth defects, finding associations between bronchodilator use and gastroschisis (1997–2002), cleft lip (1997–2005), isolated esophageal atresia (1997–2005), and anomalous pulmonary venous return (1997–2007).[26–29] Positive associations were observed between anti-inflammatory medications and isolated anorectal atresia (1997–2005) and between use of both bronchodilator and anti-inflammatory medications and omphalocele (1997–2005).[27] Those analyses did not include all birth years, were limited by small numbers of exposed women, and did not explore all birth defects collected within the NBDPS. In this analysis, we used the final NBDPS data containing pregnancies from 1997–2011 to update previous estimates and examine the association between asthma medication use and major birth defects not yet explored in the NBDPS.

Methods

The NBDPS was a large, population-based, case-control study of birth defects including pregnancies ending on or after October 1, 1997 and estimated delivery dates (EDD) on or before December 31, 2011.[32] Pregnancies affected by one or more of 30 categories of major structural birth defects (cases), excluding those attributed to known chromosomal or single-gene abnormalities, were ascertained through birth defects surveillance programs in ten states (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah). Control infants were live births without major birth defects randomly selected from hospital records or birth certificates in the same time period and geographic area as the cases; the monthly number of controls selected was proportionate to the number of births in the same month the previous year.[33] Women could only participate once. Sites obtained Institutional Review Board approval. Participants provided informed consent. Overall, 67% of eligible case and 64% of eligible control women participated.

Case inclusion criteria were described previously.[32] Case information was obtained from birth defects surveillance programs. Clinical geneticists reviewed cases for eligibility and classified cases as isolated (one major birth defect or organ system involved), multiple (major birth defects in more than one organ system), or complex.[34] CHD (congenital heart defect) cases were further classified by cardiac phenotype, complexity, and presence of noncardiac defects.[35] Oral clefts, glaucoma, cataracts, ventricular septal defects (VSDs), and pulmonary valve stenosis were not ascertained by all sites for all years; we excluded controls for sites and years with incomplete data.[32] For hypospadias, we restricted to male controls.

Trained interviewers conducted telephone interviews in English or Spanish with women between 6 weeks and 24 months post-EDD. The NBDPS did not have specific questions on asthma and its medications. Instead, women interviewed pre-2006 were asked about “any other disease or illnesses that we have not already talked about;” women interviewed in or after 2006 were asked about “any other chronic disease or illness that we have not talked about such as asthma, thyroid disease, an autoimmune disease, or other chronic or long-term diseases.” For each condition, women reported the name, timing, and frequency of medications used. Two study investigators, blinded to case-control status, reviewed text responses, ICD codes, and questionnaire comments for women who reported asthma or asthma medications to identify untreated asthma and asthma medication use for non-asthma reasons.

The Slone Epidemiology Center Drug Dictionary was used to code reported medications and link products to active ingredient components. A pharmacist helped compile the list of included asthma medications. We considered a woman exposed if she reported using an asthma medication any time in the month before conception through the third month of pregnancy (“early pregnancy”). The first three months of pregnancy include the critical period in embryonic development associated with most structural birth defects. We included the month before conception as it is often difficult to pinpoint the date of conception. In addition to any asthma medication use, we further categorized medication use by type: any bronchodilator, bronchodilator only (no anti-inflammatory), any anti-inflammatory, anti-inflammatory only (no bronchodilator), and both (including combination products). The

unexposed group included women who did not report asthma or asthma medications in the three months before pregnancy to birth.

We excluded those missing asthma medication information, those who reported asthma medications for non-asthma reasons, those who reported asthma medications during pregnancy but not in early pregnancy (included as comparator in a sub-analysis), and those who reported untreated asthma (Figure 1). Except for amniotic band sequence, heterotaxia with CHD and single ventricle, we excluded cases classified either as complex (a group of defects believed to be pathogenetically-related, but the primary defect was unknown) or an uncommon CHD association. We restricted our analysis to birth defects with >50 cases.

We compared characteristics among control infants whose mothers reported early pregnancy asthma medication use and those who did not using chi-square tests. We used logistic regression to estimate crude (cORs) and adjusted odds ratios (aORs) and 95% confidence intervals (CIs) approximating the relative risk of each birth defect among women reporting early pregnancy asthma medication use overall, by medication type and individual medication, where sample size permitted. We calculated aORs and 95% CIs for birth defects with ≥5 exposed cases, controlling for covariates selected *a priori* based on the literature and hypothesized causal pathways in a directed acyclic graph: maternal age at delivery (continuous), race/ethnicity (non-Hispanic white/non-Hispanic black/Hispanic/other), pre-pregnancy body mass index (BMI; kilograms/meters^2 <25/≥25), early pregnancy smoking (yes/no), folic acid-containing supplement use in the month before through the first month of pregnancy (yes/no), and parity (0/≥1). For birth defects with 3–4 exposed cases, we calculated cORs and Fisher's exact CIs. We did not calculate estimates for birth defects with <3 exposed cases. We had substantial power to detect small to moderate effects; power for rarer birth defects or sub-analyses was limited given smaller control-case ratios.

We conducted sub-analyses to determine whether specific changes in exposure or case groups impacted the results; for these, we implemented the change and recalculated estimates as described above. To reduce heterogeneity, we restricted analyses of noncardiac defects to isolated cases and restricted CHD analyses to "simple isolated" cases (cases with one CHD or a combination considered a single CHD). Given the lack of asthma information collected, we conducted two sub-analyses using proxies for disease and severity in an attempt to partially control for confounding by indication. Women reported the frequency of asthma medication use. We removed women who reported using medications "as needed" to assess associations among those with potentially more severe asthma. To assess confounding by asthma, we compared the risk of each birth defect among early pregnancy bronchodilator users to the risk among those who reported bronchodilator use only in late pregnancy (pregnancy month 4 or later). We excluded women from this sub-analysis if the only asthma medication reported was terbutaline (16 in early and 417 in late pregnancy) since terbutaline is used to delay preterm labor. We conducted analyses in SAS (9.4; SAS Corporation, Cary, NC).

