



# Effect of maternal asthma, exacerbations and asthma medication use on congenital malformations in offspring: a UK population-based study

L J Tata,<sup>1</sup> S A Lewis,<sup>1</sup> T M McKeever,<sup>1</sup> C J P Smith,<sup>1</sup> P Doyle,<sup>2</sup> L Smeeth,<sup>2</sup> J E Gibson,<sup>1</sup> R B Hubbard<sup>1</sup>

## See Editorial, p 944

► Additional tables are published online only at <http://thorax.bmj.com/content/vol63/issue11>

<sup>1</sup>Epidemiology & Public Health, University of Nottingham, UK;

<sup>2</sup>Epidemiology & Population Health, London School of Hygiene & Tropical Medicine, UK

Correspondence to:

Dr L J Tata, Division of Epidemiology & Public Health, Clinical Sciences Building, City Hospital, Hucknall Road, Nottingham NG5 1PB, UK; [laila.tata@nottingham.ac.uk](mailto:laila.tata@nottingham.ac.uk)

Received 28 February 2008

Accepted 6 July 2008

Published Online First

4 August 2008

## ABSTRACT

**Background:** Clinical advice to pregnant women with asthma is to maintain optimal therapeutic management; however, potential adverse effects of asthma treatments on fetal development remain uncertain. A study was undertaken to assess the association between maternal asthma and gestational exposure to asthma medications with risk of congenital malformation in offspring.

**Methods:** A matched case-control study was performed using The Health Improvement Network primary care database. Children with malformations were matched to control children on birth year, general practice and singleton or twin delivery.

**Results:** 5124 cases of liveborn children with major congenital malformations and 30 053 controls were included in the study. The risk of any malformation in children born to women with asthma was marginally higher than that in children born to women without asthma (adjusted OR 1.10, 95% CI 1.01 to 1.20). However, no association was present in children born to mothers receiving asthma treatment in the year before or during pregnancy (OR 1.06, 95% CI 0.94 to 1.20). In assessing teratogenicity of medications, no increased risk of malformation was found with gestational exposures to short- or long-acting  $\beta$  agonists, inhaled corticosteroids, oral corticosteroids, other bronchodilators or cromones. These findings were similar for each of 11 system-specific malformation groups, except for an increase in musculo-skeletal system malformation associated with cromone exposure.

**Conclusions:** Gestational exposure to commonly used asthma medications was found to be safe overall, although a moderate teratogenic risk of cromones cannot be excluded. There was some evidence of a small increased risk of congenital malformation in children born to women with asthma, but this was not explained by gestational exposure to asthma drugs.

Although clinical advice to pregnant women with asthma is to maintain optimal therapeutic management, the potential adverse effects of their condition and indicated treatments on fetal development remain uncertain. Current figures from the USA show that at least 8% of women have active asthma in pregnancy and 14% were diagnosed previously,<sup>1</sup> placing asthma medications in the second most commonly used drug class in pregnancy.<sup>2</sup>

Congenital malformations are the leading cause of infant mortality in the USA<sup>3</sup> and the second leading cause in the UK,<sup>4</sup> but currently published asthma management guidelines in these countries<sup>5 6</sup>

include only five epidemiological studies assessing teratogenic effects of asthma treatments against unexposed comparisons.<sup>7-11</sup> None of these studies reported increased risks of congenital malformation, but the available statistical power was very limited.<sup>12</sup> More recently, larger studies have been conducted in Hungary<sup>13</sup> and Sweden.<sup>14</sup> The first<sup>13</sup> found that mothers of children with malformations had a 20% greater risk of having asthma compared with mothers of children without malformations; however, asthma drug use was self-reported after a malformation outcome was known and the proportions of drug-exposed women were extremely small.<sup>15 16</sup> In Sweden<sup>14</sup> a small (9%) but statistically significant increase in congenital malformation was found in children of women reporting use of anti-asthmatic drugs in pregnancy compared with non-users, although no consistent pattern of malformations was identified and the authors concluded that further large studies were needed. There remain no large analyses of current UK prescribing of asthma medications in women with congenital malformations in offspring.

There is a clear need for further surveillance data<sup>17</sup> on the safety of asthma medications during pregnancy, particularly since pregnant women are likely to be excluded from randomised trials. We therefore undertook the first large UK population-based study assessing the risk of maternal asthma and exposure to current asthma treatments during pregnancy on overall and system-specific major congenital malformations in offspring.

## METHODS

### Dataset and study population

The Health Improvement Network (THIN) is a computerised primary care database of anonymised patient records based in the UK, with a high standard of validated recording of diagnoses, medical events and prescriptions.<sup>18</sup> Rates of consultation, drug prescription and pregnancy are similar to national data sources.<sup>19 20</sup> For this study, longitudinal THIN records were available for 255 general practices across England and Wales.

Using prospectively collected data for women of childbearing age (15–50 years), we linked birth-related codes in their record to live births of children registered in the same household at the time of delivery. Children were born between January 1988 and November 2004. We obtained 180 064 mother-child pairs with gestational data, within which we identified all major congenital malformations in the children and categorised

them using the European Surveillance of Congenital Malformations (EUROCAT) classification<sup>21</sup> which separates malformations into 11 system-specific groups. We defined cases as liveborn children with one or more major malformation and for each case we identified up to six liveborn control children matched by year of birth, general practice and singleton or twin delivery. To test the validity of congenital malformation diagnoses we compared the prevalence of congenital malformations in our overall study population with that of the UK-based EUROCAT registries. We also compared the distribution of maternal age in trisomy 21 cases and controls to confirm the expected higher maternal age distribution in cases.

### Statistical analyses

The unit of analysis was the child. Conditional logistic regression was used to assess the association of any major congenital malformation or any system-specific major congenital malformation with maternal asthma and maternal asthma drug treatment. Maternal asthma was defined on the basis of recorded diagnoses at any time before the delivery of the child or prescriptions for asthma medications issued at the general practice during pregnancy or in the year before pregnancy. Since some of the mothers had an asthma diagnosis but no asthma medication use and other mothers used asthma medications but had no diagnosis, we assessed the separate risk of congenital malformations in four groups: (1) children born to mothers with an all-inclusive definition of maternal asthma which was either diagnosed asthma or exposure to asthma maintenance medication; (2) children born to mothers with diagnosed asthma but no exposure to asthma maintenance medication; (3) children born to mothers with exposure to asthma maintenance medication but no asthma diagnosis; and (4) children born to mothers with both a diagnosis of asthma and exposure to asthma maintenance medication.

Asthma maintenance medications were classified as short-acting  $\beta$  agonists (fenoterol, salbutamol, terbutaline or bambuterol), inhaled corticosteroids (beclometasone, budesonide, fluticasone or mometasone), long-acting  $\beta$  agonists (formoterol or salmeterol), other bronchodilators (aminophylline, theophylline, ephedrine, orciprenaline, tiotropium or ipratropium) or other anti-inflammatory medications (sodium cromoglicate, nedocromil, montelukast or zafirlukast). In all children whose mothers had a record of asthma, we additionally assessed the association of congenital malformation with clinically reported maternal asthma exacerbations during pregnancy. An exacerbation was defined as a clinical code for an exacerbation, acute asthma attack or emergency hospital admission for asthma, or an oral corticosteroid prescription.

To test the teratogenicity of specific asthma drug groups we examined the risk of congenital malformation associated with gestational exposures to the asthma maintenance medications classified above as well as oral corticosteroids (betamethasone, cortisone acetate, deflazacort, dexamethasone, hydrocortisone, prednisolone or triamcinolone). Prescriptions issued by the general practice during the woman's pregnancy were used for gestational exposures. All prescriptions are issued electronically at the general practice by physicians or certified nurse practitioners, with the date of prescription and specific details of the drug name, formulation, dose and duration retained in the woman's electronic general practice record. For this study, gestational drug exposure was considered as having one or more prescriptions for any specific drugs within the drug classes listed above. We also conducted secondary analyses restricted to drug exposures in the first trimester of pregnancy only.

The models were adjusted for exact maternal age as a continuous variable and the effects of other potential confounding factors (maternal smoking, body mass index before pregnancy, household socioeconomic status measured by Townsend deprivation index<sup>22</sup> quintile, child sex, delivery before, at or after term) were assessed. Since some children in the study were born to the same woman (ie, some women contributed more than one pregnancy during the study period), we allowed for potential clustering by woman using robust standard errors.<sup>23</sup> Missing values for covariates were fitted as a separate category and all models were re-fitted using cases and controls with complete data.

### Statistical power and multiple testing

Our study population size gave us over 95% power to detect an odds ratio (OR) of  $\geq 1.2$  for any major malformation associated with maternal asthma and over 90% power to detect an OR of 2.0 for most system-specific major malformations. To assess common gestational drug exposures (eg, short-acting  $\beta$  agonists), we had 90% power to detect an OR of 1.2 and to assess less common exposures (eg, oral corticosteroids) we had 95% power to detect an OR of 2.0. A significance level of 0.05 was used for these power calculations.

