Use of asthma medication during pregnancy and risk of specific congenital anomalies: A European case-malformed control study

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Background: Pregnant women with asthma need to take medication during pregnancy.
Objective: We sought to identify whether there is an increased risk of specific congenital anomalies after exposure to antiasthma medication in the first trimester of pregnancy.
Methods: We performed a population-based case-malformed control study testing signals identified in a literature review. Odds ratios (ORs) of exposure to the main groups of asthma medication were calculated for each of the 10 signal anomalies compared with registrations with nonchromosomal, nonsignal anomalies as control registrations. In addition, exploratory analyses were done for each nonsignal anomaly. The data set included 76,249 registrations of congenital anomalies from 13 EUROmediCAT registries.
Results: Cleft palate (OR, 1.63; 95% CI, 1.05-2.52) and gastroschisis (OR, 1.89; 95% CI, 1.12-3.20) had significantly increased odds of exposure to first-trimester use of inhaled β_2-agonists compared with nonchromosomal control registrations. Odds of exposure to salbutamol were similar. Nonsignificant ORs of exposure to inhaled β_2-agonists were found for spina bifida, cleft lip, anal atresia, severe congenital heart defects in general, or tetralogy of Fallot. None of the 4 literature signals of exposure to inhaled steroids were confirmed (cleft palate, cleft lip, anal atresia, and hypospadias). Exploratory analyses found an association between renal dysplasia and exposure to the combination of long-acting β_2-agonists and inhaled corticosteroids (OR, 3.95; 95% CI, 1.99-7.85).
Conclusions: The study confirmed increased odds of first-trimester exposure to inhaled β_2-agonists for cleft palate and gastroschisis and found a potential new signal for renal dysplasia associated with combined long-acting β_2-agonists and inhaled corticosteroids. Use of inhaled corticosteroids during the first trimester of pregnancy seems to be safe in relation to the risk for a range of specific major congenital anomalies. (J Allergy Clin Immunol 2015;136:1496-502.)

Key words: *Asthma medication, congenital anomalies, pregnancy, first trimester exposure, inhaled β_2-agonists, inhaled corticosteroids*

Asthma is a chronic inflammatory respiratory disease reported with increasing prevalence over the last decades.[1] Increase in the prevalence of asthma in pregnancy has also been reported.[2,3] The prevalence of asthma in pregnancy in Europe is estimated to be 4% to 8%.[3-6]

Medical treatment of asthma is mainly through use of β_2-agonists for symptom relief (rescue treatment) and anti-inflammatory medications for reducing and preventing chronic inflammation in the airways. Women becoming pregnant are recommended to continue their medication during pregnancy, with a few exceptions.[7-9] A stepwise approach in managing asthma during pregnancy is recommended.[7-9] A British study based on prescriptions for asthma medications found that 4.8% of pregnant women with asthma had a prescription related to an exacerbation during pregnancy compared with 5.9% in the same season during the year before pregnancy.[4]

A meta-analysis concluded that maternal asthma is associated with an increased risk of adverse maternal outcomes, including

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Abbreviations used
ATC: Anatomical Therapeutic Chemical
OR: Odds ratio
TOPFA: Termination of pregnancy for fetal anomaly

preeclampsia and adverse neonatal outcomes, such as low birth weight and preterm birth.[10] Furthermore, the overall risk of congenital anomalies is slightly increased with maternal asthma, but there is lack of consensus concerning the effects of medication versus the disease itself.[11-13] Case-control studies have shown an increased risk of specific congenital anomalies, such as facial clefts, gastroschisis, and anal atresia, after first-trimester exposure to asthma medications.[14-16] Maternal asthma exacerbations during the first trimester of pregnancy have been reported to be associated with a 50% increased risk of congenital anomalies,[17] and exacerbations during pregnancy have also been associated with other unfavorable pregnancy outcomes.[18] Treatment decisions need to balance the benefits for mother and baby of disease control against the risks related to medication use. Based on current evidence, the general consensus is that uncontrolled asthma increases perinatal risks, whereas well-controlled asthma reduces these risks.[7-9,11,12]

The aim of this study is to contribute to the evidence base for clinical decision making by investigating the increased risk of specific congenital anomalies in relation to specific antiasthma medications by using data from the EUROmediCAT database for 13 EUROCAT population-based congenital anomaly registries. EUROmediCAT is a Seventh Framework Programme study funded by the European Commission that aims to make more systematic use of electronic health care databases in combination with EUROCAT congenital anomaly data and build a European system for the evaluation of medicine use in pregnancy in relation to the risk of congenital anomalies.

METHODS

Study design

This study has a case-malformed control study design[19,20] using data from EUROCAT population-based congenital anomaly registries contributing to the EUROmediCAT database. The term "registration" is used for all notifications in the database. Cases are congenital anomalies that have been reported as signals associated with asthma medication in the literature, and control registrations are all other congenital anomalies divided into nonchromosomal and chromosomal control registrations. An additional exploratory study was performed within the nonchromosomal control group to identify any new signals of congenital anomaly subgroups with raised risks.

Study population and data

EUROCAT is a network of population-based registries collecting data on congenital anomaly registrations among live births, fetal deaths of 20 weeks' gestation or later, and terminations of pregnancy for fetal anomaly (TOPFAs). Most registries include registrations diagnosed up to 1 year after birth. Detailed descriptions of registries and the methodology have been published previously.[21,22] The congenital anomalies are coded with International Classification of Diseases, ninth revision, or International Classification of Diseases, tenth revision, codes, and the codes are classified into standard EUROCAT congenital anomaly subgroups (EUROCAT Guide 1.3; http://www.eurocat-network.eu/content/EUROCAT-Guide-1.3.pdf).[19] Registrations with only minor congenital anomalies according to a specific list are excluded from the database (EUROCAT Guide 1.3).

All registries taking part in the EUROmediCAT study (www.EUROmediCAT.eu) were eligible for the study. A registry was included if first-trimester exposure to asthma medication (Anatomical Therapeutic Chemical [ATC] code R03) was recorded for at least 3 per 1000 registrations for any of the 3 time intervals of 1995-1999, 2000-2004, and 2005-2010. With this criterion set to exclude registries with low ascertainment of exposure, 13 registries in 12 countries were included for all or part of the period from, 1995-2010: Norway, Funen County (Denmark), Mainz (Germany), Northern Netherlands, Antwerp (Belgium), Paris (France), Vaud (Switzerland), Tuscany (Italy), Emilia Romagna (Italy), Zagreb (Croatia), Malta, Wales (United Kingdom), and Cork and Kerry (Ireland). Only 2 registries were excluded because of low ascertainment of exposures. The Emilia Romagna registry did not record medication use for TOPFAs, and therefore only live births and late fetal deaths with congenital anomalies were included from this registry.

