

Exposure to acid-suppressing drugs during pregnancy and the risk of asthma in childhood: an observational cohort study

L. Cea Soriano*, S. Hernández-Díaz[†], S. Johansson[‡], P. Nagy[‡] & L. A. García-Rodríguez*

*Centro Español de Investigación Farmacoepidemiológica (CEIFE), Madrid, Spain.

[†]Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, MA, USA.

[‡]AstraZeneca Gothenburg, Global Medicines Development, Mölndal, Sweden.

Correspondence to:

Dr L. Cea Soriano, Centro Español de Investigación Farmacoepidemiológica (CEIFE), c/ Almirante 28-2, Madrid 28004, Spain.
E-mail: luciaceife@gmail.com

Publication data

Submitted 2 September 2015
First decision 21 September 2015
Resubmitted 4 November 2015
Accepted 4 November 2015

This article was accepted for publication after full peer-review.

SUMMARY

Background

Some research has suggested a potential link between prenatal exposure to proton pump inhibitors (PPIs) or H₂-receptor antagonists (H₂RAs) and the development of childhood asthma.

Aim

To quantify the relative risk of asthma in children who experienced prenatal exposure to PPIs and/or H₂RAs, adjusting for potential confounders.

Methods

In this observational cohort study (NCT01787435), women aged 18–45 years with completed pregnancies between January 1996 and December 2010 were identified from The Health Improvement Network in the United Kingdom, and were linked to infants. Hazard ratios (HRs) were estimated using Cox proportional hazard models.

Results

Our analysis identified 2371 prenatally exposed and 7745 unexposed infants. The incidence of asthma (per 1000 person-years) was 19.52 in the unexposed cohort, 23.88 in the PPI cohort and 32.16 in the H₂RA cohort. After adjusting for maternal healthcare utilisation during the year before pregnancy, the HR for asthma in infants whose mothers received prescriptions at any time during pregnancy was 1.12 (95% confidence interval: 0.88–1.44) for PPIs and 1.43 (1.20–1.70) for H₂RAs, when compared with unexposed infants. With further adjustment for maternal comorbidities and other medications, the HR for asthma was 1.03 (0.76–1.40) for PPIs and 1.32 (1.05–1.64) for H₂RAs.

Conclusions

Our analysis showed no association between prenatal exposure to PPIs and asthma in childhood after adjusting for confounders. The association found for H₂RAs may be explained largely by underlying environmental or genetic factors, as suggested by reductions in hazard ratio estimates following adjustment for maternal comorbidities.

INTRODUCTION

Heartburn or gastroesophageal reflux disease (GERD) affects 30–80% of pregnant women and can be hard to manage.^{1, 2} Histamine H₂-receptor antagonists (H₂RAs) are recommended in pregnant women whose symptoms cannot be adequately controlled with lifestyle modification and antacids.^{1, 3} However, these methods are often ineffective, which has led to the increasing use of proton pump inhibitors (PPIs) in pregnancy.⁴

In epidemiological studies, the use of PPIs during pregnancy has indicated neither malformative nor fetotoxic effects.^{4, 5} However, research has suggested that there might be a link between exposure to PPIs and other acid-suppressing medications *in utero* and the development of childhood asthma.^{6–11} A Swedish registry-based cohort study was the first to show that maternal use of acid-suppressing medication (including PPIs) in pregnancy was associated with an increase in the risk of the infant developing severe childhood asthma⁶ and, since then, others have replicated this finding.^{7–9} In a Danish registry study, prenatal exposure to PPIs was associated with an increased risk of asthma in children.⁷ However, the authors also found an association with maternal postnatal use of PPIs, suggesting that such findings may be explained by common causes of both the indication for acid-suppressing medications in the mother and the development of asthma in the infant.

Many factors have been proposed to be associated with childhood asthma, including maternal asthma and maternal use of asthma medications, antibiotics and paracetamol.^{12–15} Potential confounding due to genetic and environmental factors shared by the mother, father and offspring, during and after gestation, presents a further challenge for studies examining true associations between prenatal exposures and childhood asthma.

The aim of this study (NCT01787435) was to quantify the relative risk of asthma in children who experienced any prenatal exposure to acid-suppressing drugs (PPIs and/or H₂RAs), adjusting for potential confounders. Data were obtained from The Health Improvement Network (THIN) database, which contains systematically recorded data on more than three million primary care patients in the UK. Two cohorts of infants and their mothers were identified using this database: a cohort that was exposed to acid-suppressing drugs during pregnancy and a matched unexposed cohort. The risk of developing childhood asthma was compared between the two groups of infants.