Results

After exclusions, we analyzed 28,481 birth defect cases and 10,894 controls. Of these, 1,304 (4.6%) cases and 449 (4.1%) controls reported early pregnancy asthma medication use (Figure 1). Of the exposed, any bronchodilator use was reported by 1,055 (80.9%) cases and 364 (81.1%) controls, while 739 (56.7%) cases and 255 (56.8%) controls reported only using bronchodilators. Any anti-inflammatory medications were reported by 484 (37.1%) cases and 175 (39.0%) controls, and 168 (12.9%) cases and 66 (14.7%) controls reported using only anti-inflammatory medications. Use of both medication types was reported by 316 (24.2%) cases and 109 (24.3 %) controls. Lastly, 81 (6.2 %) case and 19 (4.2%) controls reported an unknown asthma medication.

Table 1 contains the distributions of selected characteristics by early pregnancy asthma medication use among controls. Control women who reported an asthma medication differed from those who did not in terms of race/ethnicity, BMI, parity, smoking status, alcohol use, folic acid-containing supplement use, and maternal hypertension.

Albuterol was the most commonly reported bronchodilator and fluticasone was the most commonly reported anti-inflammatory medication (Table 2). Of those reporting asthma medication use, 201 (15.4%) cases and 71 (15.8%) controls reported only “as needed” use. Bronchodilators were more frequently reported “as needed” than anti-inflammatories.

Any asthma medication use was associated with a significantly elevated aOR for one of the 52 birth defects studied: longitudinal limb deficiency (aOR=1.81, 1.27–2.58; Tables 3 and 4). We observed non-significant elevated aORs ranging from 1.53–2.19 for 7 of the 52 birth defects studied: holoprosencephaly, cerebellar hypoplasia, choanal atresia, biliary atresia, bladder exstrophy, truncus arteriosus, and tricuspid atresia. Our analyses restricted to isolated noncardiac birth defects and simple isolated CHDs mirrored the main analysis, with an elevated, significant aOR for isolated longitudinal limb deficiency. Additionally, estimates for isolated holoprosencephaly, isolated choanal atresia, isolated cleft lip, and isolated gastroschisis were significant (Table E1).

Bronchodilator use was associated with significant elevated estimates for five of the 52 birth defects examined: cerebellar hypoplasia (aOR=2.70, 1.06–6.85), cleft lip (aOR=1.37, 1.01–1.87), longitudinal limb deficiency (aOR=2.04, 1.41–2.96), truncus arteriosus (aOR=2.21, 1.10–4.42) and tricuspid atresia (aOR=2.03, 1.06–3.90). We observed non-significant elevated aORs ranging from 1.52–2.05 for four birth defects: holoprosencephaly, biliary atresia, bladder exstrophy, and pulmonary atresia. The associations between bronchodilator use and cleft lip, cleft palate, longitudinal limb deficiency, and truncus arteriosus were significantly elevated among women who reported a bronchodilator only. Although associations were non-significant for holoprosencephaly, cerebellar hypoplasia, choanal atresia, total anomalous pulmonary venous return (TAPVR), and tricuspid atresia, the estimates were elevated when restricting to bronchodilator only use. Anti-inflammatory use was associated with one birth defect, biliary atresia (aOR=3.02, 1.45–6.27). We observed non-significant elevated estimates ranging from 1.51–2.94 for six birth defects: holoprosencephaly, bladder exstrophy, conoventricular VSD, pulmonary atresia, tricuspid

atresia, and muscular VSD. These estimates were crude with the exception of pulmonary atresia. Anti-inflammatory only use was not associated with the birth defects examined. Reporting both types of asthma medications was significantly associated with two birth defects: biliary atresia (aOR=3.60, 1.55–8.35) and pulmonary atresia (aOR=2.50, 1.09–5.78). We observed non-significant elevated cORs ranging from 1.51–4.71 for holoprosencephaly, bladder exstrophy, transverse limb deficiency, and tricuspid atresia, and a non-significant elevated aOR=1.52 for aortic valve stenosis.

Albuterol use was associated with cerebellar hypoplasia, cleft palate, cleft lip, longitudinal limb deficiency, and truncus arteriosus (Table E2). While the estimate for cleft lip was similar compared to any bronchodilator use, the albuterol estimates for the other four birth defects were further from the null compared to any bronchodilator use. Many of the analyses of specific asthma medication components were hampered by small numbers, resulting in imprecise estimates (Table E3).

To analyze women with more severe asthma, we removed women who reported only “as needed” medication use (Table E4). Any asthma medication use remained significantly associated with longitudinal limb deficiency. We observed significant associations for cerebellar hypoplasia and choanal atresia, although the lower limits of the CIs were close to one. Birth defects associated with bronchodilator only use in the main analysis remained associated after removing “as needed” users, with the exception of cleft palate and truncus arteriosus. The estimates for holoprosencephaly, cerebellar hypoplasia, choanal atresia, and TAPVR reached significance after removing “as needed” users.

To partially control for underlying asthma, we compared early bronchodilator users to those who reported only late pregnancy bronchodilator use. Compared to late use, early bronchodilator use was associated with cleft palate, cleft lip with cleft palate, longitudinal limb deficiency, gastroschisis, and secundum atrial septal defects (Table E5).

Discussion

We did not find associations between asthma medication use and most of the 52 birth defects examined, consistent with existing literature.[19,36,37] We found increased risk for any asthma medication use and one birth defect, bronchodilator only use and four birth defects, and use of both medication types and two birth defects. In our large study, asthma medication use was relatively rare, limiting our ability to detect moderate effects.