Literature review to identify "signals" to be tested

PubMed was used to search for English-language studies published between January 1, 1990, and February 2, 2014, by using the search term "asthma" combined with any of the following: "congenital malformations," "congenital defects," "birth defects," "congenital abnormalities," "congenital anomalies," and "pregnancy outcome." The review is described in Fig 1. The inclusion criteria of being a human epidemiologic controlled study of congenital anomaly risk related to asthma medication were met by 68 publications. Nine original studies published statistically significant associations between specific congenital anomalies and all or specific asthma medications, which could be used as signals for this EUROmediCAT study; 2 were cohort studies, and 7 were case-control studies (Table I).[13-16,23-27]

Definition of case and control registrations

Registrations classified as genetic syndromes, teratogenic syndromes, or skeletal dysplasias were excluded from the analysis. In EUROCAT registries clinical geneticists are involved in the evaluation of most patients with multiple malformation, dysmorphic features, or both. Therefore it is reasonable to assume that all conditions with known cause, including midline interruption overlap syndromes, such as DiGeorge syndrome and coloboma, heart defect, atresia choanae, retarded growth and development, genital abnormality, and ear abnormality (CHARGE) syndrome, are diagnosed, coded, and excluded from the study. Registrations with unspecified abdominal wall defects were also excluded because gastroschisis and omphalocele were signals. All exclusions are presented in Fig 2.

Cases were defined as EUROCAT registrations with at least 1 of the signal malformations: spina bifida, cleft palate, cleft lip with or without cleft palate, severe congenital heart defects, tetralogy of Fallot, esophageal atresia, gastroschisis, omphalocele, hypospadias, and anorectal atresia, stenosis, or both. Registrations with Pierre Robin sequence were excluded from the cleft palate and cleft lip with or without cleft palate case groups because the cleft palate in these cases is part of a sequence and might have a separate cause. Pierre Robin is a sequence derived from micrognathia (hypoplastic mandible), leading to displacement of the tongue and obstructing the closure of the palate. It might be part of a genetic syndrome but otherwise considered an isolated malformation (http://www.eurocat-network.eu/content/EUROCAT-Guide-1.3.pdf).

Similarly, for the exploratory analysis, registrations with bladder exstrophy, epispadias, prune belly, or the posterior urethral valve were excluded from the hydronephrosis case group because the hydronephrosis in these registrations was assumed to be secondary to the underlying anomalies.

Two control groups were used: a group of control subjects with chromosomal anomalies and 1 group comprised of other EUROCAT registrations with nongenetic, nonsignal congenital anomalies. When analyzing hypospadias as an outcome, male control subjects only were used.

Exposure

Information on medication exposure in the first trimester of pregnancy was obtained mainly from obstetric/midwife records created before birth. Additional data sources available for some registries were the medical records of the

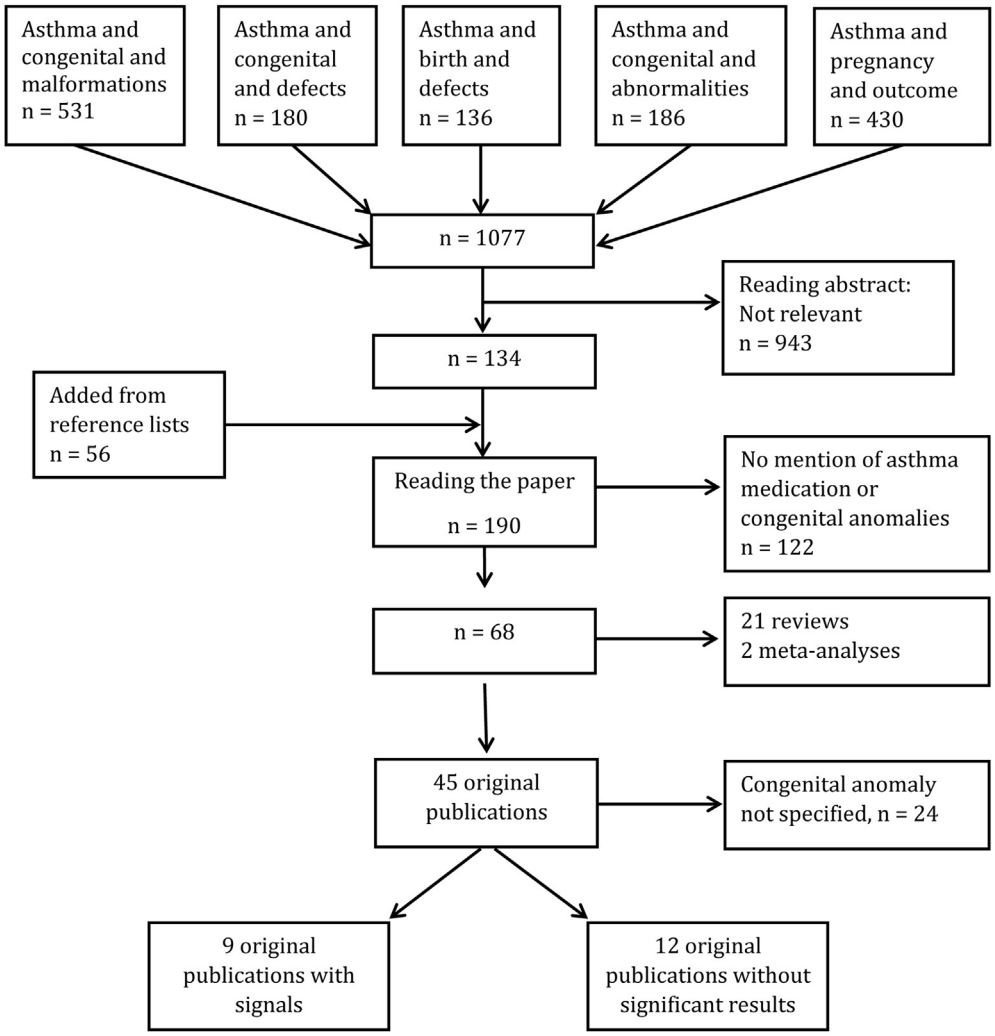

FIG 1. Flowchart describing the literature review.

infant, records from the general practitioner, maternity passports, and maternal interviews before or after birth. In the northern Netherlands prescription data were used as an additional data source. For Norway, the only data available for first-trimester exposure were prescription redemption records. For all registries, the first trimester of pregnancy was defined as the period from the first day of the last menstrual period to the end of gestational week 12.

Exposure was defined as use of asthma medication (ATC code R03) in the first trimester of pregnancy. Exposure was grouped into asthma medication classes based on 5-digit ATC codes: inhaled β_2-agonists, inhaled corticosteroids, and all asthma medications (Table II). For the Paris registry, mode of delivery for β_2-agonists was unknown. Where ATC codes for asthma medications were given as 3- or 4-digit codes, the registries were asked whether the medication could be identified in more detail, and if this was not possible, the registration was excluded to avoid exposure misclassification. Further excluded were registrations in which the mother was coded as taking an unspecified medication, as having asthma with no asthma medication use in the first trimester recorded, or as having unknown timing of the asthma medication (Fig 2). Finally, mothers recorded as using antiepileptics or antidiabetics or as having epilepsy or diabetes were excluded.

Study power

Preliminary power analyses assuming a control group size of 50,000 and an overall exposure rate of 2% showed 80% power of detecting an odds ratio (OR) of 1.72 that was significant at the 5% level for an anomaly with 1000 cases. Looking at specific asthma medication groups with exposure rates of 1% or at rarer anomalies with 500 cases, we have 80% power to detect at the 5% level an OR of 2.05.