METHODS

Data source

THIN is representative of the UK population in terms of age, sex and geographical distribution, and has been validated for use in epidemiological studies.^{16–18} Data are systematically recorded by primary care physicians (PCPs) as part of routine care, and sent anonymously to THIN for use in research projects. Data include demographics, lifestyle factors (such as body mass index), diagnoses, referrals and hospital admissions, laboratory test results and free-text comments. Prescriptions issued by PCPs are recorded automatically in the database. Specific diagnoses are coded using the Read classification, and drug prescriptions are coded using a drug dictionary based on data from the MULTILEX classification.¹⁹

Study registration and approval

This study (NCT01787435) was approved by the Scientific Research Committee (SRC: 13-002). The study was registered before data analysis began.

Identification of female participants and pregnancies

Women aged 18–45 years between 1 January 1996 and 31 December 2010, who had been registered with their PCP for at least 1 year, were identified from THIN as the source population. From these individuals, those who had completed pregnancies or pregnancy losses during this period were identified based on Read codes indicative of conception [last menstrual period (LMP)], end of pregnancy (e.g. deliveries, miscarriages) and pregnancy-related events (e.g. prenatal visits and tests). Details on cohort identification have been described previously.²⁰

The timing of the pregnancy (i.e. from LMP date to end of pregnancy) was determined from the data, and completed pregnancies were linked to live-born infants by means of the family identification number and date of birth (89% successful linkage).

Exposure to acid-suppressing drugs

Exposure during pregnancy was defined as the presence of at least one prescription of acid-suppressing drugs (PPIs and/or H₂RAs) any time between the LMP and delivery date. A woman was considered a non-user (i.e. unexposed) when there was no prescription of any acid-suppressing drug during pregnancy. PPIs and H₂RAs were considered separately, and exposure was further

categorised according to the first, second and third trimesters of pregnancy (defined as LMP date to gestational day 90, gestational day 91 to gestational day 180 and gestational day 181 to end of pregnancy, respectively). Women exposed to acid-suppressing drugs during the pre-pregnancy period (defined as the 90 days before the LMP date), but who did not receive a prescription during pregnancy, were also identified.

Identification of exposed and unexposed cohorts

Our analysis identified a cohort of 3045 women with at least one prescription for acid-suppressing medications during pregnancy (exposed cohort). These individuals were matched by both calendar time (within the same calendar quarter of LMP) and maternal age at LMP with a sample of 10 000 women who were unexposed to acid-suppressing drugs during pregnancy (unexposed cohort) (Figure 1). The 13 045 pregnancies in these two study cohorts were linked to a total of 3154 infants in the exposed cohort and 10 233 infants in the unexposed cohort.

In addition, 1135 infants were identified as being born from women who used an acid-suppressing agent during the pre-pregnancy period but not during the pregnancy itself. This control group was chosen to evaluate whether exposure before pregnancy was associated with the outcome; if so, residual confounding could account for any association with exposure *in utero*.

Selection and follow-up of infants

Infants were eligible for analysis if they had continuous enrolment in THIN until they were at least 1 year of age. A total of 2371 infants in the exposed cohort and 7745 in the unexposed cohort met inclusion criteria. Among infants in the exposed cohort, 816 (34.4%) were exposed to PPIs, 1414 (59.6%) were exposed to H₂RAs and 141 (5.9%) were exposed to both medications. Of the 1135 infants with mothers in the pre-pregnancy exposure (control) cohort, 894 were eligible for analysis; of these, 600 (67.1%), 269 (30.1%) and 25 (2.8%) were exposed to PPIs, H₂RAs and both medications, respectively. All infants in the final study cohorts (exposed, unexposed and control) were followed up from 1 year of age until the first recorded entry of one of the following endpoints: asthma diagnosis, their sixth birthday, death or end of the study follow-up period (31 December 2011).

Asthma definition and asthma case ascertainment

Potential asthma cases in the study cohorts were identified from THIN records using an automated computer

search for specific Read codes, and were confirmed by manual review of electronic medical records to ascertain asthma status. Patient profiles, including demographics and clinical information (but no details on maternal exposure during pregnancy), and free-text comments were reviewed manually to confirm asthma cases. Free-text comments assigned to Read codes suggestive of asthma symptoms or allergies and to specific Additional Health Data and screening tests related to asthma within the year before and up to 1 year after the potential case date were reviewed. Free-text comments assigned to unspecific Read codes related to referrals or other PCP visits within the month before and 2 months after the potential case date were also assessed. Doubtful cases were reviewed by two epidemiologists with medical backgrounds and blinded to the exposure of interest, and agreement was reached with the help of a respiratory consultant.