Longitudinal limb deficiency was associated with any asthma medication use, driven by higher estimates among bronchodilator users. Estimates for bronchodilators and longitudinal limb deficiency were elevated regardless of how we examined the outcome (all versus isolated). The aORs were elevated amongst any bronchodilator, only bronchodilator, and albuterol users. Additionally, aORs were further from the null after removing “as needed” bronchodilator users and remained significant when compared to late pregnancy bronchodilator users. A previous NBDPS analysis did not observe an association between limb deficiencies and bronchodilator use, but grouped all limb deficiencies.[27] While other studies observed null associations when grouping limb deficiencies, our study is consistent

with Garne and colleagues who identified increased risk for limb deficiencies among users of asthma medications, inhaled beta-2-agonists, and short-acting beta-2-agonists.[23,30,31,38,39]

We found increased risk of cleft lip among bronchodilator users, and the modest estimates were similar regardless of how we examined the outcome. Estimates were elevated among any bronchodilator, only bronchodilator, and albuterol users. The association remained significant after removing "as needed" bronchodilator users but not when compared to late pregnancy bronchodilator users. We found cleft palate was associated with bronchodilator only and albuterol use, but the findings were not as consistent. Neither cleft lip nor cleft palate were associated with anti-inflammatories, which includes inhaled and systemic steroids. While we observed an association between cleft lip with palate and any prednisone use, the association was not significant after restricting to women who reported only prednisone (data not shown). Conflicting evidence of this association exists, but our findings are consistent with a NBDPS analysis of steroids and clefts.[40,41] An earlier NBDPS analysis found an increased risk of cleft lip among bronchodilator users.[28] Most studies have not observed associations between asthma medications and clefts, or cleft lip specifically.[23,24,30,31,38] One study found an association with cleft palate, although this was non-significant in a follow-up analysis of the same population over a longer period.[24,38] Garne and colleagues reported an increased risk of cleft palate among bronchodilator users when compared to malformed controls,[30] but not when compared to non-malformed controls.[31]

We found that any bronchodilator use was associated with cerebellar hypoplasia, truncus arteriosus, and tricuspid atresia. These rare birth defects have not been examined in previous asthma medications studies.[27,29] Some studies suggest associations between bronchodilators and CHDs, but most grouped CHDs.[23,24,38] A previous NBDPS study found an association with anomalous pulmonary venous return (OR=2.3).[29] We found a non-significant aOR=1.58 overall, but a significant aOR=2.01 after removing "as needed" bronchodilator users. In earlier NBDPS analyses, bronchodilator use was associated with isolated gastroschisis and isolated esophageal atresia.[26,27] While we found a significantly elevated OR for the association between any asthma medication and isolated gastroschisis, the magnitude was modest (aOR=1.39) and the estimate non-significant when we restricted to bronchodilator use and isolated gastroschisis (data not shown). Like others, we did not find associations with all gastroschisis cases, although the lower bounds of the CIs were close to one.[31,42] We observed a moderately elevated non-significant risk for asthma medication use and isolated esophageal atresia (aOR=1.56); the estimate was similar when we looked at bronchodilator use specifically and isolated esophageal atresia cases (data not shown). Like others, we did not find any significant associations for all cases of esophageal atresia[24,30,31,38]

Anti-inflammatory only use was not associated with any birth defect, although small numbers hampered our ability to calculate several estimates. Like others, a previous NBDPS analysis found anti-inflammatories were associated with isolated anorectal atresia[24,27,31] We did not observe significantly elevated risks for anorectal atresia in any analysis. We found an elevated OR for biliary atresia and any anti-inflammatory use, due to the stronger association among users of both medications. Using both medications was also associated

with pulmonary atresia. A NBDPS analysis observed an association between omphalocele and use of both asthma medications; we did not find evidence of this nor have others.[27,30,31] Additionally, Garne et al. found associations between combination treatments and aortic valve stenosis and atrioventricular septal defects; we did not observe these associations.[31]

The mechanism through which asthma increases birth defect risk is unknown, but may include hypoxia and other blood gas abnormalities, inflammation, altered placental function, vascular disruption, or asthma medications themselves.[43–45]

Our study has strengths, including our multi-site, population-based design with strict inclusion criteria and case classification by clinical geneticists.[32,34] We were able to evaluate associations between asthma medications and individual birth defects, by medication types, and some components, including albuterol and salmeterol. We did not present estimates for short-acting or long-acting beta-agonists, as both groups were dominated by users of one component (>95% of cases and controls exposed to long-acting beta-agonists reported salmeterol and >94% of cases and controls exposed to short-acting beta-agonists reported albuterol).

Our study has limitations, including potential recall bias due to the retrospective self-reported information. Yet, we observed positive associations for some, but not all, birth defects. If recall bias strongly influenced the results, we would expect elevated ORs for a wider range of birth defects than was found. Inclusion of non-live births changed during the NBDPS (terminations excluded in Georgia before 1999 and Massachusetts for all years; non-live births excluded in New York before 2000 and New Jersey from 1997–2002).[32] Thus, certain birth defects may be underascertained. Other limitations stem from the lack of questions about asthma or asthma medications. We were unable to estimate associations with asthma and cannot rule out the possibility of confounding by the underlying disease. We do not know to what degree reporting asthma medications in early pregnancy reflects asthma severity, asthma control, or some combination. Based only on medications, it is difficult to understand asthma severity, as medication use is influenced by disease severity, presence of exacerbations, patient preferences, medication compliance and pregnancy itself. Nevertheless, we explored underlying asthma in two ways. First, we compared early pregnancy bronchodilator users to those who reported only using a bronchodilator in late pregnancy. We sought to at least partially control for confounding by indication, since all women in the sub-analysis presumably had asthma. The elevated associations observed could be due to the use of early pregnancy bronchodilators but could also be explained by differences in asthma severity or control among those who reported early versus late bronchodilator use. Second, we re-ran analyses after excluding “as needed” asthma medications users. We suspect reports of “as needed” use represents very infrequent use (versus as needed use on a regular interval), so this sub-analysis focused on women with more severe asthma. This is not a perfect proxy for severity as women who used medications only “as needed” may have less severe asthma, be non-compliant with prescribed treatments, or received inadequate treatment. There may also be uncontrolled confounding by unmeasured factors or residual confounding by measured factors. The number of exposed cases for some birth defects was small, limiting our ability to assess risk in some analyses; our main analysis was underpowered to detect effect sizes <2.5 for birth