Statistical analyses

ORs of exposure to each of the main groups of asthma medication were calculated for each of 10 signal anomalies compared with nonchromosomal, nonsignal anomalies as control registrations. Adjusted ORs of exposure were calculated by using logistic regression with random effects for registry using the SAS 9.3 GLIMMIX procedure. ORs were also adjusted for maternal age (categorized as <25 years, 25-29 years, 30-34 years, 35-39 years, and ≥40 years), and analyses for inhaled β_2-agonists were adjusted for use of inhaled corticosteroids and *vice versa*. Sensitivity analyses were adjustment for first-trimester use of systemic corticosteroids (ATC code H02AB), adjustment for period, and restriction to isolated anomalies.

In the exploratory analysis within the nonchromosomal control group, the ORs of each of 62 EUROCAT congenital anomaly subgroups of exposure to asthma medications in general or to each of the 3 asthma medication classes were calculated by using all other nonchromosomal registrations in this group as control registrations. Adjustment was made for maternal age and registry as in the main analysis. Only subgroups with at least 5 exposed cases are presented.

RESULTS

The study included 76,249 registrations of congenital anomalies in the 13 registries during the years 1995-2010. After

TABLE I. Literature signals for specific congenital anomalies after exposure to asthma medications

Congenital anomaly	Medication type	Exposed cases	OR	95% CI	Adjusted OR	95% CI	Reference
Spina bifida	Asthma medication	12	4.41	1.61-12.1	3.25*	1.29-8.16	Blais et al, 2010[13]
Cleft lip	β_2-Agonists	20			1.77†	1.08-2.88	Munsie et al, 2011[14]
Cleft lip	Albuterol	18			1.79†	1.07-2.99	
Cleft palate only	Albuterol	25			1.665†	1.06-2.58	
Cleft lip with/without cleft palate	Systemic corticosteroids	7	2.59	1.18-5.67			Pradat et al, 2003[23]
Major cardiac	Long acting β_2-agonists	7			2.38§	1.11-5.10	Eltonsy et al, 2011[26]
Severe CHD	β_2-Agonists	22			2.20‡	1.05-4.61	Lin et al 2009[25]
Tetralogy of Fallot	Asthma medication	19	1.66	1.05-2.62			Källen et al, 2007[24]
Esophageal atresia, isolated	β_2-Agonists	10			2.39‖	1.23-4.66	Lin et al, 2012[16]
Anorectal atresia	Anti-inflammatory	10			2.12‖	1.09-4.12	Lin et al, 2012[16]
Gastroschisis	β_2-Agonists	17	1.94	1.14-3.29	2.06¶	1.19-3.59	Lin et al, 2008[15]
Omphalocele	β2-Agonists and anti-inflammatory	4			4.13‖	1.43-11.95	Lin et al, 2012[16]
Hypospadias	Corticosteroids, any route	39	1.6	1.1-2.5	1.3#	0.8-2.0	Carmichael et al 2009[27]

CHD, Congenital heart defect.
*Adjusted for maternal socioeconomic variables, pregnancy-related variables, and maternal chronic conditions.
†Adjusted for maternal age, race, ethnicity, education, alcohol consumption, smoking, marijuana use, use of folic acid, vasoactive medication use, and infant's sex.
‡Adjusted for caffeine use, fever, vitamin use, trihalomethane exposure, maternal age, race, ethnicity, and body mass index.
§Adjusted for sociodemographic variables, maternal and fetal characteristics, and asthma-related variables (comedications and others).
‖Adjusted for infant's sex, maternal age, body mass index, parity, race/ethnicity, education, alcohol use, smoking, folic acid, fever, cocaine use, and asthma medications.
¶Adjusted for maternal age, ethnicity, education, smoking, use of other vasoactive drugs, and use of folic acid.
#Education, race/ethnicity, maternal age, parity, folic acid, smoking, subfertility, and study area.

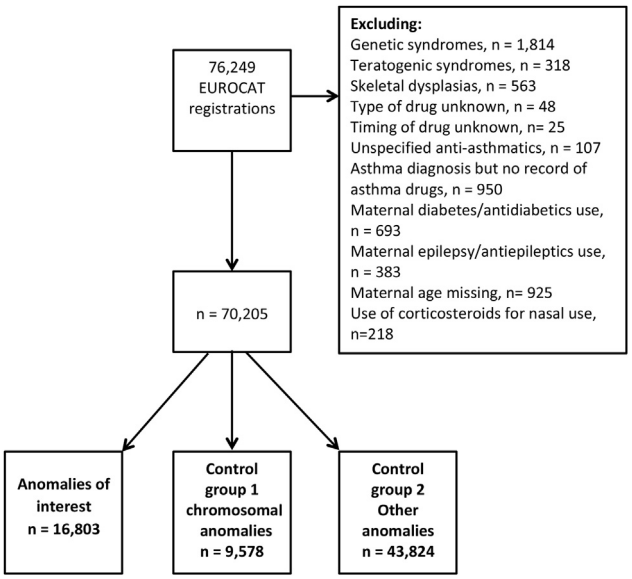

FIG 2. Flowchart describing inclusions and exclusions for the signal testing analysis. For exploratory analysis, registrations exposed to unspecified antiasthma medications were included.

exclusions (Fig 2), the number of registrations for analysis was 70,205 (92%). Of these, 16,803 had a congenital anomaly within one of the 10 signal congenital anomaly subgroups. The nonchromosomal control group included 43,824 registrations, and the chromosomal control group included 9,578 registrations.

Overall, 1,301 registrations (1.85% of all registrations) were exposed to 1 or more asthma medications defined by the ATC code R03 (Table II). Inhaled β_2-agonists were the most common medication used, with an exposure rate of 1.36%. In the signal groups 356 (2.12%) registrations were exposed to 1 or more asthma medications. In the nonchromosomal control group 809 (1.85%) were exposed, and in the chromosomal control group 136 (1.42%) were exposed to 1 or more asthma medications.

The results of the signal analysis are presented in Table III (adjusted OR). For inhaled β_2-agonists, 2 signals were confirmed: cleft palate and gastroschisis. For cleft palate, the OR of exposure to β_2-agonists was 1.63 (95% CI, 1.05-2.52) compared with nonchromosomal control registrations and 1.97 (95% CI, 1.19-3.25) compared with chromosomal control registrations. For gastroschisis, the OR was 1.89 (95% CI, 1.12-3.20) compared with nonchromosomal control registrations and 3.04 (95% CI, 1.53-6.06) compared with chromosomal control registrations. Salbutamol was the most frequently used inhaled β_2-agonist (818/953 [86%]). The OR of exposure to inhaled salbutamol was similar to that to inhaled β_2-agonists in general (cleft palate: OR, 1.63; 95% CI 1.02-2.60; gastroschisis: OR, 2.01; 95% CI, 1.18-3.44) compared with nonchromosomal control registrations. For cleft palate and gastroschisis, the OR of exposure to β_2-agonists in general (inhaled, systemic, and unknown mode of delivery) remained the same (see this article's Online Repository at www.jacionline.org).