In the exposed cohort, 252 infants were identified with asthma based on the automated search of Read codes: 173 were exposed to H₂RAs, 65 were exposed to PPIs and 14 were exposed to both drug classes *in utero*. Likewise, 571 infants were identified in the unexposed cohort. Of these 823 potential asthma cases, 763 (92.7%) were confirmed on review and used in the analysis. The proportion of confirmed asthma cases was 94.0% in the exposed group (ranging from 92% to 95% across specific treatments), 92.1% in the unexposed cohort and 94.9% in the pre-pregnancy exposed (control) cohort. Non-confirmed cases were excluded because of either insufficient information in the PCP records to confirm asthma diagnosis or confirmation of other respiratory tract disorders (such as respiratory tract infection or cystic fibrosis).

Secondary validation of cases by questionnaire

From the potential asthma cases, we selected a random sample of 100 patients (93 classified as confirmed and seven as nonconfirmed in the manual review) and asked their PCPs to complete questionnaires designed to provide additional information about asthma symptoms, diagnostic tests and treatments. In all, 91 questionnaires containing complete information were returned. PCPs confirmed an asthma diagnosis in 75 out of the 85 (88.2%) asthma cases confirmed by manual review, and in three out of the six (50.0%) nonconfirmed cases.

Covariates

Data regarding a number of potential risk factors for asthma, including demographic factors and maternal comorbidities (such as asthma, autoimmune disease,