defects with <100 cases. We conducted many statistical tests and cannot rule out that our findings may be due to chance. In our main analysis of 52 birth defects, we would expect to observe two significant aOR by chance alone (52*0.05=2.6); we observed an elevated aOR for 1 birth defect. The majority of our findings have not been identified previously and should be interpreted cautiously. Studies estimate non-Hispanic white and black women have similar prevalence of asthma.[46] Although non-Hispanic white women represented 57% of NBDPS controls, 70% of controls who reported asthma medications were non-Hispanic white. Given the lack of asthma information, observed differences in medication use by race/ethnicity may reflect differences in the prevalence of asthma or medication use or healthcare utilization.

We found most birth defects examined were not associated with asthma medication use. While reassuring, our findings suggest early pregnancy asthma medication, particularly bronchodilators, may moderately increase the risk of specific birth defects. Yet, these birth defects are relatively rare and even with an OR after exposure to bronchodilators around 2, the absolute risk is relatively small. Since previous studies observed that early pregnancy asthma exacerbations were associated with birth defects and other adverse outcomes, our research supports current guidelines that recommend women with asthma maintain adequate treatment during pregnancy.[11]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

NBDPS	National Birth Defects Prevention Study
CHD	congenital heart defect
EDD	estimated delivery date
cOR	crude odds ratio
aOR	adjusted odds ratio
CI	confidence interval
BMI	body mass index

TAPVR total anomalous pulmonary venous return

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Highlights box

What is already known about this topic?

Evidence regarding associations between maternal asthma medication use and birth defects is mixed. Few studies have examined the association between types of asthma medications and specific birth defects.

What does this article add to our knowledge?

New and previously reported associations between asthma medications and specific birth defects were observed, including moderate elevations for bronchodilators. Additionally, a few associations remained elevated after partially accounting for indication.

How does this study impact current management guidelines?

Most birth defects were not associated with asthma medications, supporting guidelines that pregnant women maintain asthma treatment and consult providers before starting or stopping medications. Additional evidence about these specific associations will inform clinical recommendations.

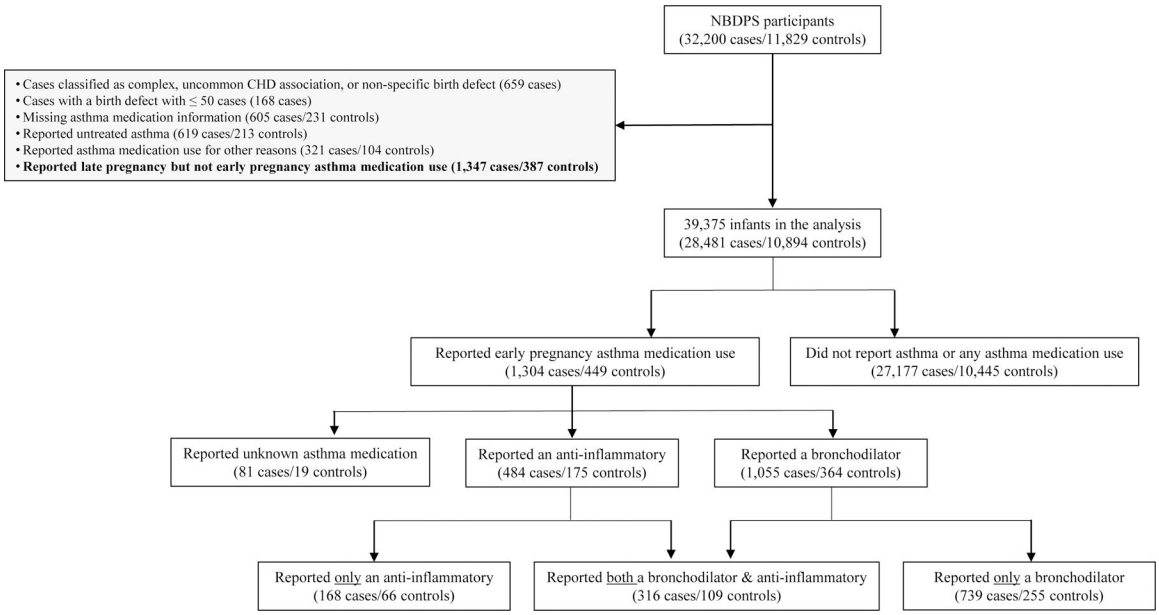

Figure 1.

Study population, exclusions, and asthma medication use in the month before pregnancy through the third month of pregnancy (early pregnancy) among women in the National Birth Defects Prevention Study, 1997–2011. Women who reported late pregnancy, but no early pregnancy asthma medication use were excluded from the main analysis (bolded font); these women were included as the reference group in a sub-analysis.

Table 1.

Selected characteristics of control women, by reported early pregnancy asthma medication use, National Birth Defects Prevention Study 1997–2011.[a]

Maternal Characteristic	Asthma Medication Use (n=449) n (%)	No Asthma Medication Use (n=10,445) n (%)	P value [b]
Age			0.43
<20	48 (10.7)	1036 (9.9)	
20–24	103 (22.9)	2362 (22.6)	
25–29	120 (26.7)	2871 (27.5)	
30–34	103 (22.9)	2703 (25.9)	
35+	75 (16.7)	1473 (14.1)	
Race/ethnicity			<0.001
Non-Hispanic white	316 (70.4)	5937 (56.9)	
Non-Hispanic black	42 (9.4)	1155 (11.1)	
Hispanic	56 (12.5)	2667 (25.6)	
Other	35 (7.8)	680 (6.5)	
Education			0.21
High School or less	169 (38.1)	4241 (41.1)	
More than high school	275 (61.9)	6083 (58.9)	
Pre-pregnancy BMI			0.002
Under/normal weight	232 (51.9)	5924 (59.4)	
Overweight/obese	215 (48.1)	4050 (40.6)	
Parity ≥1	248 (55.2)	6335 (60.7)	0.02
Early pregnancy smoking	113 (25.3)	1814 (17.5)	<0.001
Early pregnancy alcohol use	189 (42.4)	3802 (36.8)	0.02
Folic acid-containing supplement used [c]	271 (60.4)	5430 (52.0)	<0.001
Maternal hypertension	76 (17.0)	1384 (13.3)	0.02
Pre-existing diabetes	6 (1.3)	62 (0.6)	0.05
Gestational diabetes	25 (5.9)	473 (4.7)	0.26

[a] Early pregnancy defined as one month before through the third month of pregnancy. Totals vary because of missing values.