For our drug safety analyses, a large number of multiple comparisons were carried out in the gestational drug exposure assessment of six different drug families with malformations overall and with 11 system-specific groups. Some ORs will therefore be statistically significant at the 5% level by chance alone, while only ORs with highly significant p values (eg,  $p < 0.01$ ) should be considered as those more likely not to be due to chance. We present 95% confidence intervals for ORs but, in light of these multiple comparisons, we also provided exact p values to allow comprehensive interpretation of findings.

## RESULTS

### Validation of study population

The prevalence of a major congenital malformation in our population was 289 per 10 000 live births which was similar to the national prevalence for EUROCAT registries in the UK (238 per 10 000 births including live births, stillbirths, fetal deaths and pregnancy terminations).<sup>24</sup> This equated to 5200 children with major congenital malformations in our population of 180 064 children, and we successfully matched 5124 of these cases to 30 053 control children without malformation. These data confirmed an association between trisomy 21 risk and increasing maternal age (OR 1.65, 95% confidence interval (CI) 1.35 to 2.00 for each 5-year increase in maternal age).

### Description of the case-control dataset

For all 5124 cases, maternal age at birth was similar to that for the 30 053 matched controls (table 1). Compared with mothers of controls, mothers of cases were more likely to be obese before the pregnancy (OR 1.16, 95% CI 1.03 to 1.31) or to be underweight before the pregnancy (OR 1.19, 95% CI 1.00 to 1.42). Cases and controls had a similar proportion of mothers who were current smokers before the pregnancy (OR 1.00, 95% CI 0.92 to 1.08) and had the same distribution across levels of household socioeconomic status. More cases than controls were delivered before term (OR 2.62, 95% CI 2.21 to 3.11), and cases were more likely to be male (OR 1.32, 95% CI 1.25 to 1.40).

**Table 1** Description of cases and controls

	Cases (n = 5124)	Controls (n = 30053)	Unadjusted OR (95% CI)
	n (%)*	n (%)*	
Median (IQR) maternal age at delivery (years)	29.6 (25.5–33.2)	29.4 (25.5–33.1)	1.01 (1.00 to 1.01)
Maternal body mass index (kg/m <sup>2</sup> )			
Underweight (<18.5)	163 (3.2)	827 (2.8)	1.19 (1.00 to 1.42)
Normal (18.5–24.9)	2031 (39.6)	12280 (40.9)	Reference
Overweight (25–29.9)	709 (13.8)	4131 (13.7)	1.04 (0.95 to 1.14)
Obese (≥30)	385 (7.5)	1997 (6.6)	1.16 (1.03 to 1.31)
Missing	1836 (35.8)	10818 (36.0)	1.01 (0.93 to 1.10)
Maternal smoking status			
Non-smoker	2590 (50.5)	15046 (50.1)	Reference
Ex-smoker	269 (5.2)	1473 (4.9)	1.06 (0.92 to 1.22)
Current smoker	1136 (22.2)	6637 (22.1)	1.00 (0.92 to 1.08)
Missing	1129 (22.0)	6897 (23.0)	0.92 (0.84 to 1.01)
Household Townsend score quintile			
1 (least deprivation)	826 (16.1)	4976 (16.6)	Reference
2	592 (11.6)	3499 (11.6)	1.02 (0.90 to 1.15)
3	586 (11.4)	3387 (11.3)	1.05 (0.93 to 1.19)
4	506 (9.9)	2833 (9.4)	1.08 (0.95 to 1.24)
5 (most deprivation)	400 (7.8)	2337 (7.8)	1.04 (0.90 to 1.21)
Missing	2214 (43.2)	13021 (43.3)	0.87 (0.67 to 1.12)
Term of pregnancy			
Preterm	366 (7.1)	858 (2.9)	2.62 (2.21 to 3.11)
Term	705 (13.8)	4503 (15.0)	Reference
Post-term	8 (<0.5)	39 (<0.5)	1.29 (0.54 to 3.05)
Missing	4045 (78.9)	24653 (82.1)	1.01 (0.88 to 1.16)
Sex of child			
Female	2172 (42.4)	14829 (49.4)	Reference
Male	2952 (57.6)	15224 (50.7)	1.32 (1.25 to 1.40)
Singleton or multiple delivery			
Singleton	4996 (97.5)	29655 (98.7)	Matching variable
Twin	128 (2.5)	398 (1.3)	
Year of birth			
1988–9	196 (3.8)	1104 (3.7)	Matching variable
1990–4	1567 (30.6)	9192 (30.6)	
1995–9	1768 (34.5)	10389 (34.6)	
2000–4	1593 (31.1)	9368 (31.2)	

\*Proportion of cases or controls. IQR, interquartile range.

### Associations of any malformation with maternal asthma

The proportion of mothers with either a diagnosis of asthma, exposure to asthma maintenance medication before the delivery of the child, or both (our all-inclusive definition of asthma) was 14% for cases with congenital malformation and 13% for matched control children (table 2). Cases were marginally more likely than controls to have mothers with asthma in each of the four defined groups, ranging from a 6–17% relative increase. However, it was only in the all-inclusive definition of maternal asthma with the largest number of exposed cases that a statistically significant association at the 5% level was found. The highest relative increase in congenital malformation was in children born to mothers with diagnosed asthma but no asthma medication use, whereas the smallest was in children born to mothers with diagnosed asthma who were using asthma medications. Cases were no more likely than controls to have a mother with clinically reported asthma exacerbations in pregnancy (OR 1.09, 95% CI 0.65 to 1.82;  $p = 0.754$ ).

In our assessment of gestational exposure to asthma medications, cases were as likely as controls to be exposed to each of the six asthma drug categories (table 2). Most ORs for drug exposure were close to unity with the exception of

exposure to other anti-inflammatory medications (OR 2.02, 95% CI 0.96 to 4.28;  $p = 0.065$ ). This OR was based on only a small number of gestational exposures and all nine exposed cases were to cromones while, in controls, 26 were exposed to cromones and 1 was exposed to montelukast. We repeated all analyses using only first trimester gestational drug exposures and the results were similar to the overall analyses: short-acting  $\beta$  agonists (OR 1.01, 95% CI 0.86 to 1.18,  $p = 0.941$ ), inhaled corticosteroids (OR 1.06, 95% CI 0.86 to 1.31,  $p = 0.603$ ), long-acting  $\beta$  agonists (OR 1.09, 95% CI 0.62 to 1.90,  $p = 0.770$ ), oral corticosteroids (OR 1.16, 95% CI 0.71 to 1.89,  $p = 0.550$ ), other bronchodilators (OR 1.05, 95% CI 0.44 to 2.51,  $p = 0.905$ ), other anti-inflammatory medications (OR 2.00, 95% CI 0.72 to 5.52,  $p = 0.183$ ).

In multivariate analyses of all defined maternal asthma groups and gestational drug exposures, none of the potential confounding factors (maternal smoking, body mass index before pregnancy, household socioeconomic status, child sex and term of delivery) changed our risk estimates by more than 10% (eg, fully adjusted OR 1.05, 95% CI 0.93 to 1.19 for maternal diagnosis and asthma medication before delivery), so all ORs presented are only adjusted for maternal age. The effect

**Table 2** Risk of any major congenital malformation in children born to mothers with asthma

	Cases (n = 5124)	Controls (n = 30053)	Adjusted OR‡ (95% CI)	p Value
	n (%)†	n (%)†		
<i>Maternal asthma status</i>				
No asthma diagnosis or medications before delivery	4420 (86.3)	26235 (87.3)	Reference	
Asthma diagnosis or medication§ before delivery	704 (13.7)	3818 (12.7)	1.10 (1.01 to 1.20)	0.032
Diagnosis with no medication before delivery	171 (3.3)	881 (2.9)	1.17 (0.99 to 1.39)	0.071
Asthma medication§ but no diagnosis before delivery	183 (3.6)	968 (3.2)	1.13 (0.96 to 1.33)	0.132
Diagnosis and asthma medication§ before delivery	350 (6.8)	1969 (6.6)	1.06 (0.94 to 1.20)	0.329
≥1 asthma exacerbation during pregnancy	18 (<0.5)	94 (<0.5)	1.09 (0.65 to 1.82)	0.754
<i>≥1 medication exposure during pregnancy*</i>				
Any asthma medication	410 (8.0)	2240 (7.5)	1.05 (0.94 to 1.18)	0.367
Short-acting β agonist	375 (7.3)	2085 (6.9)	1.06 (0.94 to 1.19)	0.336
Inhaled corticosteroid	220 (4.3)	1209 (4.0)	1.07 (0.92 to 1.24)	0.407
Long-acting β agonist	25 (<0.5)	131 (<0.5)	1.12 (0.72 to 1.75)	0.614
Oral corticosteroid	46 (0.9)	216 (0.7)	1.23 (0.89 to 1.69)	0.201
Other bronchodilator medication¶	13 (<0.5)	72 (<0.5)	1.05 (0.59 to 1.87)	0.872
Other anti-inflammatory medication**	9 (<0.5)	27 (<0.5)	2.02 (0.96 to 4.28)	0.065

\*Reference groups are mothers with no prescriptions for the selected drug group in pregnancy.