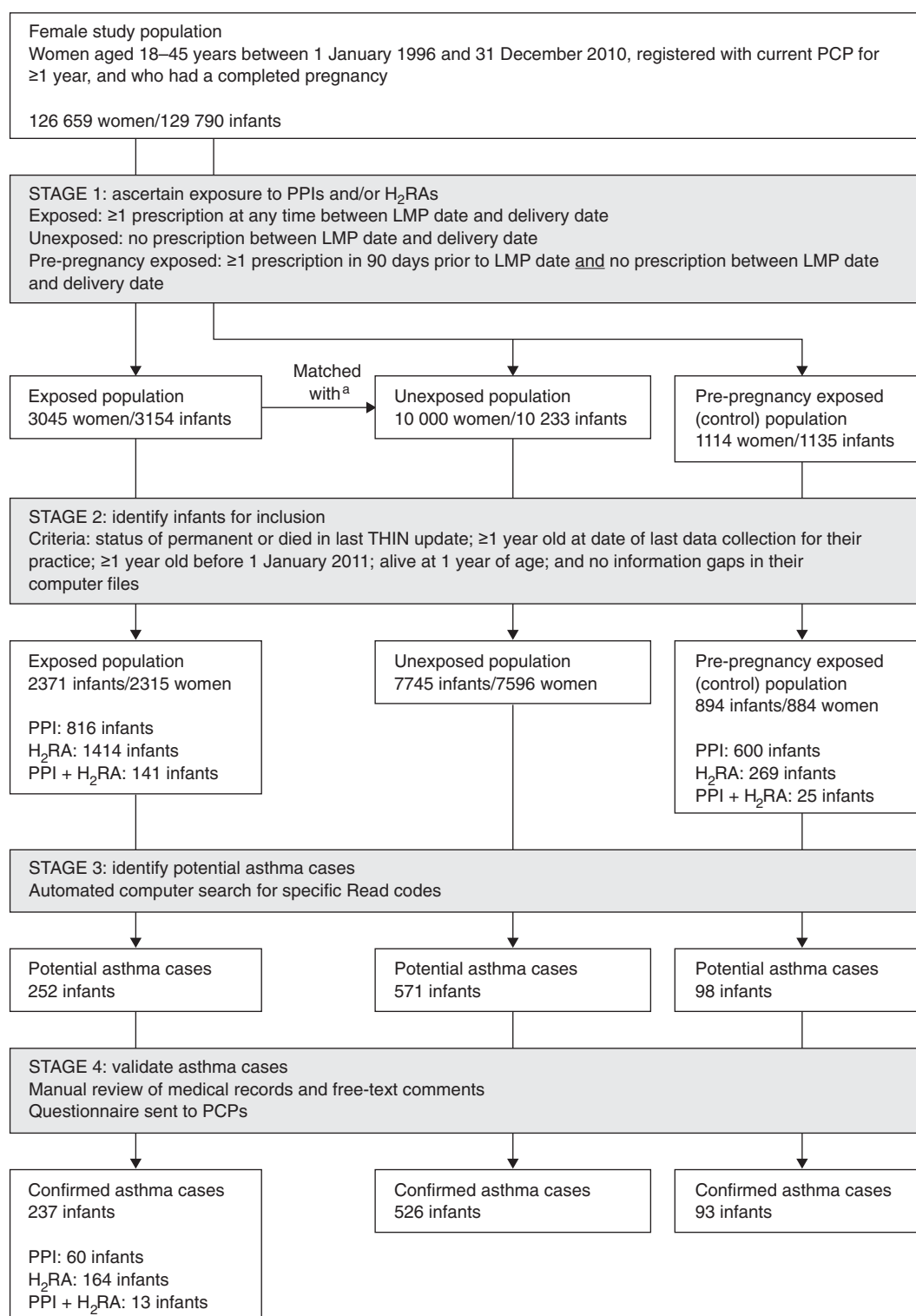


Figure 1 | Identification of exposure to acid-suppressing drugs and asthma cases. ^aExposed women were matched by both calendar time (within the same calendar quarter of LMP) and maternal age at LMP with a sample of 10 000 women who were unexposed to acid-suppressing drugs during pregnancy. H₂RA, histamine H₂-receptor antagonist; LMP, last menstrual period; PCP, primary care physician; PPI, proton pump inhibitor; THIN, The Health Improvement Network.

allergic rhinitis and GERD) were collected any time before the LMP date and during pregnancy. Data on maternal drug use (e.g. antibiotics, asthma medications and antacids) were collected in both the year before pregnancy and during pregnancy.

Statistical analysis

Among the matched infant cohorts, Cox proportional hazard models were used to estimate the hazard ratio (HR) and 95% confidence intervals (CIs) of developing asthma associated with maternal prenatal exposure to acid-suppressing drugs. For PPIs and H₂RAs, exposure was assessed at any time during pregnancy and in each trimester of pregnancy. Different Cox regression models were used to adjust for various confounding factors: number of maternal PCP visits and referrals in the year before the LMP date and year of delivery (Model A); maternal asthma (Model B); maternal comorbidities any time before delivery (allergies, GERD, peptic ulcer; Model C); maternal use of nonsteroidal anti-inflammatory drugs during pregnancy (Model D); and maternal use of antacids, antibiotics or anti-histamine medications during pregnancy, and sex of infant (Model E). Each successive model included the factors from the previous model(s). Data are presented for Models A and E. Furthermore, a sensitivity analysis also assessed pre-pregnancy exposure.

Statistical analyses were performed using the STATA package version 12.0 (StataCorp LP, College Station, TX, USA).

RESULTS

Baseline maternal characteristics

Baseline maternal characteristics according to acid-suppressing drug exposure are shown in Table 1. Mean age was approximately 30 years across the groups, and women in the unexposed group showed less healthcare utilisation on average in the year before pregnancy than those in the exposed groups. Women exposed to acid-suppressing medications were more likely to have gastrointestinal as well as other comorbidities (such as depression, asthma and allergies), compared with the unexposed group, at any time before the LMP date (Table 1) and during pregnancy (data not shown). During the year before the LMP date, women in the exposed group received more prescriptions of other medications (i.e. not including acid-suppressing drugs) compared with the unexposed group (Table 2). Exposure to acid-suppressing agents is shown in Table 3. Exposure to

PPIs was greatest in the first trimester, whereas H₂RA exposure was highest in the third trimester.

Incidence of asthma

The incidence of asthma (per 1000 person-years) in the offspring of women in the study was 19.52 (95% CI: 17.92–21.26) in the unexposed cohort, compared with 23.88 (18.54–30.75) in the PPI cohort, 32.16 (27.60–37.48) in the H₂RA cohort and 28.65 (16.63–49.34) in the PPI + H₂RA cohort. Among infants whose mothers were exposed to an acid-suppressing drug during the pre-pregnancy period only, the incidence of asthma was 29.73 (95% CI: 24.26–36.43).

Compared with the unexposed group, the crude incidence rate ratio (IRR) of asthma associated with drug exposure during pregnancy was 1.22 (95% CI: 0.94–1.60) for PPIs, 1.65 (1.38–1.96) for H₂RAs and 1.47 (0.85–2.54) in the PPI + H₂RA cohort. The crude HR of asthma associated with drug exposure during pregnancy was 1.21 (95% CI: 0.93–1.58) for PPIs, 1.66 (1.39–1.97) for H₂RAs and 1.46 (0.84–2.52) for both drugs, compared with the unexposed group. For exposure to acid-suppressing drugs during the pre-pregnancy period only, the HR (age-adjusted) was 1.50 (95% CI: 1.20–1.87) relative to non-exposure; the corresponding HR estimates according to type of acid-suppressing agent were 1.41 (1.07–1.87) for PPIs, 1.60 (1.13–2.26) for H₂RAs and 2.35 (0.88–6.28) for both drugs.