[b] Chi-square test for the difference in the distribution within each covariate.

[c] From one month before pregnancy through the first month of pregnancy.

Table 2.

Asthma medications reported by women who reported early pregnancy asthma medication use, National Birth Defects Prevention Study 1997–2011. [a]

Medication [b]	Reported any use in early pregnancy		Reported only "as needed" asthma medication use in early pregnancy	
	Case n (%)	Control n (%)	Case n (%)	Control n (%)
Any Asthma Medication [c]	**1,304 (100)**	**449 (100)**	**201 (100)**	**71 (100)**
Bronchodilators [c]	**1,055 (80.9)**	**364 (81.1)**	**179 (89.1)**	**65 (91.5)**
Short acting beta-agonist				
Albuterol	958 (73.5)	312 (69.5)	170 (84.6)	60 (84.5)
Bitolterol	1 (0.1)	0	0	0
Ephedrine	5 (0.4)	2 (0.4)	0	0
Epinephrine	10 (0.8)	1 (0.2)	2 (1.0)	0
Fenoterol	0 1	(0.2)	0	0
Levalbuterol	7 (0.5)	4 (0.9)	1 (0.5)	0
Metaproterenol	4 (0.3)	1 (0.2)	1 (0.5)	0
Pirbuterol	16 (1.2)	4 (0.9)	0	1 (1.4)
Procaterol	2 (0.2)	0	0	0
Terbutaline	14 (1.1)	6 (1.3)	0	0
Long acting beta-agonist				
Formoterol	7 (0.5)	2 (0.4)	0	0
Salmeterol	138 (10.6)	62 (13.8)	9 (4.5)	5 (7.0)
Other				
Ipratropium bromide	15 (1.2)	9 (2.0)	3 (1.5)	2 (2.8)
Theophylline	17 (1.3)	3 (0.7)	0	0
Anti-Inflammatories [c]	**484 (37.1)**	**175 (39.0)**	**27 (13.4)**	**12 (16.9)**
Beclomethasone	41 (3.1)	8 (1.8)	4 (2.0)	2 (2.8)
Budesonide	38 (2.9)	13 (2.9)	1 (0.5)	1 (1.4)
Ciclesonide	0 1	(0.2)	0	0
Flunisolide	2 (0.2)	2 (0.4)	0 2	(2.8)
Fluticasone	169 (13.0)	72 (16.0)	12 (6.0)	4 (5.6)
Mometasone	6 (0.5)	0	0	0
Triamcinolone	27 (2.1)	4 (0.9)	2 (1.0)	0
Methylprednisolone	19 (1.5)	6 (1.3)	1 (0.5)	0
Prednisolone	4 (0.3)	1 (0.2)	1 (0.5)	0
Prednisone	73 (5.6)	22 (4.9)	2 (1.0)	2 (2.8)
Cromolyn sodium	8 (0.6)	4 (0.9)	3 (1.5)	0
Nedocromil sodium	3 (0.2)	1 (0.2)	0 1	(1.4)
Montelukast sodium	102 (7.8)	40 (8.9)	2 (1.0)	1 (1.4)
Zafirlukast	5 (0.4)	5 (1.1)	0	0
Unknown steroid	61 (4.7)	20 (4.5)	1 (0.5)	2 (2.8)

Medication [b]	Reported any use in early pregnancy		Reported only "as needed" asthma medication use in early pregnancy	
	Case n (%)	Control n (%)	Case n (%)	Control n (%)
Unknown medications	**81 (6.2)**	**19 (1.2)**	**15 (7.5)**	**4 (5.6)**
Unknown inhalant	30 (2.3)	8 (1.8)	13 (6.5)	2 (2.8)
Unknown asthma medication	74 (5.7)	15 (3.3)	2 (1.0)	2 (2.8)

[a] Early pregnancy defined as one month before through the third month of pregnancy.

[b] Other asthma medications were examined, but had 0 exposed cases and 0 exposed controls, including: clenbuterol, omalizumab, indacaterol, aformoterol, aclidinium bromide, umeclidinium bromide, vilanterol, bambuterol, isoproterenol, tiotropium, aminophylline, pranlukast, zileuton, and unknown bronchodilators.

[c] Totals (in bold) may not equal the sum of the specific medication components, as women could report multiple medications with varying frequencies during early pregnancy.

Table 3.

Associations between early pregnancy asthma medication use and noncardiac birth defects, National Birth Defects Prevention Study 1997–2011.