None of the 4 signals for inhaled corticosteroids (cleft lip and palate, cleft palate, anal atresia/stenosis, and hypospadias) were confirmed. The odds of exposure to asthma medication in general for anal atresia/stenosis was significantly increased (OR, 1.64; 95% CI, 1.08-2.51). The ORs of exposure to β_2-agonists and inhaled corticosteroids for anal atresia/stenosis were both nonsignificantly increased (Table III).

Sensitivity analysis was performed by adjusting for use of systemic steroids (asthma severity), period (5-year intervals), and restricting to isolated anomalies only and showed almost no difference in the ORs (see this article's Online Repository).

In the exploratory analysis using nonsignal EUROCAT subgroups, there were 3 statistically significant positive associations at the 5% level of significance and 1 positive association at the 1% level (Table IV). The 3 associations at the 5% significance level were clubfoot (OR, 1.38; 95% CI, 1.08-1.76) for exposure to any asthma medications and encephalocele and Pierre Robin sequence for exposure to inhaled β_2-agonists (OR, 2.24 [95% CI, 1.04-4.80] and 2.65 [95% CI, 1.15-6.09], respectively). The

TABLE II. Asthma medications and number of exposed among all registrations, 13 registries, 1995-2010

		All registrations		Exposed to 1 asthma medication only		Exposed to 2 asthma medications		Exposed to ≥3 asthma medications	
	ATC codes	No.	Percent	No.	Percent	No.	Percent	No.	Percent
Total no. of registrations		70,205	100						
Exposed to asthma medications	R03	1,301	1.85	806	1.15	452	0.64	43	0.06
Inhaled β_2-agonists	R03AC	953	1.36	507	0.72	408	0.58	38	0.05
Short-acting β_2-agonists	R03AC02-R03AC07	924	1.32	498	0.71	389	0.55	37	0.05
Long acting β_2-agonists	R03AC12-R03AC13	47	0.07	10	0.01	31	0.04	6	0.01
Systemic β_2-agonists	R03CC	8	0.01	4	0.01	2	0.00	2	0.00
β_2-Agonists, mode of delivery unknown	R03CC*	37	0.05	22	0.03	13	0.02	2	0.00
Inhaled corticosteroids	R03BA	533	0.76	170	0.24	337	0.48	26	0.04
Combination β_2-agonists and inhaled corticosteroids	R03AK	191	0.27	94	0.13	77	0.11	20	0.03
Anticholinergic inhaled medications	R03BB	11	0.02	2	0.00	5	0.01	4	0.01
Theophyllines	R03DA	9	0.01	2	0.00	3	0.00	4	0.01
Leukotriene receptor antagonists	R03DC	12	0.02	2	0.00	5	0.01	5	0.01
Cromoglycate and nedocromil	R03BC	10	0.01	3	0.00	4	0.01	3	0.00

*Medication could not be confirmed as being for systemic use.

TABLE III. Results of the signal analysis: OR for anomaly with exposure to the signal medications compared with no exposure in nonchromosomal and chromosomal control registrations

	Any asthma medication		Inhaled β_2-agonists, ATC code R03AC		Inhaled corticosteroids, ATC code R03BA	
Control group	Nonchromosomal	Chromosomal	Nonchromosomal	Chromosomal	Nonchromosomal	Chromosomal
Controls	43,824	9,578	43,824	9,578	43,824	9,578
Exposed controls	809	136	592	97	349	51

	Total cases	Exposed cases	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Exposed cases	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Exposed cases	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Any signal anomaly	16,803	356	**1.15 (1.01-1.30)**	**1.42 (1.15-1.76)**	264	**1.23 (1.05-1.46)**	**1.46 (1.10-1.93)**	133	0.85 (0.68-1.07)	1.01 (0.68-1.49)
Spina bifida	1,194	20	0.88 (0.56-1.38)	1.06 (0.66-1.72)	17	0.90 (0.52-1.56)	1.39 (0.74-2.60)	7	*1.46 (0.63-3.38)*	*0.67 (0.26-1.74)*
Cleft palate	1,392	39	**1.53 (1.10-2.12)**	**1.68 (1.15-2.45)**	28	**1.63 (1.05-2.52)**	**1.97 (1.19-3.25)**	13	0.83 (0.44-1.57)	0.95 (0.46-1.97)
Cleft lip with/ without cleft palate	2,402	51	1.19 (0.89-1.59)	1.34 (0.95-1.90)	39	1.32 (0.91-1.92)	1.57 (0.98-2.52)	22	0.98 (0.60-1.61)	1.15 (0.61-2.16)
Severe CHD	4,738	87	1.00 (0.80-1.25)	1.21 (0.91-1.60)	64	1.21 (0.91-1.61)	1.38 (0.95-2.02)	27	*0.61 (0.40-0.94)*	*0.74 (0.43-1.29)*
Tetralogy of Fallot	730	10	0.77 (0.41-1.44)	0.83 (0.43-1.60)	9	1.29 (0.63-2.62)	1.54 (0.70-3.38)	3	*0.43 (0.13-1.45)*	*0.48 (0.13-1.78)*
Esophageal atresia	648	12	1.09 (0.61-1.95)	1.67 (0.96-2.90)	7	1.31 (0.59-2.90)	1.68 (0.72-3.94)	2	*0.33 (0.08-1.43)*	*0.40 (0.09-1.89)*
Gastroschisis	615	22	**1.61 (1.04-2.50)**	**1.76 (1.03-2.98)**	19	**1.89 (1.12-3.20)**	**3.04 (1.53-6.06)**	5	*0.59 (0.22-1.60)*	*0.33 (0.10-1.11)*
Omphalocele	467	11	1.36 (0.74-2.49)	1.18 (0.65-2.15)	9	1.52 (0.69-3.33)	1.76 (0.74-4.20)	5	*1.08 (0.38-3.06)*	*1.26 (0.39-4.05)*
Hypospadias	5097	107	1.06 (0.86-1.32)	**1.60 (1.11-2.31)**	76	*1.03 (0.77-1.37)*	*1.31 (0.82-2.11)*	43	0.99 (0.68-1.45)	1.32 (0.68-2.55)
Anal atresia/ stenosis	772	23	**1.64 (1.08-2.51)**	**2.04 (1.30-3.20)**	18	1.51 (0.85-2.68)	1.78 (0.92-3.44)	12	1.49 (0.74-3.02)	1.66 (0.73-3.77)

Analyses were adjusted for registry and maternal age. Analyses of β_2-agonists were adjusted for use of corticosteroids and *vice versa*. Italics denote results for an anomaly for which there is not a signal for inhaled β_2-agonists or antiasthma medication in general but for which there exists a signal for corticosteroids or *vice versa*.
Boldface denotes associations significant at the 5% level.
CHD, Congenital heart defect.

only positive association at the 1% significance level was renal dysplasia for exposure to the combination of long-acting β_2-agonists and inhaled corticosteroids (OR, 3.96; 95% CI, 1.99-7.87).