Adjusted Cox regression analysis in the exposed vs. unexposed cohorts

Compared with unexposed infants, the HR for asthma in exposed infants whose mothers received prescriptions at any time during pregnancy was 1.12 (95% CI: 0.88–1.44) for PPIs and 1.43 (1.20–1.70) for H₂RAs after adjusting for maternal PCP visits and referrals during the year before the LMP date and year of delivery (Model A; Figure 2a). When further adjustments for maternal comorbidities and use of other medications during pregnancy were applied, the HR for asthma was 1.03 (95% CI: 0.76–1.40) for PPI exposure and 1.32 (1.05–1.64) for H₂RA exposure, compared with unexposed infants (Model E; Figure 2b). There was no trend of increased risk of asthma with greater number of prescriptions during pregnancy (data not shown).

When the risk of asthma was analysed by the trimester of exposure, HRs with PPIs were similar in the first and second trimesters, and lowest in the third trimester (Figure 2); with H₂RAs, the risk of asthma was greatest for exposure in the second trimester. For infants whose

Table 1 | Baseline characteristics for maternal study population, according to acid-suppressing drug exposure group

	Unexposed (n = 7596)	Exposed to PPI only (n = 808)	Exposed to H ₂ RA only (n = 1368)	Exposed to PPI + H ₂ RA (n = 139)	Exposed to PPI and/or H ₂ RA pre-pregnancy (n = 884)
Age (years)					
18–19	284 (3.7)	36 (4.5)	52 (3.8)	4 (2.9)	42 (4.8)
20–29	3015 (39.7)	340 (42.1)	532 (38.9)	50 (36.0)	379 (42.9)
30–39	3944 (51.9)	397 (49.1)	721 (52.7)	74 (53.2)	434 (49.1)
≥40	353 (4.6)	35 (4.3)	63 (4.6)	11 (7.9)	29 (3.3)
BMI* (kg/m²)					
<20	627 (8.3)	49 (6.1)	94 (6.9)	5 (3.6)	59 (6.7)
20–24	2493 (32.8)	212 (26.2)	411 (30.0)	38 (27.3)	298 (33.7)
25–29	1378 (18.1)	173 (21.4)	260 (19.0)	38 (27.3)	178 (20.1)
≥30	827 (10.9)	171 (21.2)	220 (16.1)	27 (19.4)	127 (14.4)
Unknown	2271 (29.9)	203 (25.1)	383 (28.0)	31 (22.3)	222 (25.1)
Townsend score					
Least deprived	2025 (26.7)	139 (17.2)	277 (20.2)	27 (19.4)	170 (19.2)
Intermediate I	1568 (20.6)	136 (16.8)	243 (17.8)	23 (16.5)	166 (18.8)
Intermediate II	1521 (20.0)	164 (20.3)	317 (23.2)	27 (19.4)	185 (20.9)
Intermediate III	1263 (16.6)	180 (22.3)	265 (19.4)	24 (17.3)	159 (18.0)
Most deprived	893 (11.8)	149 (18.4)	204 (14.9)	31 (22.3)	148 (16.7)
Unknown	326 (4.3)	40 (5.0)	62 (4.5)	7 (5.0)	56 (6.3)
PCP visits†, n					
0–4	3432 (45.2)	164 (20.3)	405 (29.6)	19 (13.7)	126 (14.3)
5–9	2460 (32.4)	230 (28.5)	460 (33.6)	43 (30.9)	263 (29.8)
10–19	1405 (18.5)	278 (34.4)	365 (26.7)	48 (34.5)	355 (40.2)
≥20	299 (3.9)	136 (16.8)	138 (10.1)	29 (20.9)	140 (15.8)
Referrals‡, n					
0–1	5427 (71.4)	410 (50.7)	856 (62.6)	58 (41.7)	474 (53.6)
2–4	1515 (19.9)	220 (27.2)	322 (23.5)	44 (31.7)	254 (28.7)
5–9	533 (7.0)	123 (15.2)	155 (11.3)	23 (16.5)	119 (13.5)
≥10	121 (1.6)	55 (6.8)	35 (2.6)	14 (10.1)	37 (4.2)
Prescriptions†, n					
None	1442 (19.0)	45 (5.6)	118 (8.6)	5 (3.6)	0 (0.0)
1	1588 (20.9)	63 (7.8)	188 (13.7)	10 (7.2)	37 (4.2)
2–4	2988 (39.3)	245 (30.3)	456 (33.3)	28 (20.1)	302 (34.2)
5–9	1312 (17.3)	265 (32.8)	426 (31.1)	59 (42.4)	357 (40.4)
10–14	230 (3.0)	120 (14.9)	128 (9.4)	16 (11.5)	129 (14.6)
15–19	29 (0.4)	48 (5.9)	33 (2.4)	13 (9.4)	39 (4.4)
≥20	7 (0.1)	22 (2.7)	19 (1.4)	8 (5.8)	20 (2.3)
Comorbidity‡					
Allergy suggestion	2234 (29.4)	321 (39.7)	456 (33.3)	61 (43.9)	313 (35.4)
Depression	1511 (19.9)	297 (36.8)	435 (31.8)	59 (42.4)	295 (33.4)
Asthma	1088 (14.3)	179 (22.2)	264 (19.3)	34 (24.5)	171 (19.3)
Allergic rhinitis	1004 (13.2)	131 (16.2)	196 (14.3)	22 (15.8)	138 (15.6)
Infertility suggestion	722 (9.5)	70 (8.7)	124 (9.1)	17 (12.2)	75 (8.5)
Hay fever	718 (9.5)	84 (10.4)	142 (10.4)	19 (13.7)	95 (10.7)
Dyspepsia	538 (7.1)	292 (36.1)	254 (18.6)	64 (46.0)	427 (48.3)
GERD	323 (4.3)	200 (24.8)	194 (14.2)	50 (36.0)	203 (23.0)
Autoimmune disease	97 (1.3)	15 (1.9)	14 (1.0)	4 (2.9)	16 (1.8)
Diabetes	44 (0.6)	13 (1.6)	17 (1.2)	2 (1.4)	4 (0.5)
Rheumatoid arthritis	40 (0.5)	11 (1.4)	8 (0.6)	1 (0.7)	5 (0.6)
Peptic ulcer	38 (0.5)	21 (2.6)	31 (2.3)	8 (5.8)	28 (3.2)
Multiple sclerosis	11 (0.1)	4 (0.5)	2 (0.1)	2 (1.4)	3 (0.3)