†Proportion of cases or controls whose mothers had a diagnosis or at least one selected drug prescription in pregnancy.

‡Odds ratios (95% confidence intervals) adjusted for maternal age at birth of case or control child; maternal smoking status, body mass index, socioeconomic status, sex of the child, gestation of pregnancy had no confounding effects.

§Any asthma medication except oral corticosteroids during pregnancy or in the year before the pregnancy.

¶Aminophylline, theophylline, ephedrine, orciprenaline, tiotropium or ipratropium.

\*\*Cromoglicic acid, nedocromil, montelukast or zafirlukast.

estimates were also similar when we repeated each analysis using only those with full data for covariates (eg, fully adjusted OR 1.07, 95% CI 0.88 to 1.29 for maternal diagnosis and asthma medication before delivery for 1730 cases and 10 138 controls with full covariate data).

### Associations of system-specific malformation with maternal asthma

When we carried out analyses of maternal asthma (all-inclusive definition and grouped by diagnoses/medication use) and clinically reported exacerbations in pregnancy for the 11 major system-specific malformation groups, we found similar results to those for any major congenital malformation (full data available in additional tables published online only). All ORs were <2.00 and had p values >0.01, with the exception of an association of musculoskeletal system malformations with the all-inclusive definition of maternal asthma (OR 1.25, 95% CI 1.06 to 1.47; p = 0.009) and with asthma medication but no diagnosis before delivery (OR 1.46, 95% CI 1.11 to 1.93; p = 0.007). The associations of system-specific malformations in children born to mothers with diagnosed asthma who were using asthma medications are presented in table 3.

For gestational exposure to asthma medications (table 3), there was no evidence of an increased risk of system-specific malformations (ORs <2.00 or p values >0.01), apart from a large relative increase in musculoskeletal system malformations in children born to mothers with gestational exposure to cromones (OR 9.38, 95% CI 2.31 to 38.10; p = 0.002) compared with no exposure; however, this was based on only five exposed cases (full data available in additional tables published in online supplement). The specific malformations in these five cases were congenital hip dislocation (n = 3), congenital shortening of leg (n = 1) and imperfect fusion of the skull (n = 1).

Malformations in the remaining four cases with gestational exposure to cromones also showed no consistent pattern; one child had major congenital malformation of the lacrimal passages, one had cleft palate with bilateral cleft lip, one had Down's syndrome with ventricular septal defect and one had hypospadias.

## DISCUSSION

### Principal findings

The results of this first UK general population-based study show that the risk of major congenital malformation in children born to mothers with asthma is similar to that in children born to mothers without asthma. Cases were only marginally more likely than controls to have mothers with asthma in each of our defined groups of maternal asthma, and there was only a statistically significant association at the 5% level when the number of maternal asthma-exposed cases was highest and hence statistical power greatest. Since the effect seen here was small (10% increase) and was not present for cases whose mothers were treated for asthma, this pattern of results overall does not support an increased risk of malformation in children born to women with asthma.

Gestational exposure to asthma therapies did not appear to increase the risk of any major congenital malformation or system-specific malformation, providing evidence of their general safety in pregnancy. The only exposure of possible concern was a marked increase in the risk of musculoskeletal malformations associated with cromone anti-inflammatory medications based on a small number of exposed cases.

### Strengths and limitations

We have conducted the largest comprehensive multivariate analysis in the UK population to assess the potential teratogenic effects of current asthma medications associated with overall

**Table 3** Risk of major system-specific congenital malformation in children born to mothers with actively treated diagnosed asthma and in children with gestational exposure to asthma medication

	Cases		Controls	
	n (%)†	n (%)†	Adjusted OR‡ (95% CI)	p Value
<i>Maternal asthma (diagnosis and medication before delivery)</i>				
Any congenital malformation§	5124 (6.8)	30053 (6.6)	1.06 (0.94 to 1.20)	0.329
Any system-specific malformation¶				
Nervous system	237 (7.2)	1377 (6.8)	1.08 (0.63 to 1.86)	0.783
Eye, ear, face, neck	293 (5.8)	1718 (5.8)	1.01 (0.58 to 1.76)	0.972
Circulatory system	1256 (7.6)	7356 (6.6)	1.18 (0.94 to 1.49)	0.163
Respiratory system	46 (10.9)	265 (7.2)	1.71 (0.50 to 5.78)	0.390
Cleft lip and/or palate	255 (7.1)	1513 (6.8)	1.05 (0.62 to 1.77)	0.852
Digestive system	166 (7.2)	974 (7.0)	1.03 (0.53 to 2.00)	0.932
Genital organs	913 (6.2)	5345 (6.3)	0.98 (0.73 to 1.31)	0.874
Urinary system	313 (6.7)	1850 (6.6)	1.03 (0.63 to 1.68)	0.921
Musculoskeletal system	1431 (7.3)	8372 (6.6)	1.14 (0.91 to 1.43)	0.241
"Other"	407 (7.1)	2400 (6.5)	1.15 (0.75 to 1.77)	0.518
Chromosomal abnormality	260 (2.3)	1519 (5.7)	0.43 (0.18 to 1.02)	0.054
<i>≥1 Asthma medication exposure during pregnancy*</i>				
Any congenital malformation§	5124 (8.0)	30053 (7.5)	1.05 (0.94 to 1.18)	0.367
Any system-specific malformation¶				
Nervous system	237 (6.8)	1377 (7.2)	0.93 (0.55 to 1.57)	0.781
Eye, ear, face, neck	293 (5.8)	1718 (7.1)	0.81 (0.48 to 1.38)	0.439
Circulatory system	1256 (9.0)	7356 (7.3)	1.27 (1.02 to 1.58)	0.032
Respiratory system	46 (13.0)	265 (7.9)	1.92 (0.65 to 5.65)	0.236
Cleft lip and/or palate	255 (6.3)	1513 (8.3)	0.73 (0.43 to 1.24)	0.246
Digestive system	166 (12.0)	974 (7.9)	1.65 (0.99 to 2.74)	0.053
Genital organs	913 (7.6)	5345 (7.6)	0.98 (0.74 to 1.28)	0.865
Urinary system	313 (8.0)	1850 (7.1)	1.13 (0.72 to 1.77)	0.594
Musculoskeletal system	1431 (8.7)	8372 (7.6)	1.16 (0.95 to 1.43)	0.143
"Other"	407 (7.4)	2400 (7.2)	1.04 (0.69 to 1.58)	0.842
Chromosomal abnormality	260 (3.5)	1519 (7.0)	0.45 (0.22 to 0.95)	0.035

\*Any short-acting  $\beta$  agonists, inhaled corticosteroids, long-acting  $\beta$  agonists, other bronchodilators or other anti-inflammatory medications (see tables published in online supplement for full analyses of individual gestational drug exposures).

†First section of table: Proportion of cases or controls whose mothers have an asthma diagnosis and medication before delivery. Second section of table: Proportion of cases or controls exposed to one or more asthma medications during pregnancy.

‡Odds ratios (95% confidence intervals) adjusted for maternal age at birth of case or control child; maternal smoking status, body mass index, socioeconomic status, sex of the child, gestation of pregnancy had no confounding effects.

§Children with more than one malformation are counted only once in "any congenital malformation" total.

¶Children with more than one malformation in the same system-specific group are counted only once in each system-specific malformation total.

and system-specific malformations. Our data were obtained from a national database of prospectively collected clinical records, thus excluding the possibility of recall bias in our exposures of maternal asthma and prescription medication use. Although THIN is a relatively new database, respiratory diagnoses and perinatal outcomes in the General Practice Research Database (GPRD), a similar database from which over half of THIN practices originate, have shown high validity and completeness.<sup>25, 26</sup> A recent study also demonstrated that non-GPRD practices in THIN have the same high standard of data validity as GPRD practices.<sup>18</sup>

In assessing the external validity of our study, our population-based prevalence of current asthma in women of child-bearing age is similar to both UK<sup>27</sup> and US<sup>1</sup> national figures. Since congenital malformations have not previously been investigated in THIN, we compared prevalence figures for any malformation and system-specific malformations in our study population with those from UK registries of EUROCAT over the same time period and found these to be similar.<sup>24</sup> We also demonstrated the expected increase in risk of having a child with trisomy 21 for women of older maternal age in our data.

Our study power enabled us to assess the effects of potential confounding factors in multivariate analyses for each drug exposure with overall and system-specific malformation. We recognise the presence of some missing data for maternal smoking (23%), body mass index (36%) and socioeconomic status (43%). At the time of data collection, THIN were only able to provide Townsend deprivation index—our measure of socioeconomic status—for 176 of the 255 general practices because the process of integrating this variable into the database for research purposes was in development. Although the proportion of missing data for each covariate was the same between cases and controls, we repeated analyses using only those with full data for covariates and obtained similar effect sizes to the overall analyses.