DISCUSSION

In this large population-based case-malformed control study combining data from 13 congenital anomaly registers throughout Europe, we confirmed previous findings that cleft palate and gastroschisis are associated with first-trimester exposure to β_2-agonists. We did not confirm any of the signals for specific congenital anomalies with first-trimester exposure to inhaled corticosteroids.

Our finding of increased odds of exposure to inhaled β_2-agonists (nonchromosomal control registrations: OR, 1.63; 95% CI, 1.05-2.52) for cleft palate is consistent with 2 previous studies using different methodologies. A case-control study of cleft palate found significantly increased odds of exposure to albuterol

TABLE IV. Exploratory analysis for nonsignal congenital anomaly subgroups

All nonsignal, nonchromosomal registrations	Total cases	Any asthma medication		Inhaled β_2-agonists		Inhaled steroids		Long-acting β_2-agonists and inhaled steroids	
		No.	Adjusted OR* (95% CI)	No.	Adjusted OR* (95% CI)	No.	Adjusted OR* (95% CI)	No.	Adjusted OR* (95% CI)
Anencephalus	826	17	1.06 (0.65-1.73)	13	1.03 (0.59-1.80)	6	0.9 (0.40-2.04)	5	2.13 (0.87-5.23)
Encephalocele	223	7	1.70 (0.80-3.64)	7	**2.24 (1.04-4.80)**	<5		<5	
Hydrocephalus	1,205	21	1.05 (0.68-1.63)	14	0.96 (0.56-1.64)	8	0.97 (0.48-1.97)	<5	
Microcephaly	459	8	0.81 (0.40-1.64)	8	1.01 (0.50-2.05)	<5		<5	
Congenital heart defects	13,860	242	0.90 (0.77-1.05)	183	0.93 (0.78-1.11)	107	0.95 (0.76-1.20)	37	0.85 (0.58-1.25)
VSD	8,227	136	0.92 (0.76-1.11)	100	0.95 (0.77-1.18)	61	0.96 (0.72-1.27)	20	0.82 (0.51-1.33)
ASD	3,228	70	1.07 (0.83-1.37)	56	1.11 (0.84-1.47)	23	0.83 (0.54-1.27)	8	0.82 (0.40-1.68)
Pulmonary valve stenosis	1,118	27	1.14 (0.77-1.68)	19	1.03 (0.65-1.63)	15	1.34 (0.79-2.27)	<5	
PDA as only CHD in term infants	843	15	0.81 (0.48-1.37)	10	0.70 (0.37-1.31)	5	0.78 (0.32-1.89)	6	1.80 (0.78-4.15)
Duodenal atresia or stenosis	206	5	1.34 (0.55,3.28)	<5		<5		<5	
Hirschsprung disease	352	5	0.73 (0.30-1.79)	<5		<5		<5	
Diaphragmatic hernia	608	7	0.63 (0.30-1.33)	6	0.78 (0.35-1.75)	<5		<5	
Renal dysplasia	965	23	1.40 (0.92-2.14)	15	1.21 (0.72-2.04)	6	0.81 (0.36-1.82)	9	**3.96 (1.99-7.87)**†
Congenital hydronephrosis	3,367	74	1.23 (0.96-1.57)	58	1.30 (0.99-1.72)	34	1.33 (0.93-1.91)	9	0.98 (0.49-1.93)
Posterior urethral valve/ prune belly	350	9	1.44 (0.74-2.81)	8	1.74 (0.85-3.53)	<5		<5	
Limb reduction	1,198	26	1.22 (0.82-1.81)	21	1.37 (0.88-2.13)	11	1.15 (0.63-2.11)	<5	
Club foot–talipes equinovarus	2,857	74	**1.38 (1.08-1.76)**	48	1.22 (0.91-1.65)	28	1.16 (0.78-1.71)	12	1.37 (0.75-2.48)
Hip dislocation and/or dysplasia	3,669	79	1.00 (0.78-1.27)	66	1.13 (0.86-1.48)	30	0.80 (0.54-1.18)	11	0.87 (0.46-1.65)
Polydactyly	2,366	40	0.95 (0.69-1.31)	26	0.87 (0.58-1.29)	21	1.14 (0.73-1.78)	8	1.21 (0.59-2.48)
Syndactyly	1,189	26	1.19 (0.80-1.77)	16	1.00 (0.60-1.65)	14	1.50 (0.87-2.57)	<5	
Craniosynostosis	601	6	0.51 (0.23-1.14)	<5		<5		<5	
Congenital skin disorders	500	8	0.81 (0.40-1.64)	5	0.68 (0.28-1.65)	<5		<5	
Pierre Robin sequence	128	6	2.10 (0.92-4.79)	6	**2.65 (1.15-6.09)**	<5		<5	

Anomaly subgroups with less than 5 exposures are not presented.
Boldface denotes associations significant at the 5% level.
ASD, Atrial septal defect; *CHD*, Congenital heart defect; *VSD*, ventricular septal defect.
*Adjusted for registry and maternal age.
†Significant at the 1% level.

(same as salbutamol; OR, 1.65; 95% CI, 1.06-2.58) and borderline significant odds of exposure to β_2-agonists combined (OR, 1.53; 0.99-2.37).[14] A cohort study of cleft palate from Sweden found increased odds of exposure to any asthma medication with the majority of women being exposed to inhaled β_2-agonists (OR, 1.45; 95% CI, 1.06-1.98).[28] In both studies it is not clear whether it is the asthma medication or the underlying asthma that is responsible for the cleft palate. In our study the lack of association with inhaled corticosteroids suggests that if it is the underlying asthma, it is not the type of underlying asthma treated by corticosteroids.

Our case-malformed control study showing increased odds of exposure to inhaled β_2-agonists and salbutamol for gastroschisis specifically supports a previous case-control study[15] that found increased odds (adjusted OR, 2.06; 95% CI, 1.19-3.59) of exposure to bronchodilators in general.

We were not able to confirm the remaining 8 literature signals (spina bifida, cleft lip with or without cleft palate, severe congenital heart defect, tetralogy of Fallot, esophageal atresia, omphalocele, hypospadias, and anal atresia/stenosis), although we found an OR of greater than 1 for most β_2-agonist exposures, which was not statistically significant. For inhaled steroids, the ORs in general were closer to 1.

The exploratory analysis identified only 1 association at the 1% significance level, namely renal dysplasia and exposure to the combination product of inhaled long-acting β_2-agonists and corticosteroids. Furthermore, there were 3 positive associations at a 5% significance level. We think the observation of a 3-fold increase for renal dysplasia in odds of exposure needs attention. The OR for Pierre Robin sequence of exposure to inhaled β_2-agonists was higher than for cleft palate without Pierre Robin sequence (OR, 2.67 [95% CI, 1.16-6.13] and 1.63 [95% CI, 1.05-2.52], respectively). The cause for Pierre Robin sequence is thought to be heterogeneous,[29] and this finding suggests that some Pierre Robin sequences share etiologic factors with cleft palate.

For the other findings, they might be explained by the large number of comparisons that have been performed, and therefore these associations could be chance findings, although this could be confirmed in independent data sets.