Data are presented as number (%) of women. BMI, body mass index; GERD, gastroesophageal reflux disease; H₂RA, histamine H₂-receptor antagonist; LMP, last menstrual period; PCP, primary care physician; PPI, proton pump inhibitor.

*Recorded in the previous 5 years.

†In the year before LMP date.

‡At any time before LMP date.

Table 2 | Maternal medication use in the year before the start of pregnancy and during pregnancy, according to acid-suppressing drug exposure group

	Unexposed (n = 7596)	Exposed to PPI only (n = 808)	Exposed to H ₂ RA only (n = 1368)	Exposed to PPI+H ₂ RA (n = 139)	Exposed to PPI and/or H ₂ RA pre-pregnancy (n = 884)
Year before LMP date					
Antibiotics	3119 (41.1)	465 (57.5)	736 (53.8)	85 (61.2)	540 (61.1)
Respiratory medications*	1064 (14.0)	230 (28.5)	338 (24.7)	39 (28.1)	227 (25.7)
Anti-histamines	839 (11.0)	220 (27.2)	281 (20.5)	47 (33.8)	252 (28.5)
Beta-2 agonists	585 (7.7)	135 (16.7)	184 (13.5)	20 (14.4)	122 (13.8)
NSAIDs	1009 (13.3)	202 (25.0)	299 (21.9)	36 (25.9)	252 (28.5)
Paracetamol	733 (9.6)	221 (27.4)	331 (24.2)	41 (29.5)	229 (25.9)
Anti-emetics	267 (3.5)	124 (15.3)	119 (8.7)	28 (20.1)	151 (17.1)
Antacids	123 (1.6)	101 (12.5)	92 (6.7)	16 (11.5)	141 (16.0)
Prokinetics	115 (1.5)	72 (8.9)	53 (3.9)	18 (12.9)	94 (10.6)
Fertility treatment†	105 (1.4)	16 (2.0)	33 (2.4)	2 (1.4)	9 (1.0)
During pregnancy					
Antibiotics	3141 (41.4)	473 (58.5)	810 (59.2)	92 (66.2)	480 (54.3)
Antacids	1983 (26.1)	454 (56.2)	883 (64.5)	97 (69.8)	420 (47.5)
Respiratory medications*	1125 (14.8)	226 (28.0)	409 (29.9)	56 (40.3)	217 (24.5)
Anti-histamines	776 (10.2)	219 (27.1)	425 (31.1)	61 (43.9)	157 (17.8)
Beta-2 agonists	597 (7.9)	113 (14.0)	196 (14.3)	25 (18.0)	110 (12.4)
Paracetamol	828 (10.9)	237 (29.3)	374 (27.3)	47 (33.8)	257 (29.1)
Anti-emetics	464 (6.1)	166 (20.5)	336 (24.6)	50 (36.0)	103 (11.7)
NSAIDs	175 (2.3)	66 (8.2)	67 (4.9)	12 (8.6)	40 (4.5)
Prokinetics	109 (1.4)	72 (8.9)	140 (10.2)	19 (13.7)	33 (3.7)

Data are presented as number (%) of women receiving at least one prescription in the year before pregnancy (i.e. before the LMP date) or during pregnancy (i.e. between the LMP date and delivery date). H₂RA, histamine H₂-receptor antagonist; LMP, last menstrual period; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.