All studies using repeated statistical analyses to assess several drug exposures in one population are at risk of revealing spurious associations because high numbers of multiple comparison tests result in statistically significant p values by chance alone, and it is important to consider whether these associations are causal. Studies of drug safety typically use a 5% level for statistical significance ( $p < 0.05$ ) but, in consideration of

**Table 4** Publications reporting statistical analyses of the risk of congenital malformation associated with gestational exposure to asthma medication compared with no exposure

Reference	Gestational exposure	Children with congenital malformation (number born to women with asthma/without asthma)	Multivariate analysis	Increased risk†
Schatz <i>et al</i> <sup>7</sup>	Inhaled bronchodilators	<50/<50*	Yes	No
Stenius-Aarniala <i>et al</i> <sup>11</sup>	Theophylline	10/2	No	No
Schatz <i>et al</i> <sup>6</sup>	β agonists, theophylline, cromolyn, CS, antihistamines, decongestants	<50/<50*	No	No
Alexandre <i>et al</i> <sup>10</sup>	β agonists, CS	88/981	Yes	No
Schatz <i>et al</i> <sup>9</sup>	β agonist, ICS, OCS, theophylline, cromoglicates	42/0*	No	No
Tamasi <i>et al</i> <sup>13</sup>	SABA, ICS, LABA, OCS, xanthines, sodium cromoglicate	511/2232‡	No	Yes with fenoterol, no with other medications
Blais <i>et al</i> <sup>8</sup>	ICS	418/0	Yes	No
Bakhireva <i>et al</i> <sup>77</sup>	β agonists, leucotriene receptor antagonists	9/1	Yes	Yes
Kallen <i>et al</i> <sup>14</sup>	SABA, ICS, LABA, other bronchodilators¶, other anti-inflammatories**	1263/41223	Yes	Yes§
Current publication	SABA, ICS, LABA, OCS, other bronchodilators¶, other anti-inflammatories**	704/4420	Yes	No

\*Numbers estimated from published percentages (no numbers presented in paper).

†Statistically significant increase in malformation with gestational drug exposure (at 5% level).

‡Mostly major malformations but included some minor (clubfoot, pyloric stenosis, undescended testis).

§Although system-specific malformations had no generally consistent pattern and statistically significant associations found only for severe cardiac defects, orofacial clefts, anal atresia.

¶Other bronchodilators: aminophylline, theophylline, ephedrine, orciprenaline, tiotropium or ipratropium.

\*\*Other anti-inflammatories: cromoglicate, nedocromil, montelukast or zafirlukast.

CS, corticosteroid (unspecified formula); ICS, inhaled corticosteroid; LABA, long-acting β agonist; OCS, oral corticosteroid; SABA, short-acting β agonist.

the multiple comparisons in our study, ORs with highly significant p values ( $p < 0.01$ ) should be considered most likely to be real effects not due to chance. Only the association of musculoskeletal malformation with cromone medications had a p value smaller than this ( $p = 0.002$ ); however, cromone exposure was still extremely rare and thus statistical power was low, so this result should be interpreted with caution. Furthermore, there was no consistent pattern in specific types of malformation associated with the exposure. Exposure to newer leucotriene receptor antagonists was also rare in this population, which limited a current assessment of their teratogenic safety in pregnancy.

### Interpretation in context of previous studies

Most previous studies have found no relative increase in congenital malformation in children born to mothers with asthma compared with those born to mothers without asthma,<sup>28–35</sup> which is in keeping with our results of currently active asthma in women. Only three of these studies had adequate statistical power and adjusted for potential confounding factors.<sup>28–30</sup> A study of approximately 600 children with malformations reported a relative increase of congenital malformation in children born to mothers with asthma<sup>36</sup> and, although the largest study of over 20 000 malformations in Hungary<sup>13</sup> found a marginal increased risk overall (OR 1.2, 95% CI 1.0 to 1.3), the only system-specific malformation to reach statistical significance at the 5% level was club foot, which the authors attribute to more preterm births in women with asthma.

Regarding asthma treatment in pregnancy, in 2000 Jadad<sup>12</sup> emphasised the need for large observational studies as the only current way to assess the safety of conventional and new asthma medications. However, a 2005 report again raised the lack of sufficient data.<sup>17</sup> The British Thoracic Society (BTS) continues to grade asthma medications as C or D,<sup>6</sup> which provide the weakest evidence for safety in pregnancy. The US Food and Drug Administration (FDA) classifies asthma medications as B or C,<sup>37</sup> which stipulate that only animal studies have

provided evidence against teratogenicity and there are no adequate human data to estimate true risks. Table 4 shows studies that have reported statistical analyses of congenital malformations associated with specific gestational drug exposures in maternal asthma and have used unexposed comparison groups.<sup>7 8 10 11 13 14 38–40</sup> Five drug analyses were controlled for potential confounding factors,<sup>7 10 14 38 39</sup> although only two previous studies<sup>13 14</sup> had adequate statistical power to test the effects of varying asthma medications and only one<sup>14</sup> could adjust these for potential confounders. In the largest study, Kallen *et al* found an OR of 1.09 (95% CI 1.03 to 1.15) for any congenital malformation in offspring associated with maternally-reported exposure to any anti-asthmatic drug reported at initial maternal healthcare visits in pregnancy. They reported small statistically significant increases in severe cardiac defects, orofacial clefts and anal atresia, although they stated these may have been chance findings. They did not present a teratogenic assessment of specific exposure to gestational cromones or to oral corticosteroids, although cromoglicic acid was included in the overall group of anti-asthma drugs. In another case-control study, Tamasi *et al*<sup>13</sup> only found an increased risk of malformation associated with gestational fenoterol exposure (unadjusted OR 1.6, 95% CI 1.3 to 2.0) but not with cromones or other specific medications, although they did not assess gestational drug exposures with system-specific malformations. Relative methodological differences to our study include asthma drug exposures that were recorded via postal questionnaires to mothers after the birth of the child in the study by Tamasi *et al*, probable differential ascertainment of information between mothers of cases and controls, inclusion of minor malformations such as club foot and undescended testis, and an earlier study period (1980–96) resulting in less asthma medication use overall and rare use of newer asthma therapies such as long-acting β agonists.<sup>13 15 16</sup> In an early 1982 case series, Wilson<sup>41</sup> reported that, among 296 women exposed to sodium cromoglicate in pregnancy, only 4 (1.4%) of their offspring had congenital malformations which was lower than the 2–3%

expected in the general population. Schatz *et al*<sup>9</sup> found a congenital malformation prevalence of 6.2% in children born to 243 women exposed to cromolyn in pregnancy, which showed no statistically significant difference from the prevalence in unexposed women (4.9%), although no multivariate analyses were conducted. Currently, both sodium cromoglicate and nedocromil are assigned to US FDA category B with no evidence of congenital malformations in animal studies,<sup>37</sup> yet no adequately well-controlled studies have been conducted in pregnant women. The BTS assigns grade C to cromones and suggests that they be used as normal during pregnancy.<sup>6</sup>

## CONCLUSIONS

Our findings indicate no increase in the risk of major congenital malformation in children born to mothers with currently treated asthma. Management of asthma with medications during pregnancy in accordance with the current guidelines appears to be safe overall. However, older cromones may carry a moderate teratogenic risk and their use in pregnancy should be cautioned.

**Funding:** This study was funded by a grant from Asthma UK. Asthma UK did not have any role in the design and conduct of the study; collection, management, analysis and interpretation of the data; the preparation, review or approval of the manuscript; or in the decision to submit the paper for publication. No authors work for Asthma UK and all authors are thus independent researchers from the funders.

**Competing interests:** None.

**Ethics approval:** Ethical approval for this study was obtained from the Medical Research Ethics Committee in 2004. All patient records in THIN are anonymised to ensure that researchers cannot identify individuals.

LJT participated in the literature review, development of the study design, data management, data analysis, writing the article and revising article drafts for publication. SAL, PD and LS participated in the development of the study design, interpretation of the data and revising article drafts for publication. TMMCK participated in the interpretation of the data and revising article drafts for publication. CJPS participated in the initial data management and revising article drafts for publication. JEG participated in the data management, interpretation of the data and revising article drafts for publication. RBH (guarantor) had the initial idea for the study and its design and participated in the initial literature review, development of the study design, interpretation of the data and revising article drafts for publication. He had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors have seen and approved the final version.