Although we have found increased odds of cleft palate and gastroschisis after exposure to β_2-agonists, the excess risk for the individual woman is low. The nonchromosomal prevalence of these 2 congenital anomalies in the EUROCAT registries is 8 to 9 per 10,000 births.[21] Even with a 5-fold increased risk, the risk for the individual pregnancy is still less than 1 in 100. This is

very important because the risks of uncontrolled asthma might be much greater than these specific risks.

It is reassuring that we did not find any increased risk for specific congenital anomalies of exposure to inhaled steroids in the signal testing analysis. Both maternal asthma and asthma exacerbation during the first trimester of pregnancy have been found to increase the risk of congenital anomalies.[12,17] Further asthma exacerbations during pregnancy have been associated with other unfavorable pregnancy outcomes for both the mother and infant.[18] Use of prophylactic inhaled steroids seems to be the best solution for treatment of asthma in pregnancy to prevent asthma exacerbations and to reduce the need for β_2-agonists.

The strength of the present study is the ability to combine population-based data from a number of congenital anomaly registers throughout Europe, all of which use the same methods for case registration and classification and all of which have information about maternal medication use in pregnancy. This ensures an adequate number of exposed cases to evaluate specific congenital anomalies, although power might still be too low to study specific medications in relation to some specific anomalies. The congenital anomaly registers all use multiple data sources to collect information about congenital anomaly cases for all types of birth outcomes, including TOPFAs, in geographically defined residential populations. A common guide for classification of congenital anomalies is used by all registers, ensuring similar definitions for all cases. The main limitation is the information about medication exposure, which might be less specific according to both the dosage and timing of exposure. For one registry, medication exposure was available for births but not for TOPFAs. For another registry, the exposure data were based on information from a prescription database. Therefore we do not know whether these mothers took the medication they picked up at the pharmacy. Most importantly, although the fetuses were exposed to asthma medication, we cannot know whether it was the medication that caused the congenital anomalies or whether it was the maternal asthma because different types of antiasthma medications are used for different severities of asthma. There was limited information on potential confounding factors, but because registries collect standardized data on congenital anomalies for both exposed and unexposed cases and information on medication was obtained prospectively, the potential for bias is reduced.

Although this study included more than 70,000 registrations of congenital anomalies in the 13 registries during the years 1995-2010, the power to detect any individual associations was low. Therefore it is important to continue European collaboration to be able to improve the detection of such associations in future.

Clinical implications: Use of prophylactic inhaled steroids seems to be the best solution for treatment of asthma in pregnancy to prevent asthma exacerbations and to reduce the need for β_2-agonists.

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TABLE E1. Combination treatments and all asthma medications

		Combination treatments			Any asthma medications		
Control group		**Nonchromosomal**	**Chromosomal**		**Nonchromosomal**		**Chromosomal**
Controls		43,824	9,578		43,824		9,578
Exposed controls		131	26		809		136
	Total cases	**Exposed cases**	**Adjusted OR (95% CI)**	**Adjusted OR (95% CI)**	**Exposed cases**	**Adjusted OR (95% CI)**	**Adjusted OR (95% CI)**
Any signal anomaly	16,803	60	1.09 (0.79-1.49)	1.09 (0.65-1.83)	356	**1.15 (1.01-1.30)**	**1.42 (1.15-1.76)**
Spina bifida	1,194	3	0.84 (0.26-2.69)	1.18 (0.38-3.69)	20	0.88 (0.56-1.38)	1.06 (0.66-1.72)
Cleft palate	1,392	3	0.57 (0.18-1.83)	0.56 (0.16-1.97)	39	**1.53 (1.10-2.12)**	**1.68 (1.15-2.45)**
Cleft lip with/without cleft palate	2,402	8	0.89 (0.43-1.86)	0.76 (0.32-1.83)	51	1.19 (0.89-1.59)	1.34 (0.95-1.90)
Severe CHD	4,738	19	1.33 (0.81-2.18)	1.18 (0.61-2.27)	87	1.00 (0.80-1.25)	1.21 (0.91-1.60)
Tetralogy of Fallot	730	2	0.98 (0.23-4.06)	1.04 (0.23-4.72)	10	0.77 (0.41-1.44)	0.83 (0.43-1.60)
Esophageal atresia	648	3	1.69 (0.52-5.48)	**3.63 (1.26-10.42)**	12	1.09 (0.61-1.95)	1.67 (0.96-2.90)
Gastroschisis	615	4	1.77 (0.61-5.13)	1.99 (0.57-6.98)	22	**1.61 (1.04-2.50)**	**1.76 (1.03-2.98)**
Omphalocele	467	0			11	1.36 (0.74-2.49)	1.18 (0.65-2.15)
Hypospadias	5097	20	1.26 (0.75-2.10)	2.75 (0.99-7.63)	107	1.06 (0.86-1.32)	1.60 (1.11-2.31)
Anal atresia/stenosis	772	3	1.00 (0.31-3.24)	1.36 (0.43-4.28)	23	**1.64 (1.08-2.51)**	**2.04 (1.30-3.20)**

Analyses were adjusted for center and maternal age, and combination treatment was adjusted for use of short-acting β_2-agonists. All asthma medications groups encompasses medications with ATC code R03, and combination treatments are medications with ATC code R03AK or a long-acting β_2-agonist in combination with inhaled steroids.
Boldface denotes associations significant at the 5% level.
CHD, Congenital heart defect.

TABLE E2. Salbutamol and β_2-agonists in general

	Salbutamol, ATC code R03AC02				β_2-Agonists in general, ATC codes R03AC & R03CC			
Control group	**Nonchromosomal**		**Chromosomal**		**Nonchromosomal**		**Chromosomal**	
Controls	43,824		9,578		43,824		9,578	
Exposed controls	504		85		596		97	
	Total cases	**Exposed cases**	**Adjusted OR (95% CI)**	**Adjusted OR (95% CI)**	**Exposed cases**	**Adjusted OR (95% CI)**	**Adjusted OR (95% CI)**	
Any signal anomaly	16,803	229	1.26 (1.06-1.50)	1.46 (1.09-1.96)	265	1.23 (1.04-1.45)	1.47 (1.11-1.94)	
Spina bifida	1,194	15	1.15 (0.65-2.04)	1.28 (0.67-2.43)	17	1.10 (0.64-1.90)	1.30 (0.70-2.43)	
Cleft palate	1,392	24	1.63 (1.02-2.60)	1.62 (0.95-2.77)	28	1.62 (1.04-2.50)	1.70 (1.03-2.79)	
Cleft lip with/without cleft palate	2,402	33	1.36 (0.91-2.03)	1.45 (0.89-2.38)	39	1.31 (0.90-1.91)	1.39 (0.87-2.21)	
Severe CHD	4,738	53	1.17 (0.85-1.59)	1.17 (0.79-1.73)	64	1.20 (0.90-1.60)	1.23 (0.85-1.78)	
Tetralogy of Fallot	730	8	1.37 (0.64-2.90)	1.38 (0.61-3.13)	9	1.27 (0.62-2.60)	1.36 (0.62-2.95)	
Esophageal atresia	648	6	1.41 (0.60-3.29)	1.49 (0.60-3.69)	8	1.51 (0.72-3.17)	1.69 (0.76-3.75)	
Gastroschisis	615	18	2.01 (1.18-3.44)	2.81 (1.40-5.64)	19	1.89 (1.11-3.19)	2.92 (1.48-5.77)	
Omphalocele	467	9	1.92 (0.89-4.15)	1.62 (0.75-3.52)	10	1.75 (0.83-3.67)	1.57 (0.75-3.32)	
Hypospadias	5,097	68	1.11 (0.82-1.49)	1.33 (0.81-2.19)	76	1.02 (0.76-1.35)	1.27 (0.79-2.04)	
Anal atresia/stenosis	772	16	1.58 (0.87-2.88)	1.54 (0.78-3.04)	18	1.49 (0.84-2.66)	1.53 (0.79-2.93)	

Analyses were adjusted for center, maternal age, and use of inhaled corticosteroids.
CHD, Congenital heart defect.