*Includes beta-2 agonists, theophylline, cromoglycate and anti-histamines.

†Includes clomifene and gonadotrophins, as well as treatments used in assisted reproductive techniques (cetrotrelix, ganirelix and gonadorelin analogues).

Table 3 | Maternal use of acid-suppressing agents during pregnancy, according to time of exposure and acid-suppressing drug exposure group

	Unexposed (n = 7596)	Exposed to PPI only (n = 808)	Exposed to H ₂ RA only (n = 1368)	Exposed to PPI+H ₂ RA (n = 139)	Exposed to PPI and/or H ₂ RA pre-pregnancy (n = 884)
PPI					
At any time	NA	808 (100.0)	NA	139 (100.0)	NA
First trimester	NA	564 (69.8)	NA	90 (64.7)	NA
Second trimester	NA	211 (26.1)	NA	32 (23.0)	NA
Third trimester	NA	303 (37.5)	NA	53 (38.1)	NA
All three trimesters*	NA	94 (11.6)	NA	7 (5.0)	NA
H ₂ RA					
At any time	NA	NA	1368 (100.0)	139 (100.0)	NA
First trimester	NA	NA	296 (21.6)	48 (34.5)	NA
Second trimester	NA	NA	344 (25.1)	65 (46.8)	NA
Third trimester	NA	NA	990 (72.4)	90 (64.7)	NA
All three trimesters*	NA	NA	50 (3.7)	18 (12.9)	NA

Data are presented as number (%) of women. H₂RA, histamine H₂-receptor antagonist; NA, not applicable; PPI, proton pump inhibitor.

*At least one prescription of the corresponding acid-suppressing drug per trimester.