## REFERENCES

1. **Kwon HL**, Belanger K, Bracken MB. Asthma prevalence among pregnant and childbearing-aged women in the United States: estimates from national health surveys. *Ann Epidemiol* 2003;**13**:317–24.
2. **Andrade SE**, Gurwitz JH, Davis RL, *et al*. Prescription drug use in pregnancy. *Am J Obstet Gynecol* 2004;**191**:398–407.
3. **Petrini J**, Damus K, Russell R, *et al*. Contribution of birth defects to infant mortality in the United States. *Teratology* 2002;**66**(Suppl 1):S3–6.
4. **Cooper N**. Analysis of infant mortality risk factors and by cause of death in England and Wales. In: *Geographic variations in health*. Decennial Supplement DS16. Chapter 7. Published with permission of the Controller of Her Majesty's Stationery Office (HMSO). London: Office for National Statistics, 2002.
5. **National Institutes of Health (NIH)**. *NAEPP Working Group Report on managing asthma during pregnancy: recommendations for pharmacologic treatment*. Updated 2004. Bethesda, MD: Department of Health and Human Services; National Institutes of Health; National Heart, Lung and Blood Institute, March 2005.
6. **British Thoracic Society/Scottish Intercollegiate Guidelines Network**. British guideline on the management of asthma: a national clinical guideline. Revised edition. 2008. <http://www.brit-thoracic.org.uk/ClinicalInformation/Asthma/AsthmaGuidelines/tabid/83/Default.aspx> (accessed 2 September 2008).
7. **Schatz M**, Zeiger RS, Harden KM, *et al*. The safety of inhaled beta-agonist bronchodilators during pregnancy. *J Allergy Clin Immunol* 1988;**82**:686–95.
8. **Schatz M**, Zeiger RS, Harden K, *et al*. The safety of asthma and allergy medications during pregnancy. *J Allergy Clin Immunol* 1997;**100**:301–6.
9. **Kallen B**, Rydhstroem H, Aberg A. Congenital malformations after the use of inhaled budesonide in early pregnancy. *Obstet Gynecol* 1999;**93**:392–5.
10. **Alexander S**, Dodds L, Armson BA. Perinatal outcomes in women with asthma during pregnancy. *Obstet Gynecol* 1998;**92**:435–40.
11. **Stenius-Aarniala B**, Riikonen S, Teramo K. Slow-release theophylline in pregnant asthmatics. *Chest* 1995;**107**:642–7.
12. **Jadad AR**, Sigouin C, Mohide PT, *et al*. Risk of congenital malformations associated with treatment of asthma during early pregnancy. *Lancet* 2000;**355**:119.
13. **Tamasi L**, Somoskovi A, Muller V, *et al*. A population-based case-control study on the effect of bronchial asthma during pregnancy for congenital abnormalities of the offspring. *J Asthma* 2006;**43**:81–6.
14. **Kallen B**, Otterblad Olausson P. Use of anti-asthmatic drugs during pregnancy. 3. Congenital malformations in the infants. *Eur J Clin Pharmacol* 2007;**63**:383–8.
15. **Czeizel AE**, Petik D, Vargha P. Validation studies of drug exposures in pregnant women. *Pharmacoepidemiol Drug Saf* 2003;**12**:409–16.
16. **Czeizel AE**. The role of pharmacoepidemiology in pharmacovigilance: rational drug use in pregnancy. *Pharmacoepidemiol Drug Saf* 1999;**8**(Suppl 1):S55–61.
17. **Demoly P**, Daures JP. Managing asthma during pregnancy. *Lancet* 2005;**365**:1212–3.
18. **Lewis JD**, Schinnar R, Bilker WB, *et al*. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. *Pharmacoepidemiol Drug Saf* 2007;**16**:393–401.
19. **Bourke A**, Dattani H, Robinson M. Feasibility study and methodology to create a quality-evaluated database of primary care data. *Inform Prim Care* 2004;**12**:171–7.
20. **Tata L**, Hubbard R, McKeever T, *et al*. Fertility rates in women with asthma, eczema, and hay fever: a general population-based cohort study. *Am J Epidemiol* 2007;**165**:1023–30.
21. **EUROCAT**. European Surveillance of Congenital Anomalies. Malformation coding guides. <http://www.eurocat.ulster.ac.uk/pubdata/Publications.html>.
22. **Morris R**, Carstairs V. Which deprivation? A comparison of selected deprivation indexes. *J Public Health Med* 1991;**13**:318–26.
23. **Williams RL**. A note on robust variance estimation for cluster-correlated data. *Biometrics* 2000;**56**:645–6.
24. **EUROCAT**. European Surveillance of Congenital Anomalies. Prevalence data 1988–2004. <http://www.bio-medical.co.uk/eurocative/search.cgi> (accessed October 2006).
25. **Hansell A**, Hollowell J, Nichols T, *et al*. Use of the General Practice Research Database (GPRD) for respiratory epidemiology: a comparison with the 4th Morbidity Survey in General Practice (MSGP4). *Thorax* 1999;**54**:413–9.
26. **Howard LM**, Goss C, Leese M, *et al*. Medical outcome of pregnancy in women with psychotic disorders and their infants in the first year after birth. *Br J Psychiatry* 2003;**182**:63–7.
27. **Hoare J**, Bruce M, Majeed A. Prevalence of treated asthma and its management in general practice in England and Wales, 1994–1998. *Health Statistics Quarterly* Volume 17, Spring 2003.
28. **Kallen B**, Rydhstroem H, Aberg A. Asthma during pregnancy: a population based study. *Eur J Epidemiol* 2000;**16**:167–71.
29. **Enriquez R**, Griffin MR, Carroll KN, *et al*. Effect of maternal asthma and asthma control on pregnancy and perinatal outcomes. *J Allergy Clin Immunol* 2007;**120**:625–30.
30. **Liu S**, Wen SW, Demissie K, *et al*. Maternal asthma and pregnancy outcomes: a retrospective cohort study. *Am J Obstet Gynecol* 2001;**184**:90–6.
31. **Sobande AA**, Archibong EI, Akinola SE. Pregnancy outcome in asthmatic patients from high altitudes. *Int J Gynaecol Obstet* 2002;**77**:117–21.
32. **Stenius-Aarniala B**, Piirila P, Teramo K. Asthma and pregnancy: a prospective study of 198 pregnancies. *Thorax* 1988;**43**:12–8.
33. **Stenius-Aarniala BS**, Hedman J, Teramo KA. Acute asthma during pregnancy. *Thorax* 1996;**51**:411–4.
34. **Schatz M**, Zeiger RS, Hoffman CP, *et al*. Perinatal outcomes in the pregnancies of asthmatic women: a prospective controlled analysis. *Am J Respir Crit Care Med* 1995;**151**:1170–4.
35. **Dombrowski MP**, Schatz M, Wise R, *et al*. Asthma during pregnancy. *Obstet Gynecol* 2004;**103**:5–12.
36. **Demissie K**, Breckenridge MB, Rhoads GG. Infant and maternal outcomes in the pregnancies of asthmatic women. *Am J Respir Crit Care Med* 1998;**158**:1091–5.
37. **Liccardi G**, Cazzola M, Canonica GW, *et al*. General strategy for the management of bronchial asthma in pregnancy. *Respir Med* 2003;**97**:778–89.
38. **Bakhireva LN**, Jones KL, Schatz M, *et al*. Safety of leukotriene receptor antagonists in pregnancy. *J Allergy Clin Immunol* 2007;**119**:618–25.
39. **Blais L**, Beaudesne MF, Rey E, *et al*. Use of inhaled corticosteroids during the first trimester of pregnancy and the risk of congenital malformations among women with asthma. *Thorax* 2007;**62**:320–8.
40. **Schatz M**, Dombrowski MP, Wise R, *et al*. The relationship of asthma medication use to perinatal outcomes. *J Allergy Clin Immunol* 2004;**113**:1040–5.
41. **Wilson J**. Utilisation du chromoglycate de sodium au cours de la grossesse. [Disodium cromoglicate use during pregnancy]. *Acta Ther* 1982;**8**:45–51.

## **Congenital Malformations in Children Born to Women with Asthma**

### **Additional Data Tables for 11 System-specific Malformation Groups**

Table 1	Risk of nervous system malformation in children born to women with asthma.....	2
Table 2	Risk of eye, ear, face or neck malformation in children born to women with asthma.....	3
Table 3	Risk of circulatory system malformation in children born to women with asthma.....	4
Table 4	Risk of respiratory system malformation in children born to women with asthma.....	5
Table 5	Risk of cleft lip and palate in children born to women with asthma.....	6
Table 6	Risk of digestive system malformation in children born to women with asthma.....	7
Table 7	Risk of genital organ malformation in children born to women with asthma.....	8
Table 8	Risk of urinary system malformation in children born to women with asthma.....	9
Table 9	Risk of musculoskeletal system malformation in children born to women with asthma.....	10
Table 10	Risk of other non-categorised malformation in children born to women with asthma.....	11
Table 11	Risk of chromosomal abnormalities not elsewhere classified in children born to women with asthma.....	12



**Table 1 Risk of nervous system malformation in children born to women with asthma**

	cases (n=237)		controls (n=1,377)		Adjusted Odds Ratio <sup>β</sup> (95% CI)	p-value
	n	(%) <sup>α</sup>	n	(%) <sup>α</sup>		
<b>Maternal asthma:</b>						
no asthma diagnosis or medications before delivery	204	(86.1)	1,205	(87.5)	reference	
asthma diagnosis or medication <sup>γ</sup> before delivery	33	(13.9)	172	(12.5)	1.14(0.78-1.69)	0.495
diagnosis with no medication before delivery	10	(4.2)	38	(2.8)	1.59(0.78-3.25)	0.205
asthma medication <sup>γ</sup> but no diagnosis before delivery	6	(2.5)	41	(3.0)	0.88(0.38-2.03)	0.765
diagnosis and asthma medication <sup>γ</sup> before delivery	17	(7.2)	93	(6.8)	1.08(0.63-1.86)	0.783
≥1 asthma exacerbation during pregnancy	0	(<0.5)	2	(<0.5)	n/a	0.627
<b>≥1 medication exposure during pregnancy*:</b>						
Any asthma medication	16	(6.8)	99	(7.2)	0.93(0.55-1.57)	0.781
Short acting β-agonist	16	(6.8)	94	(6.8)	0.98(0.58-1.65)	0.942
Inhaled corticosteroid	8	(3.4)	46	(3.3)	1.04(0.47-2.31)	0.915
Long acting β-agonist	2	(0.8)	5	(<0.5)	2.60(0.39-17.17)	0.322
Oral corticosteroid	3	(1.3)	6	(<0.5)	2.93(0.74-11.66)	0.126
Other bronchodilator medication**	0	(<0.5)	3	(<0.5)	n/a	
Other anti-inflammatory medication***	0	(<0.5)	2	(<0.5)	n/a	

<sup>α</sup> Proportion of cases or controls whose mothers have diagnosis or at least one selected drug prescription in pregnancy

<sup>β</sup> Odds Ratios (95% Confidence Intervals) adjusted for maternal age at birth of case or control child; Maternal smoking status, body mass index, socioeconomic status, sex of the child, gestation of pregnancy had no confounding effects.