TABLE E3. Crude ORs

	Inhaled β_2-agonists, ATC code R03AC				Inhaled corticosteroids, ATC code R03BA			
Control group	**Nonchromosomal**		**Chromosomal**		**Nonchromosomal**		**Chromosomal**	
Controls	43,824		9,578		43,824		9,578	
Exposed controls	592		97		349		51	
	Total cases	**Exposed cases**	**Crude OR (95% CI)**	**Crude OR (95% CI)**	**Exposed cases**	**Crude OR (95% CI)**	**Crude OR (95% CI)**	
Any signal anomaly	16,803	264	1.17 (1.01-1.35)	1.56 (1.23-1.97)	133	0.99 (0.81-1.21)	1.49 (1.08-2.06)	
Spina bifida	1,194	17	1.05 (0.65-1.71)	1.31 (0.78-2.21)	7	0.73 (0.35-1.56)	1.03 (0.46-2.27)	
Cleft palate	1,392	28	1.50 (1.02-2.20)	1.81 (1.18-2.76)	13	1.17 (0.67-2.05)	1.59 (0.86-2.92)	
Cleft lip with/without cleft palate	2,402	39	1.21 (0.87-1.67)	1.46 (1.00-2.12)	22	1.15 (0.75-1.78)	1.56 (0.94-2.57)	
Severe CHD	4,738	64	1.00 (0.77-1.30)	1.32 (0.97-1.81)	27	0.71 (0.48-1.06)	1.27 (0.81-1.98)	
Tetralogy of Fallot	730	9	0.91 (0.47-1.77)	1.06 (0.53-2.10)	3	0.51 (0.16-1.61)	0.67 (0.21-2.15)	
Esophageal atresia	648	7	0.80 (0.38-1.69)	0.95 (0.44-2.06)	2	0.39 (0.10-1.55)	0.52 (0.13-2.12)	
Gastroschisis	615	19	2.33 (1.46-3.70)	3.03 (1.84-5.00)	5	1.02 (0.42-2.48)	1.49 (0.59-3.75)	
Omphalocele	467	9	1.44 (0.74-2.79)	1.37 (0.71-2.64)	5	1.35 (0.55-3.27)	1.29 (0.51-3.23)	
Hypospadias	5,097	76	1.08 (0.84-1.39)	1.59 (1.08-2.34)	43	1.04 (0.74-1.45)	1.80 (1.06-3.06)	
Anal atresia/stenosis	772	18	1.74 (1.08-2.80)	2.28 (1.39-3.75)	12	1.97 (1.10-3.51)	3.29 (1.81-5.98)	

CHD, Congenital heart defect.

TABLE E4. Effect of medications when not adjusted for other medication use

	Inhaled β_2-agonists, ATC code R03AC				Inhaled corticosteroids, ATC code R03BA			
Control group	**Nonchromosomal**		**Chromosomal**		**Nonchromosomal**		**Chromosomal**	
Controls	43,824		9,578		43,824		9,578	
Exposed controls	592		97		349		51	
	Total cases	**Exposed cases**	**Adjusted OR (95% CI)**	**Adjusted OR (95% CI)**	**Exposed cases**	**Adjusted OR (95% CI)**	**Adjusted OR (95% CI)**
Any signal anomaly	16,803	264	**1.17 (1.01-1.35)**	**1.46 (1.13-1.88)**	133	0.97 (0.80-1.19)	1.27 (0.89-1.80)
Spina bifida	1,194	17	0.98 (0.60-1.59)	1.13 (0.66-1.94)	7	0.73 (0.35-1.56)	0.81 (0.36-1.83)
Cleft palate	1,392	28	1.53 (1.04-2.25)	1.65 (1.06-2.57)	13	1.14 (0.65-1.99)	1.28 (0.67-2.43)
Cleft lip with/without cleft palate	2,402	39	1.31 (0.94-1.83)	1.44 (0.97-2.15)	22	1.16 (0.75-1.79)	1.38 (0.81-2.35)
Severe CHD	4,738	64	1.03 (0.80-1.34)	1.22 (0.88-1.70)	27	0.69 (0.46-1.02)	1.10 (0.68-1.77)
Tetralogy of Fallot	730	9	1.01 (0.52-1.96)	1.07 (0.53-2.16)	3	0.50 (0.16-1.56)	0.56 (0.17-1.84)
Esophageal atresia	648	7	0.98 (0.46-2.08)	1.10 (0.50-2.42)	2	0.38 (0.09-1.54)	0.49 (0.12-2.05)
Gastroschisis	615	19	**1.64 (1.02-2.63)**	**2.02 (1.13-3.61)**	5	0.98 (0.40-2.40)	0.86 (0.31-2.36)
Omphalocele	467	9	1.56 (0.80-3.05)	1.35 (0.70-2.62)	5	1.42 (0.58-3.45)	1.21 (0.48-3.08)
Hypospadias	5,097	76	1.03 (0.80-1.32)	1.38 (0.91-2.10)	43	1.01 (0.72-1.41)	1.51 (0.84-2.70)
Anal atresia/stenosis	772	18	**1.78 (1.11-2.87)**	**2.11 (1.26-3.54)**	12	**1.95 (1.09-3.48)**	**2.77 (1.48-5.17)**

Analyses were adjusted for center and maternal age.
Boldface denotes associations significant at the 5% level.
CHD, Congenital heart defect.