Birth Defect	Unexp N	Any Asthma Medication		Bronchodilators				Anti-Inflammatories				Bronchodilators & anti-inflammatories	
				Any Use		Only		Any Use		Only			
		N [a]	aOR/cOR (95% CI) [b]	N	aOR/cOR (95% CI) [b]	N	aOR/cOR (95% CI) [b]	N	aOR/cOR (95% CI) [b]	N	aOR/cOR (95% CI) [b]	N	aOR/cOR (95% CI) [b]
Controls	10,445	449		364		255		175		66		109	
Amniotic band sequence	292	15	1.13 (0.66, 1.93)	15	1.36 (0.80, 2.33)	12	1.47 (0.81, 2.68)	3	0.61 (0.12, 1.84)	0	NC	3	0.98 (0.20, 2.98)
Anencephaly	593	25	1.07 (0.71, 1.62)	18	0.94 (0.58, 1.53)	16	1.20 (0.72, 2.01)	6	0.67 (0.29, 1.51)	4	1.07 (0.28, 2.88)	2	NC
Spina bifida	1,137	47	0.99 (0.73, 1.36)	39	1.03 (0.74, 1.45)	25	0.94 (0.62, 1.43)	19	1.07 (0.66, 1.73)	5	0.77 (0.31, 1.92)	14	1.24 (0.71, 2.17)
Encephalocele	202	6	0.76 (0.33, 1.72)	6	0.92 (0.41, 2.10)	5	1.08 (0.44, 2.65)	1	NC	0	NC	1	NC
Holoprosencephaly	146	10	1.62 (0.82, 3.22)	9	1.75 (0.84, 3.61)	6	1.86 (0.81, 4.26)	4	1.64 (0.43, 4.35)	1	NC	3	1.97 (0.40, 6.02)
Dandy-Walker malformation	157	9	1.27 (0.62, 2.63)	6	1.15 (0.50, 2.63)	5	1.34 (0.54, 3.32)	2	NC	1	NC	1	NC
Hydrocephaly	444	21	1.06 (0.67, 1.68)	14	0.91 (0.53, 1.57)	8	0.73 (0.36, 1.49)	11	1.41 (0.74, 2.69)	5	1.51 (0.55, 4.18)	6	1.35 (0.59, 3.09)
Cerebellar hypoplasia	51	5	2.19 (0.86, 5.56)	5	**2.70 (1.06, 6.85)**	4	3.21 (0.84, 8.84)	1	NC	0	NC	1	NC
Ano/microphthalmia	205	6	0.69 (0.31, 1.58)	4	0.56 (0.15, 1.47)	4	0.80 (0.21, 2.10)	2	NC	2	NC	0	NC
Congenital cataracts [c]	313	14	0.92 (0.52, 1.63)	13	1.13 (0.64, 1.99)	9	1.11 (0.56, 2.18)	4	0.76 (0.20, 2.01)	0	NC	4	1.22 (0.32, 3.26)
Glaucoma [c]	163	5	0.75 (0.31, 1.84)	3	0.52 (0.11, 1.57)	2	NC	3	1.10 (0.22, 3.33)	2	NC	1	NC
Ano/microtia	631	22	0.97 (0.62, 1.53)	16	0.92 (0.55, 1.54)	13	1.07 (0.60, 1.90)	7	0.85 (0.40, 1.84)	4	1.00 (0.26, 2.71)	3	0.46 (0.09, 1.37)
Choanal atresia	136	11	1.79 (0.95, 3.35)	7	1.44 (0.66, 3.11)	7	2.14 (0.99, 4.66)	2	NC	2	NC	0	NC
Cleft palate only [d]	1,415	78	1.17 (0.91, 1.50)	70	1.30 (0.99, 1.69)	56	**1.50 (1.11, 2.02)**	17	0.63 (0.38, 1.06)	3	0.33 (0.07, 1.01)	14	0.84 (0.47, 1.49)
Cleft lip only [d]	962	58	1.31 (0.99, 1.74)	49	**1.37 (1.01, 1.87)**	40	**1.58 (1.12, 2.23)**	16	0.96 (0.57, 1.61)	7	1.07 (0.49, 2.35)	9	0.88 (0.44, 1.75)

Birth Defect	Unexp N	Any Asthma Medication		Bronchodilators				Anti-Inflammatories				Bronchodilators & anti-inflammatories	
				Any Use		Only		Any Use		Only			
		N [a]	aOR/cOR (95% CI) [b]	N	aOR/cOR (95% CI) [b]	N	aOR/cOR (95% CI) [b]	N	aOR/cOR (95% CI) [b]	N	aOR/cOR (95% CI) [b]	N	aOR/cOR (95% CI) [b]
Cleft lip with cleft palate [d]	1,819	86	1.10 (0.87, 1.40)	65	1.03 (0.79, 1.35)	43	0.96 (0.69, 1.33)	38	1.29 (0.90, 1.86)	16	1.42 (0.81, 2.51)	22	1.21 (0.76, 1.93)
Esophageal atresia	640	36	1.25 (0.88, 1.77)	27	1.18 (0.79. 1.77)	19	1.21 (0.75, 1.95)	14	1.16 (0.67, 2.02)	6	1.21 (0.52, 2.81)	8	1.13 (0.55, 2.33)
Duodenal atresia/stenosis	192	12	1.48 (0.81, 2.68)	9	1.35 (0.68, 2.67)	7	1.46 (0.67, 3.15)	4	1.24 (0.33, 3.29)	2	NC	2	NC
Small intestinal atresia/ stenosis	416	22	1.28 (0.81, 2.01)	15	1.04 (0.60, 1.80)	12	1.17 (0.63, 2.16)	7	1.13 (0.53, 2.43)	4	1.52 (0.40, 4.11)	3	0.69 (0.14, 2.09)
Colonic atresia/stenosis	51	1	NC	1	NC	1	NC	0	NC	0	NC	0	NC
Anorectal atresia/stenosis	960	31	0.71 (0.49, 1.05)	23	0.67 (0.43, 1.04)	16	0.70 (0.42, 1.16)	11	0.58 (0.29, 1.14)	4	0.66 (0.17, 1.78)	7	0.61 (0.27, 1.40)
Biliary atresia	176	11	1.53 (0.82, 2.85)	9	1.52 (0.77, 3.01)	3	0.70 (0.14, 2.10)	8	**3.02 (1.45, 6.27)**	2	NC	6	**3.60 (1.55, 8.35)**
Hypospadias [e]	2,242	105	1.02 (0.79, 1.30)	82	0.94 (0.72, 1.24)	49	0.79 (0.56, 1.12)	53	1.34 (0.93, 1.93)	20	1.42 (0.77, 2.59)	33	1.30 (0.83, 2.05)
Renal agenesis/hypoplasia	169	8	1.10 (0.54, 2.27)	6	1.01 (0.44, 2.31)	6	1.44 (0.63, 3.30)	2	NC	2	NC	0	NC
Bladder exstrophy	61	5	1.64 (0.65, 4.11)	5	2.05 (0.82, 5.16)	2	NC	3	2.94 (0.58, 9.13)	0	NC	3	4.71 (0.93, 14.8)
Cloacal exstrophy	91	3	0.77 (0.15, 2.33)	2	NC	2	NC	1	NC	1	NC	0	NC
Longitudinal limb deficiency [f]	458	37	**1.81 (1.27, 2.58)**	34	**2.04 (1.41, 2.96)**	27	**2.35 (1.55, 3.54)**	8	0.94 (0.44, 2.02)	1	NC	7	1.29 (0.56, 2.95)
Transverse limb deficiency	643	29	1.00 (0.67, 1.48)	24	1.05 (0.68, 1.61)	13	0.85 (0.48, 1.49)	15	1.23 (0.69, 2.18)	4	0.98 (0.26, 2.65)	11	1.51 (0.79, 2.91)
Craniosynostosis	1,412	63	0.93 (0.71, 1.23)	51	0.94 (0.69, 1.28)	35	0.95 (0.65, 1.37)	26	0.92 (0.60, 1.39)	10	0.89 (0.45, 1.74)	16	0.94 (0.55, 1.59)
Diaphragmatic hernia	764	22	0.67 (0.43, 1.03)	17	0.64 (0.39, 1.05)	10	0.54 (0.28, 1.02)	11	0.85 (0.46, 1.57)	4	0.83 (0.22, 2.23)	7	0.87 (0.40, 1.88)
Omphalocele	382	18	1.05 (0.65, 1.71)	17	1.23 (0.75, 2.03)	12	1.23 (0.68, 2.22)	6	0.90 (0.39, 2.05)	1	NC	5	1.23 (0.50, 3.05)
Gastroschisis	1,216	74	1.31 (0.99, 1.75)	61	1.34 (0.98, 1.83)	45	1.33 (0.93, 1.90)	22	1.18 (0.70, 1.99)	6	0.82 (0.31, 2.22)	16	1.39 (0.75, 2.56)
Sacral agenesis	96	3	0.73 (0.15, 2.20)	3	0.90 (0.18, 2.72)	2	NC	1	NC	0	NC	1	NC