<sup>γ</sup> Any asthma medication except oral corticosteroids

\*Reference groups are mothers with no prescriptions for the selected drug group in pregnancy

\*\*Aminophylline, theophylline, ephedrine, orciprenaline, tiotropium, or ipratropium

\*\*\*Cromoglicic acid, nedocromil, montelukast or zafirlukast

**Table 2 Risk of eye, ear, face or neck malformation in children born to women with asthma**

	cases (n=293)		controls (n=1,718)		Adjusted Odds Ratio <sup>β</sup>	p-value
	n (%) <sup>α</sup>	n (%) <sup>α</sup>	n (%) <sup>α</sup>	n (%) <sup>α</sup>	(95% CI)	
<b>Maternal asthma:</b>						
no asthma diagnosis or medications before delivery	262 (89.4)	1,529 (89.0)			reference	
asthma diagnosis or medication <sup>γ</sup> before delivery	31 (10.6)	189 (11.0)			0.96(0.64-1.44)	0.844
diagnosis with no medication before delivery	7 (2.4)	31 (1.8)			1.30(0.55-3.04)	0.552
asthma medication <sup>γ</sup> but no diagnosis before delivery	7 (2.4)	58 (3.4)			0.70(0.32-1.50)	0.356
diagnosis and asthma medication <sup>γ</sup> before delivery	17 (5.8)	100 (5.8)			1.01(0.58-1.76)	0.972
≥1 asthma exacerbation during pregnancy	1 (<0.5)	7 (<0.5)			0.85(0.10-7.02)	0.880
<b>≥1 medication exposure during pregnancy*:</b>						
Any asthma medication	17 (5.8)	122 (7.1)			0.81(0.48-1.38)	0.439
Short acting β-agonist	15 (5.1)	109 (6.3)			0.80(0.46-1.40)	0.431
Inhaled corticosteroid	9 (3.1)	65 (3.8)			0.82(0.41-1.62)	0.565
Long acting β-agonist	1 (<0.5)	8 (<0.5)			0.75(0.09-6.04)	0.786
Oral corticosteroid	4 (1.4)	12 (0.7)			1.99(0.64-6.22)	0.238
Other bronchodilator medication**	1 (<0.5)	5 (<0.5)			1.19(0.14-10.13)	0.872
Other anti-inflammatory medication***	1 (<0.5)	5 (<0.5)			1.20(0.14-10.30)	0.868

<sup>α</sup> Proportion of cases or controls whose mothers have diagnosis or at least one selected drug prescription in pregnancy

<sup>β</sup> Odds Ratios (95% Confidence Intervals) adjusted for maternal age at birth of case or control child; Maternal smoking status, body mass index, socioeconomic status, sex of the child, gestation of pregnancy had no confounding effects.

<sup>γ</sup> Any asthma medication except oral corticosteroids

\*Reference groups are mothers with no prescriptions for the selected drug group in pregnancy

\*\*Aminophylline, theophylline, ephedrine, orciprenaline, tiotropium, or ipratropium

\*\*\*Cromoglicic acid, nedocromil, montelukast or zafirlukast

**Table 3 Risk of circulatory system malformation in children born to women with asthma**

	cases (n=1,256)		controls (n=7,356)		Adjusted Odds Ratio <sup>β</sup>	p-value
	n	(%) <sup>α</sup>	n	(%) <sup>α</sup>	(95% CI)	
<b>Maternal asthma:</b>						
no asthma diagnosis or medications before delivery	1,073	(85.4)	6,429	(87.4)	reference	
asthma diagnosis or medication <sup>γ</sup> before delivery	183	(14.6)	927	(12.6)	1.20(1.01-1.43)	0.037
diagnosis with no medication before delivery	37	(2.9)	213	(2.9)	1.07(0.74-1.54)	0.714
asthma medication <sup>γ</sup> but no diagnosis before delivery	51	(4.1)	227	(3.1)	1.36(0.99-1.86)	0.055
diagnosis and asthma medication <sup>γ</sup> before delivery	95	(7.6)	487	(6.6)	1.18(0.94-1.49)	0.163
≥1 asthma exacerbation during pregnancy	6	(<0.5)	24	(<0.5)	1.44(0.51-4.05)	0.495
<b>≥1 medication exposure during pregnancy*:</b>						
Any asthma medication	113	(9.0)	535	(7.3)	1.27(1.02-1.58)	0.032
Short acting β-agonist	107	(8.5)	497	(6.8)	1.29(1.03-1.61)	0.024
Inhaled corticosteroid	68	(5.4)	293	(4.0)	1.38(1.04-1.82)	0.025
Long acting β-agonist	9	(0.7)	49	(0.7)	1.05(0.48-2.27)	0.910
Oral corticosteroid	15	(1.2)	48	(0.7)	1.85(1.03-3.33)	0.040
Other bronchodilator medication**	6	(<0.5)	20	(<0.5)	1.80(0.74-4.42)	0.198
Other anti-inflammatory medication***	1	(<0.5)	4	(<0.5)	1.47(0.16-13.65)	0.733

<sup>α</sup> Proportion of cases or controls whose mothers have diagnosis or at least one selected drug prescription in pregnancy

<sup>β</sup> Odds Ratios (95% Confidence Intervals) adjusted for maternal age at birth of case or control child; Maternal smoking status, body mass index, socioeconomic status, sex of the child, gestation of pregnancy had no confounding effects.

<sup>γ</sup> Any asthma medication except oral corticosteroids

\*Reference groups are mothers with no prescriptions for the selected drug group in pregnancy

\*\*Aminophylline, theophylline, ephedrine, orciprenaline, tiotropium, or ipratropium

\*\*\*Cromoglicate, nedocromil, montelukast or zafirlukast

**Table 4 Risk of respiratory system malformation in children born to women with asthma**

	cases (n=46)	controls (n=265)	Adjusted Odds Ratio <sup>β</sup>	p-value
	n (%) <sup>α</sup>	n (%) <sup>α</sup>	(95% CI)	
<b>Maternal asthma:</b>				
no asthma diagnosis or medications before delivery	38 (82.6)	228 (86.0)	reference	
asthma diagnosis or medication <sup>γ</sup> before delivery	8 (17.4)	37 (14.0)	1.30(0.50-3.39)	0.596
diagnosis with no medication before delivery	1 (2.2)	7 (2.6)	0.70(0.07-6.93)	0.761
asthma medication <sup>γ</sup> but no diagnosis before delivery	2 (4.3)	11 (4.2)	1.14(0.25-5.20)	0.865
diagnosis and asthma medication <sup>γ</sup> before delivery	5 (10.9)	19 (7.2)	1.71(0.50-5.78)	0.390
≥1 asthma exacerbation during pregnancy	0 (<0.5)	0 (<0.5)	n/a	
<b>≥1 medication exposure during pregnancy*:</b>				
Any asthma medication	6 (13.0)	21 (7.9)	1.92(0.65-5.65)	0.236
Short acting β-agonist	6 (13.0)	20 (7.5)	2.04(0.68-6.13)	0.203
Inhaled corticosteroid	3 (6.5)	12 (4.5)	1.67(0.35-8.02)	0.519
Long acting β-agonist	0 (<0.5)	1 (<0.5)	n/a	
Oral corticosteroid	0 (<0.5)	1 (<0.5)	n/a	
Other bronchodilator medication**	0 (<0.5)	0 (<0.5)	n/a	
Other anti-inflammatory medication***	0 (<0.5)	0 (<0.5)	n/a	

<sup>α</sup> Proportion of cases or controls whose mothers have diagnosis or at least one selected drug prescription in pregnancy

<sup>β</sup> Odds Ratios (95% Confidence Intervals) adjusted for maternal age at birth of case or control child; Maternal smoking status, body mass index, socioeconomic status, sex of the child, gestation of pregnancy had no confounding effects.