TABLE E5. Adjustment for use of systemic steroids

	Inhaled β_2-agonists, ATC code R03AC				Inhaled corticosteroids, ATC code R03BA			
Control group	**Nonchromosomal**		**Chromosomal**		**Nonchromosomal**		**Chromosomal**	
Controls	43,824		9,578		43,824		9,578	
Exposed controls	592		97		349		51	
	Total cases	**Exposed cases**	**Adjusted OR (95% CI)**	**Adjusted OR (95% CI)**	**Exposed cases**	**Adjusted OR (95% CI)**	**Adjusted OR (95% CI)**
Any signal anomaly	1,6803	264	1.24 (1.05-1.46)	1.46 (1.10-1.93)	133	0.85 (0.68-1.07)	1.01 (0.68-1.49)
Spina bifida	1,194	17	1.11 (0.64-1.92)	1.30 (0.70-2.43)	7	0.69 (0.30-1.59)	0.68 (0.26-1.75)
Cleft palate	1,392	28	1.64 (1.06-2.53)	1.70 (1.03-2.80)	13	0.84 (0.45-1.58)	0.93 (0.45-1.92)
Cleft lip with/without cleft palate	2,402	39	1.33 (0.91-1.93)	1.39 (0.87-2.21)	22	0.98 (0.60-1.61)	1.12 (0.60-2.09)
Severe CHD	4,738	64	1.20 (0.90-1.61)	1.23 (0.85-1.78)	27	0.61 (0.40-0.94)	0.97 (0.57-1.64)
Tetralogy of Fallot	730	9	1.28 (0.63-2.60)	1.36 (0.62-2.94)	3	0.43 (0.13-1.45)	0.46 (0.13-1.67)
Esophageal atresia	648	7	1.28 (0.58-2.82)	1.43 (0.62-3.32)	2	0.32 (0.07-1.38)	0.35 (0.08-1.64)
Gastroschisis	615	19	1.91 (1.13-3.24)	2.91 (1.47-5.76)	5	0.59 (0.22-1.60)	0.34 (0.10-1.13)
Omphalocele	467	9	1.50 (0.69-3.28)	1.37 (0.63-2.99)	5	1.06 (0.37-3.01)	0.95 (0.31-2.85)
Hypospadias	5,097	76	1.03 (0.78-1.38)	1.27 (0.79-2.05)	43	1.00 (0.68-1.46)	1.29 (0.67-2.50)
Anal atresia/stenosis	772	18	1.51 (0.85-2.69)	1.53 (0.79-2.94)	12	1.50 (0.74-3.03)	2.06 (0.94-4.51)

Analyses were adjusted for center, maternal age, and use of systemic steroids. Analyses of β_2-agonists were adjusted for use of corticosteroids and *vice versa*.
CHD, Congenital heart defect.

TABLE E6. Adjustment for period

	Inhaled β_2-agonists, ATC code R03AC				Inhaled corticosteroids, ATC code R03BA			
Control group	**Nonchromosomal**		**Chromosomal**		**Nonchromosomal**		**Chromosomal**	
Controls	43,824		9,578		43,824		9,578	
Exposed controls	592		97		349		51	
	Total cases	**Exposed cases**	**Adjusted OR (95% CI)**	**Adjusted OR (95% CI)**	**Exposed cases**	**Adjusted OR (95% CI)**	**Adjusted OR (95% CI)**	
Any signal anomaly	16,803	264	1.24 (1.05-1.46)	1.47 (1.11-1.95)	133	0.85 (0.68-1.07)	0.99 (0.67-1.46)	
Spina bifida	1,194	17	0.90 (0.52-1.56)	1.39 (0.74-2.60)	7	1.45 (0.63-3.37)	0.67 (0.26-1.73)	
Cleft palate	1,392	28	1.62 (1.05-2.51)	1.99 (1.20-3.29)	13	0.84 (0.44-1.57)	0.90 (0.44-1.87)	
Cleft lip with/without palate	2,402	39	1.34 (0.92-1.94)	1.59 (0.99-2.55)	22	0.98 (0.60-1.61)	1.13 (0.60-2.13)	
severe CHD	4,738	64	1.21 (0.91-1.62)	1.40 (0.95-2.04)	27	0.61 (0.40-0.95)	0.73 (0.42-1.28)	
Tetralogy of Fallot	730	9	1.31 (0.64-2.67)	1.58 (0.72-3.46)	3	0.42 (0.13-1.44)	0.46 (0.13-1.72)	
Esophageal atresia	648	7	1.31 (0.59-2.90)	1.72 (0.73-4.03)	2	0.32 (0.07-1.40)	0.37 (0.08-1.76)	
Gastroschisis	615	19	1.90 (1.12-3.22)	3.04 (1.53-6.06)	5	0.60 (0.22-1.62)	0.33 (0.10-1.11)	
Omphalocele	467	9	1.53 (0.69-3.35)	1.76 (0.74-4.20)	5	1.10 (0.38-3.13)	1.26 (0.39-4.05)	
Hypospadias	5,097	76	1.04 (0.78-1.39)	1.39 (0.86-2.25)	43	0.94 (0.64-1.37)	1.21 (0.62-2.36)	
Anorectal atresia/stenosis	772	18	1.47 (0.83-2.63)	1.78 (0.92-3.45)	12	1.52 (0.75-3.07)	1.64 (0.72-3.73)	

Analyses were adjusted for center, maternal age, and period (5-year intervals). Analyses of β_2-agonists were adjusted for use of corticosteroids and *vice versa*.
CHD, Congenital heart defect.

TABLE E7. Isolated anomalies

Control group	Inhaled β_2-agonists, ATC code R03AC		Inhaled corticosteroids, ATC code R03BA	
	Nonchromosomal	Chromosomal	Nonchromosomal	Chromosomal
Controls	33,237	9,578	33,237	9,578
Exposed controls	452	97	292	51

	Total cases	Exposed cases	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Exposed cases	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Any signal anomaly	11,678	166	1.12 (0.91-1.37)	1.22 (0.89-1.67)	95	0.85 (0.65-1.11)	0.96 (0.63-1.46)
Spina bifida	771	8	0.73 (0.32-1.64)	0.75 (0.31-1.81)	5	0.96 (0.35-2.67)	0.98 (0.32-3.01)
Cleft palate	886	17	1.73 (0.99-3.01)	1.52 (0.82-2.81)	7	0.60 (0.26-1.40)	0.66 (0.26-1.68)
Cleft lip with/without palate	1,690	27	1.41 (0.89-2.23)	1.37 (0.80-2.34)	16	0.87 (0.48-1.57)	0.97 (0.48-1.96)
Severe CHD	3,436	38	0.95 (0.65-1.38)	0.97 (0.64-1.49)	22	0.72 (0.44-1.18)	1.14 (0.65-2.00)
Tetralogy of Fallot	515	5	1.09 (0.42-2.84)	1.00 (0.37-2.73)	2	0.42 (0.09-1.85)	0.48 (0.10-2.27)
Esophageal atresia	274	3	1.72 (0.51-5.84)	1.49 (0.42-5.25)	1	0.32 (0.04-2.62)	0.39 (0.05-3.31)
Gastroschisis	416	14	1.89 (1.01-3.54)	2.58 (1.18-5.64)	4	0.60 (0.19-1.88)	0.36 (0.10-1.34)
Omphalocele	207	2	0.54 (0.10-2.86)	0.51 (0.13-2.01)	3	2.65 (0.68-10.35)	1.78 (0.44-7.17)
Hypospadias	3,747	54	0.97 (0.69-1.38)	1.15 (0.69-1.93)	35	1.03 (0.67-1.58)	1.29 (0.65-2.57)
Anorectal atresia/stenosis	265	4	1.15 (0.35-3.73)	0.80 (0.23-2.76)	3	1.21 (0.31-4.68)	2.73 (0.78-9.58)

Analyses were adjusted for center, maternal age, and period (5-year intervals). Analyses of β_2-agonists were adjusted for use of corticosteroids and *vice versa*. Cases and nonchromosomal controls were restricted to isolated anomalies.
CHD, Congenital heart defect.