Unexp=unexposed, aOR=adjusted odds ratio, cOR=crude odds ratio, CI=confidence interval, NC=not calculated. Bold font indicates a statistically significant finding.

[a] Any asthma medication use includes case and control who reported unknown inhalants or asthma medications (81 cases/19 controls); these cases and controls are not in other columns.

[b] For defects with 5+ exposed cases, estimates were adjusted for maternal age (continuous), race/ethnicity, BMI, smoking, folic acid-containing supplement use, and parity. Counts in the adjusted analysis were slightly lower due to missing values for some covariates. Crude ORs and exact 95% CIs are presented for defects groups with 3–4 exposed cases. Estimates are not presented when < 3 exposed cases.

[c] 8,883 unexposed controls, 379 any asthma medication exposed controls, 312 any bronchodilator exposed controls, 219 only bronchodilator exposed controls, 149 any anti-inflammatory exposed controls, 56 only anti-inflammatory exposed controls, 93 bronchodilator and anti-inflammatory exposed controls.

[d] 10,316 unexposed controls, 446 any asthma medication exposed controls, 361 any bronchodilator exposed controls, 255 only bronchodilator exposed controls, 172 any anti-inflammatory exposed controls, 66 only anti-inflammatory exposed controls, 106 bronchodilator and anti-inflammatory exposed controls.

[e] 5,306 unexposed controls, 221 any asthma medication exposed controls, 188 any bronchodilator exposed controls, 134 only bronchodilator exposed controls, 80 any anti-inflammatory exposed controls, 26 only anti-inflammatory exposed controls, 54 bronchodilator and anti-inflammatory exposed controls.

[f] Includes longitudinal and intercalary limb deficiencies.

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Table 4.

Associations between early pregnancy asthma medication use and congenital heart defects, National Birth Defects Prevention Study 1997–2011.