<sup>γ</sup> Any asthma medication except oral corticosteroids

\*Reference groups are mothers with no prescriptions for the selected drug group in pregnancy

\*\*Aminophylline, theophylline, ephedrine, orciprenaline, tiotropium, or ipratropium

\*\*\*Cromoglicic acid, nedocromil, montelukast or zafirlukast

**Table 5 Risk of cleft lip and/or palate in children born to women with asthma**

	cases (n=255)		controls (n=1,513)		Adjusted Odds Ratio <sup>β</sup> (95% CI)	p-value
	n	(%) <sup>α</sup>	n	(%) <sup>α</sup>		
<b>Maternal asthma:</b>						
no asthma diagnosis or medications before delivery	214	(83.9)	1,296	(85.7)	reference	
asthma diagnosis or medication <sup>γ</sup> before delivery	41	(16.1)	217	(14.3)	1.15(0.79-1.67)	0.477
diagnosis with no medication before delivery	11	(4.3)	55	(3.6)	1.25(0.60-2.61)	0.559
asthma medication <sup>γ</sup> but no diagnosis before delivery	12	(4.7)	59	(3.9)	1.24(0.65-2.37)	0.506
diagnosis and asthma medication <sup>γ</sup> before delivery	18	(7.1)	103	(6.8)	1.05(0.62-1.77)	0.852
≥1 asthma exacerbation during pregnancy	0	(<0.5)	7	(<0.5)	n/a	
<b>≥1 medication exposure during pregnancy*:</b>						
Any asthma medication	16	(6.3)	126	(8.3)	0.73(0.43-1.24)	0.246
Short acting β-agonist	14	(5.5)	115	(7.6)	0.69(0.39-1.24)	0.216
Inhaled corticosteroid	5	(2.0)	64	(4.2)	0.45(0.18-1.11)	0.082
Long acting β-agonist	0	(<0.5)	7	(<0.5)	n/a	
Oral corticosteroid	1	(<0.5)	13	(0.9)	0.47(0.06-3.67)	0.471
Other bronchodilator medication**	1	(<0.5)	8	(0.5)	0.80(0.10-6.44)	0.832
Other anti-inflammatory medication***	1	(<0.5)	2	(<0.5)	3.21(0.29-35.08)	0.340

<sup>α</sup> Proportion of cases or controls whose mothers have diagnosis or at least one selected drug prescription in pregnancy

<sup>β</sup> Odds Ratios (95% Confidence Intervals) adjusted for maternal age at birth of case or control child; Maternal smoking status, body mass index, socioeconomic status, sex of the child, gestation of pregnancy had no confounding effects.

<sup>γ</sup> Any asthma medication except oral corticosteroids

\*Reference groups are mothers with no prescriptions for the selected drug group in pregnancy

\*\*Aminophylline, theophylline, ephedrine, orciprenaline, tiotropium, or ipratropium

\*\*\*Cromoglicic acid, nedocromil, montelukast or zafirlukast

**Table 6 Risk of digestive system malformation in children born to women with asthma**

	cases (n=166)		controls (n=974)		Adjusted Odds Ratio <sup>β</sup>	p-value
	n	(%) <sup>α</sup>	n	(%) <sup>α</sup>	(95% CI)	
<b>Maternal asthma:</b>						
no asthma diagnosis or medications before delivery	139	(83.7)	825	(84.7)	reference	
asthma diagnosis or medication <sup>γ</sup> before delivery	27	(16.3)	149	(15.3)	1.10(0.71-1.70)	0.670
diagnosis with no medication before delivery	4	(2.4)	45	(4.6)	0.54(0.19-1.52)	0.243
asthma medication <sup>γ</sup> but no diagnosis before delivery	11	(6.6)	36	(3.7)	1.86(0.96-3.62)	0.066
diagnosis and asthma medication <sup>γ</sup> before delivery	12	(7.2)	68	(7.0)	1.03(0.53-2.00)	0.932
≥1 asthma exacerbation during pregnancy	0	(<0.5)	2	(<0.5)	n/a	
<b>≥1 medication exposure during pregnancy*:</b>						
Any asthma medication	20	(12.0)	77	(7.9)	1.65(0.99-2.74)	0.053
Short acting β-agonist	18	(10.8)	76	(7.8)	1.47(0.86-2.51)	0.156
Inhaled corticosteroid	8	(4.8)	41	(4.2)	1.17(0.50-2.69)	0.719
Long acting β-agonist	0	(<0.5)	2	(<0.5)	n/a	
Oral corticosteroid	2	(1.2)	8	(0.8)	1.38(0.32-5.97)	0.669
Other bronchodilator medication**	1	(0.6)	0	(<0.5)	n/a	
Other anti-inflammatory medication***	0	(<0.5)	0	(<0.5)	n/a	

<sup>α</sup> Proportion of cases or controls whose mothers have diagnosis or at least one selected drug prescription in pregnancy

<sup>β</sup> Odds Ratios (95% Confidence Intervals) adjusted for maternal age at birth of case or control child; Maternal smoking status, body mass index, socioeconomic status, sex of the child, gestation of pregnancy had no confounding effects.

<sup>γ</sup> Any asthma medication except oral corticosteroids

\*Reference groups are mothers with no prescriptions for the selected drug group in pregnancy

\*\*Aminophylline, theophylline, ephedrine, orciprenaline, tiotropium, or ipratropium

\*\*\*Cromoglicic acid, nedocromil, montelukast or zafirlukast

**Table 7 Risk of genital organ malformation in children born to women with asthma**

	cases (n=913)		controls (n=5,345)		Adjusted Odds Ratio <sup>β</sup>	p-value
	n	(%) <sup>α</sup>	n	(%) <sup>α</sup>	(95% CI)	
<b>Maternal asthma:</b>						
no asthma diagnosis or medications before delivery	797	(87.3)	4,675	(87.5)	reference	
asthma diagnosis or medication <sup>γ</sup> before delivery	116	(12.7)	670	(12.5)	1.01(0.82-1.26)	0.904
diagnosis with no medication before delivery	30	(3.3)	138	(2.6)	1.31(0.87-1.97)	0.203
asthma medication <sup>γ</sup> but no diagnosis before delivery	29	(3.2)	194	(3.6)	0.89(0.59-1.33)	0.559
diagnosis and asthma medication <sup>γ</sup> before delivery	57	(6.2)	338	(6.3)	0.98(0.73-1.31)	0.874
≥1 asthma exacerbation during pregnancy	3	(<0.5)	21	(<0.5)	0.66(0.23-1.89)	0.439
<b>≥1 medication exposure during pregnancy*:</b>						
Any asthma medication	69	(7.6)	408	(7.6)	0.98(0.74-1.28)	0.865
Short acting β-agonist	64	(7.0)	375	(7.0)	0.98(0.74-1.30)	0.905
Inhaled corticosteroid	37	(4.1)	225	(4.2)	0.93(0.65-1.32)	0.681
Long acting β-agonist	3	(<0.5)	24	(<0.5)	0.72(0.22-2.35)	0.582
Oral corticosteroid	10	(1.1)	40	(0.7)	1.33(0.68-2.61)	0.407
Other bronchodilator medication**	3	(<0.5)	15	(<0.5)	1.11(0.34-3.63)	0.863
Other anti-inflammatory medication***	1	(<0.5)	9	(<0.5)	0.67(0.08-5.23)	0.699

<sup>α</sup> Proportion of cases or controls whose mothers have diagnosis or at least one selected drug prescription in pregnancy

<sup>β</sup> Odds Ratios (95% Confidence Intervals) adjusted for maternal age at birth of case or control child; Maternal smoking status, body mass index, socioeconomic status, sex of the child, gestation of pregnancy had no confounding effects.

<sup>γ</sup> Any asthma medication except oral corticosteroids

\*Reference groups are mothers with no prescriptions for the selected drug group in pregnancy

\*\*Aminophylline, theophylline, ephedrine, orciprenaline, tiotropium, or ipratropium

\*\*\*Cromoglicate, nedocromil, montelukast or zafirlukast

**Table 8 Risk of urinary system malformation in children born to women with asthma**

	cases (n=313)		controls (n=1,850)		Adjusted Odds Ratio <sup>β</sup>	p-value
	n	(%) <sup>α</sup>	n	(%) <sup>α</sup>	(95% CI)	
<b>Maternal asthma:</b>						
no asthma diagnosis or medications before delivery	267	(85.3)	1,628	(88.0)	reference	
asthma diagnosis or medication <sup>γ</sup> before delivery	46	(14.7)	222	(12.0)	1.25(0.89-1.76)	0.193
diagnosis with no medication before delivery	14	(4.5)	54	(2.9)	1.59(0.87-2.90)	0.132
asthma medication <sup>γ</sup> but no diagnosis before delivery	11	(3.5)	45	(2.4)	1.50(0.77-2.90)	0.232
diagnosis and asthma medication <sup>γ</sup> before delivery	21	(6.7)	123	(6.6)	1.03(0.63-1.68)	0.921
≥1 asthma exacerbation during pregnancy	2	(0.6)	3	(<0.5)	4.32(0.74-25.21)	0.104
<b>≥1 medication exposure during pregnancy*:</b>						
Any asthma medication	25	(8.0)	131	(7.1)	1.13(0.72-1.77)	0.594
Short acting β-agonist	24	(7.7)	122	(6.6)	1.16(0.74-1.83)	0.518
Inhaled corticosteroid	11	(3.5)	75	(4.1)	0.83(0.42-1.63)	0.587
Long acting β-agonist	0	(<0.5)	12	(0.6)	n/a	
Oral corticosteroid	4	(1.3)	10	(0.5)	2.40(0.76-7.60)	0.138
Other bronchodilator medication**	1	(<0.5)	1	(<0.5)	6.39(0.40-102.91)	0.191
Other anti-inflammatory medication***	0	(<0.5)	0	(<0.5)	n/a	

<sup>α</sup> Proportion of cases or controls whose mothers have diagnosis or at least one selected drug prescription in pregnancy

<sup>β</sup> Odds Ratios (95% Confidence Intervals) adjusted for maternal age at birth of case or control child; Maternal smoking status, body mass index, socioeconomic status, sex of the child, gestation of pregnancy had no confounding effects.