Birth Defect	Unexp N	Any Asthma Medication		Bronchodilators				Anti-Inflammatories				Bronchodilators & anti-inflammatories	
				Any Use		Only		Any Use		Only			
		N [a]	aOR/cOR (95% CI) [b]	N	aOR/cOR (95% CI) [b]	N	aOR/cOR (95% CI) [b]	N	aOR/cOR (95% CI) [b]	N	aOR/cOR (95% CI) [b]	N	aOR/cOR (95% CI) [b]
Controls	10,445	449		364		255		175		66		109	
Truncus arteriosus	112	9	1.78 (0.89, 3.55)	9	**2.21 (1.10, 4.42)**	7	**2.48 (1.13, 5.42)**	2	NC	0	NC	2	NC
Tetralogy of Fallot	1,082	50	0.95 (0.69, 1.30)	35	0.86 (0.60, 1.24)	21	0.71 (0.45, 1.15)	21	1.11 (0.70, 1.76)	7	0.97 (0.44, 2.13)	14	1.20 (0.68, 2.10)
D-TGA	679	28	0.94 (0.63, 1.38)	23	0.96 (0.62, 1.47)	14	0.84 (0.49, 1.45)	12	1.00 (0.55, 1.81)	3	0.70 (0.14, 2.14)	9	1.23 (0.62, 2.44)
DORV-TGA	181	4	0.51 (0.14, 1.35)	3	0.48 (0.10, 1.42)	2	NC	2	NC	1	NC	1	NC
Conoventricular VSD [c]	102	6	1.12 (0.45, 2.78)	5	1.12 (0.41, 3.09)	3	1.16 (0.23, 3.55)	3	2.03 (0.40, 6.30)	1	NC	2	NC
Atrioventricular septal defect	328	17	1.05 (0.63, 1.75)	15	1.13 (0.65, 1.95)	12	1.25 (0.68, 2.32)	4	0.73 (0.20, 1.92)	1	NC	3	0.88 (0.18, 2.65)
TAPVR	277	12	1.09 (0.61, 1.97)	11	1.22 (0.66, 2.26)	10	1.58 (0.83, 3.02)	2	NC	1	NC	1	NC
Hypoplastic heart syndrome	591	26	1.01 (0.68, 1.52)	22	1.05 (0.68, 1.63)	17	1.17 (0.71, 1.93)	8	0.80 (0.39, 1.63)	3	0.80 (0.16, 2.46)	5	0.79 (0.32, 1.94)
Coarctation of the aorta	1,044	38	0.83 (0.59, 1.17)	33	0.90 (0.63, 1.29)	18	0.71 (0.44, 1.16)	18	0.96 (0.59, 1.58)	3	0.45 (0.09, 1.39)	15	1.31 (0.76, 2.27)
Aortic valve stenosis	455	23	1.08 (0.70, 1.67)	18	1.06 (0.65, 1.72)	10	0.85 (0.45, 1.62)	10	1.15 (0.60, 2.20)	2	NC	8	1.52 (0.73, 3.14)
Pulmonary atresia	237	14	1.43 (0.82, 2.47)	13	1.63 (0.92, 2.88)	7	1.24 (0.58, 2.67)	6	1.59 (0.69, 3.64)	0	NC	6	**2.50 (1.09, 5.78)**
Pulmonary valve stenosis *d*	1,371	63	0.99 (0.75, 1.30)	56	1.06 (0.79, 1.42)	36	0.98 (0.69, 1.41)	24	0.96 (0.62, 1.50)	4	0.47 (0.12. 1.27)	20	1.24 (0.76, 2.04)
Tricuspid atresia	158	11	1.82 (0.97, 3.40)	10	**2.03 (1.06, 3.90)**	7	2.01 (0.93, 4.37)	4	1.51 (0.40, 4.02)	1	NC	3	1.82 (0.37, 5.56)
Ebstein anomaly	163	8	1.17 (0.57, 2.40)	6	1.07 (0.47, 2.45)	4	1.01 (0.27, 2.66)	3	1.10 (0.22, 3.32)	1	NC	2	NC
Perimembranous VSD [c]	1,261	53	0.91 (0.67, 1.25)	47	0.99 (0.71, 1.39)	34	0.97 (0.66, 1.44)	18	0.90 (0.53, 1.52)	5	0.67 (0.26, 1.72)	13	1.05 (0.56, 1.96)

Birth Defect	Unexp N	Any Asthma Medication		Bronchodilators				Anti-Inflammatories				Bronchodilators & anti-inflammatories	
				Any Use		Only		Any Use		Only			
		N [a]	aOR/cOR (95% CI) [b]	N	aOR/cOR (95% CI) [b]	N	aOR/cOR (95% CI) [b]	N	aOR/cOR (95% CI) [b]	N	aOR/cOR (95% CI) [b]	N	aOR/cOR (95% CI) [b]
Muscular VSD [e]	172	7	0.78 (0.32, 1.93)	4	0.63 (0.16, 1.88)	3	0.60 (0.11, 2.08)	4	1.52 (0.35, 5.35)	3	2.28 (0.35, 11.8)	1	NC
Secundum ASD	2,703	136	1.14 (0.93, 1.39)	108	1.12 (0.89, 1.40)	73	1.07 (0.81, 1.39)	55	1.20 (0.88, 1.65)	20	1.14 (0.67, 1.93)	35	1.24 (0.84, 1.83)
Single ventricle	162	6	0.74 (0.30, 1.81)	4	0.71 (0.19, 1.87)	2	NC	4	1.47 (0.39, 3.91)	2	NC	2	NC
Heterotaxy	304	18	1.40 (0.85, 2.31)	15	1.39 (0.80, 2.41)	10	1.40 (0.73, 2.67)	6	1.12 (0.46, 2.76)	1	NC	5	1.39 (0.51, 3.80)

Unexp = unexposed, aOR = adjusted odds ratio, cOR=crude odds ratio. CI = confidence interval, NC = not calculated, TGA = transposition of the great arteries, DORV = double outlet right ventricle, VSD = ventricular septal defect, TAPVR = total anomalous pulmonary venous return, ASD = atrial septal defect. Bold font indicates a statistically significant finding.

[a] Any asthma medication use includes case and control who reported unknown inhalants or asthma medications (81 cases/19 controls); these cases and controls are not in other columns.

[b] For defects with 5+ exposed cases, estimates were adjusted for maternal age (continuous), race/ethnicity, BMI, smoking, folic acid-containing supplement use, and parity. Counts in the adjusted analysis were slightly lower due to missing values for some covariates. Crude ORs and exact 95% CIs are presented for defects groups with 3–4 exposed cases. Estimates are not presented when < 3 exposed cases.

[c] 6,145 unexposed controls, 260 any asthma medication exposed controls, 211 any bronchodilator exposed controls, 156 only bronchodilator exposed controls, 89 any anti-inflammatory exposed controls, 34 only anti-inflammatory exposed controls, 55 bronchodilator and anti-inflammatory exposed controls.

[d] 10,015 unexposed controls, 429 any asthma medication exposed controls, 353 any bronchodilator exposed controls, 246 only bronchodilator exposed controls, 169 any anti-inflammatory exposed controls, 62 only anti-inflammatory exposed controls, 107 bronchodilator and anti-inflammatory exposed controls.

[e] 654 unexposed controls, 31 any asthma medication exposed controls, 24 any bronchodilator exposed controls, 19 only bronchodilator exposed controls, 10 any anti-inflammatory exposed controls, 5 only anti-inflammatory exposed controls, 5 bronchodilator and anti-inflammatory exposed controls.

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