<sup>γ</sup> Any asthma medication except oral corticosteroids

\*Reference groups are mothers with no prescriptions for the selected drug group in pregnancy

\*\*Aminophylline, theophylline, ephedrine, orciprenaline, tiotropium, or ipratropium

\*\*\*Cromoglicate, nedocromil, montelukast or zafirlukast



**Table 9 Risk of musculoskeletal system malformation in children born to women with asthma**

	cases (n=1,431)		controls (n=8,372)		Adjusted Odds Ratio <sup>β</sup>	p-value
	n	(%) <sup>α</sup>	n	(%) <sup>α</sup>	(95% CI)	
<b>Maternal asthma:</b>						
no asthma diagnosis or medications before delivery	1,213	(84.8)	7,304	(87.2)	reference	
asthma diagnosis or medication <sup>γ</sup> before delivery	218	(15.2)	1,068	(12.8)	1.25(1.06-1.47)	0.009
diagnosis with no medication before delivery	50	(3.5)	246	(2.9)	1.23(0.89-1.70)	0.214
asthma medication <sup>γ</sup> but no diagnosis before delivery	64	(4.5)	266	(3.2)	1.46(1.11-1.93)	0.007
diagnosis and asthma medication <sup>γ</sup> before delivery	104	(7.3)	556	(6.6)	1.14(0.91-1.43)	0.241
≥1 asthma exacerbation during pregnancy	6	(<0.5)	22	(<0.5)	1.71(0.70-4.17)	0.241
<b>≥1 medication exposure during pregnancy*:</b>						
Any asthma medication	125	(8.7)	638	(7.6)	1.16(0.95-1.43)	0.143
Short acting β-agonist	118	(8.2)	598	(7.1)	1.17(0.95-1.45)	0.132
Inhaled corticosteroid	68	(4.8)	355	(4.2)	1.13(0.86-1.48)	0.383
Long acting β-agonist	10	(0.7)	29	(<0.5)	2.12(1.00-4.49)	0.050
Oral corticosteroid	8	(0.6)	65	(0.8)	0.71(0.33-1.52)	0.381
Other bronchodilator medication**	2	(<0.5)	14	(<0.5)	0.84(0.19-3.63)	0.814
Other anti-inflammatory medication***	5	(<0.5)	4	(<0.5)	9.38(2.31-38.10)	0.002

<sup>α</sup> Proportion of cases or controls whose mothers have diagnosis or at least one selected drug prescription in pregnancy

<sup>β</sup> Odds Ratios (95% Confidence Intervals) adjusted for maternal age at birth of case or control child; Maternal smoking status, body mass index, socioeconomic status, sex of the child, gestation of pregnancy had no confounding effects.

<sup>γ</sup> Any asthma medication except oral corticosteroids

\*Reference groups are mothers with no prescriptions for the selected drug group in pregnancy

\*\*Aminophylline, theophylline, ephedrine, orciprenaline, tiotropium, or ipratropium

\*\*\*Cromoglicic acid, nedocromil, montelukast or zafirlukast

**Table 10 Risk of other non-categorised malformation in children born to women with asthma**

	cases (n=407)		controls (n=2,400)		Adjusted Odds Ratio <sup>β</sup>	p-value
	n	(%) <sup>α</sup>	n	(%) <sup>α</sup>	(95% CI)	
<b>Maternal asthma:</b>						
no asthma diagnosis or medications before delivery	356	(87.5)	2,102	(87.6)	reference	
asthma diagnosis or medication <sup>γ</sup> before delivery	51	(12.5)	298	(12.4)	1.04(0.76-1.44)	0.795
diagnosis with no medication before delivery	14	(3.4)	70	(2.9)	1.23(0.68-2.21)	0.499
asthma medication <sup>γ</sup> but no diagnosis before delivery	8	(2.0)	73	(3.0)	0.65(0.31-1.36)	0.258
diagnosis and asthma medication <sup>γ</sup> before delivery	29	(7.1)	155	(6.5)	1.15(0.75-1.77)	0.518
≥1 asthma exacerbation during pregnancy	2	(<0.5)	7	(<0.5)	1.94(0.40-9.37)	0.408
<b>≥1 medication exposure during pregnancy*:</b>						
Any asthma medication	30	(7.4)	173	(7.2)	1.04(0.69-1.58)	0.842
Short acting β-agonist	25	(6.1)	164	(6.8)	0.50(0.24-1.06)	0.070
Inhaled corticosteroid	19	(4.7)	92	(3.8)	1.27(0.76-2.13)	0.361
Long acting β-agonist	1	(<0.5)	8	(<0.5)	0.80(0.10-6.58)	0.837
Oral corticosteroid	3	(0.7)	21	(0.9)	0.81(0.24-2.78)	0.741
Other bronchodilator medication**	1	(<0.5)	6	(<0.5)	0.95(0.12-7.84)	0.963
Other anti-inflammatory medication***	0	(<0.5)	0	(<0.5)	n/a	

<sup>α</sup> Proportion of cases or controls whose mothers have diagnosis or at least one selected drug prescription in pregnancy

<sup>β</sup> Odds Ratios (95% Confidence Intervals) adjusted for maternal age at birth of case or control child; Maternal smoking status, body mass index, socioeconomic status, sex of the child, gestation of pregnancy had no confounding effects.

<sup>γ</sup> Any asthma medication except oral corticosteroids

\*Reference groups are mothers with no prescriptions for the selected drug group in pregnancy

\*\*Aminophylline, theophylline, ephedrine, orciprenaline, tiotropium, or ipratropium

\*\*\*Cromoglicate, nedocromil, montelukast or zafirlukast

**Table 11 Risk of chromosomal abnormalities not elsewhere classified in children born to women with asthma**

	cases (n=260)		controls (n=1,519)		Adjusted Odds Ratio <sup>β</sup>	p-value
	n	(%) <sup>α</sup>	n	(%) <sup>α</sup>	(95% CI)	
<b>Maternal asthma:</b>						
no asthma diagnosis or medications before delivery	238	(91.5)	1,320	(86.9)	reference	
asthma diagnosis or medication <sup>γ</sup> before delivery	22	(8.5)	199	(13.1)	0.62(0.37-1.03)	0.066
diagnosis with no medication before delivery	9	(3.5)	57	(3.8)	1.01(0.43-2.36)	0.984
asthma medication <sup>γ</sup> but no diagnosis before delivery	7	(2.7)	55	(3.6)	0.59(0.25-1.41)	0.236
diagnosis and asthma medication <sup>γ</sup> before delivery	6	(2.3)	87	(5.7)	0.43(0.18-1.02)	0.054
≥1 asthma exacerbation during pregnancy	0	(<0.5)	2	(<0.5)	n/a	
<b>≥1 medication exposure during pregnancy*:</b>						
Any asthma medication	9	(3.5)	106	(7.0)	0.45(0.22-0.95)	0.035
Short acting β-agonist	9	(3.5)	99	(6.5)	0.50(0.24-1.06)	0.070
Inhaled corticosteroid	1	(<0.5)	52	(3.4)	0.11(0.01-0.80)	0.030
Long acting β-agonist	0	(<0.5)	1	(<0.5)	n/a	
Oral corticosteroid	1	(<0.5)	12	(0.8)	0.74(0.09-5.95)	0.774
Other bronchodilator medication**	1	(<0.5)	7	(<0.5)	0.87(0.10-7.71)	0.901
Other anti-inflammatory medication***	1	(<0.5)	2	(<0.5)	5.04(0.40-63.36)	0.211

<sup>α</sup> Proportion of cases or controls whose mothers have diagnosis or at least one selected drug prescription in pregnancy

<sup>β</sup> Odds Ratios (95% Confidence Intervals) adjusted for maternal age at birth of case or control child; Maternal smoking status, body mass index, socioeconomic status, sex of the child, gestation of pregnancy had no confounding effects.

<sup>γ</sup> Any asthma medication except oral corticosteroids

\*Reference groups are mothers with no prescriptions for the selected drug group in pregnancy

\*\*Aminophylline, theophylline, ephedrine, orciprenaline, tiotropium, or ipratropium

\*\*\*Cromoglicate, nedocromil, montelukast or zafirlukast