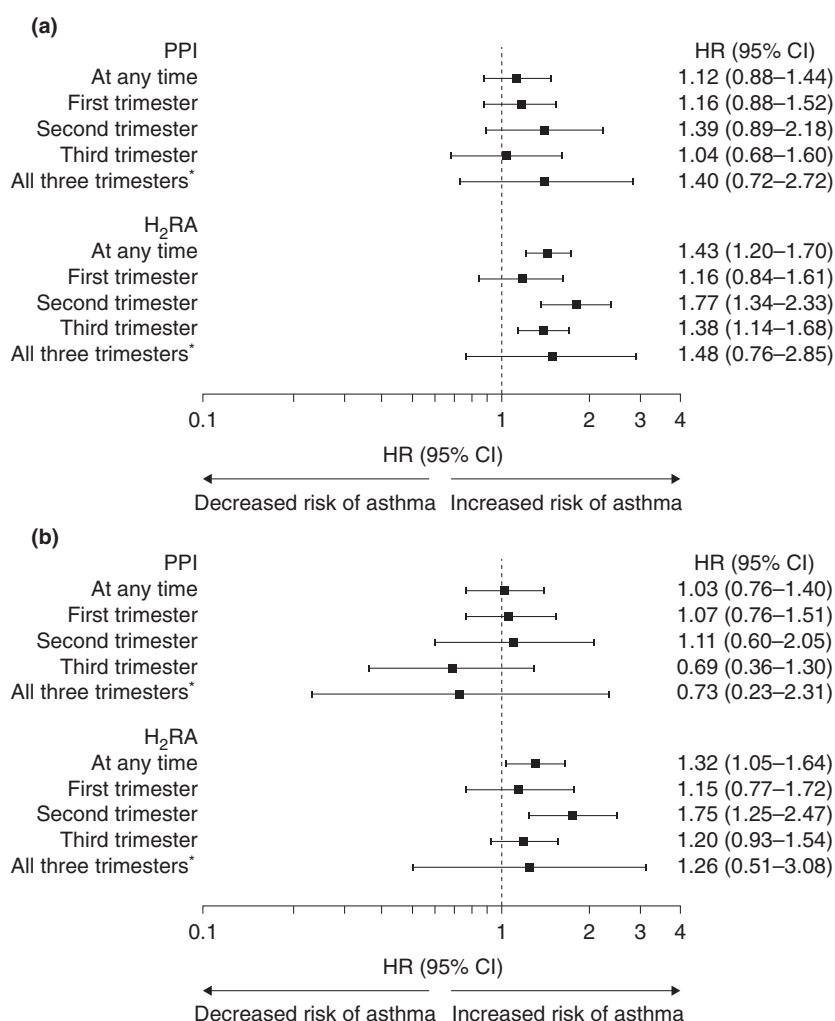


Figure 2 | Hazard ratio estimates for asthma associated with PPI or H₂RA use during pregnancy. (a) Model A – Cox proportional hazard model adjusted for number of maternal PCP visits and referrals during the year prior to the LMP date and year of delivery; (b) Model E – Cox proportional hazard model adjusted for number of maternal PCP visits and referrals during the year prior to the LMP date and year of delivery, maternal comorbidities (asthma, allergies, GERD, peptic ulcer), maternal use of NSAIDs, antacids, antibiotics and antihistamine medications during pregnancy, and sex of infant. *At least one prescription of the corresponding acid-suppressing drug per trimester. CI, confidence interval; GERD, gastroesophageal reflux disease; HR, hazard ratio; H₂RA, histamine H₂-receptor antagonist; LMP, last menstrual period; NSAID, nonsteroidal anti-inflammatory drug; PCP, primary care physician; PPI, proton pump inhibitor.

mothers had prescriptions in all three trimesters of pregnancy, the HR for asthma was 0.73 (95% CI: 0.23–2.31) for PPI exposure and 1.26 (0.51–3.08) for H₂RA exposure (Model E; Figure 2b).

When including only women who received more than one prescription during pregnancy, exposure to PPI in the first, second or third trimester or at any time during pregnancy was not associated with an increased risk of asthma (Models A and E); for H₂RAs, the risk of asthma was increased with prescriptions any time during pregnancy and in the first and second trimester (Models A

and E), and in the third trimester (Model A only) (data not shown).

Several other factors were associated with an increased risk of asthma in infants, including pre-existing maternal asthma, other pre-existing maternal autoimmune diseases, prescription of respiratory drugs during pregnancy and prescription of acetaminophen (Table 4). For pre-natal exposure to antacids, the HR for asthma was 1.37 (1.18–1.58) when adjusting for Model A (Table 4) and 1.44 (0.95–2.17) when adjusting for the full model (Model E).

Table 4 | Hazard ratio estimates for asthma associated with maternal comorbidities or maternal drug use during pregnancy

	Adjusted HR (95% CI)*
Maternal comorbidity	
Allergy	
Pre-existing	1.10 (0.93–1.29)
Diagnosed during pregnancy	1.93 (1.24–2.99)
Asthma	
Pre-existing	1.55 (1.21–2.00)
Diagnosed during pregnancy	0.99 (0.76–1.28)
Autoimmune disease	
Pre-existing	1.78 (1.03–3.10)
Diagnosed during pregnancy	0.64 (0.09–4.57)
GERD	
Pre-existing	1.07 (0.79–1.44)
Diagnosed during pregnancy	1.17 (0.92–1.48)
Hay fever†	
Pre-existing	1.21 (0.96–1.52)
Multiple sclerosis†	
Pre-existing	2.66 (0.99–7.11)
Drug use during pregnancy	
Beta-2 agonists	2.26 (1.87–2.71)
Asthma medications	1.58 (1.34–1.86)
Acetaminophen	1.41 (1.18–1.69)
Antacids	1.37 (1.18–1.58)
NSAIDs	1.20 (0.71–1.31)
Anti-histamines	1.08 (0.89–1.32)
Antibiotics	1.04 (0.90–1.21)
Prokinetics	0.54 (0.33–0.89)

CI, confidence interval; GERD, gastroesophageal reflux disease; HR, hazard ratio; LMP, last menstrual period; NSAID, nonsteroidal anti-inflammatory drug; PCP, primary care physician.

*Cox proportional hazard model adjusted for number of maternal PCP visits and referrals during the year before the LMP date and year of delivery.

†No cases of newly diagnosed disease during pregnancy.

DISCUSSION

The results of our study showed that prescription of PPIs during pregnancy was not associated with an increased risk of childhood asthma in their offspring; a modest increase in risk was observed following exposure to H₂RAs. Interestingly, we did not find an excess risk of asthma in infants whose mothers had prescriptions for either class of acid-suppressing drug in all three trimesters of pregnancy. In addition, there was no increased risk of asthma with first trimester exposure for either PPIs or H₂RAs. Exposure during the second trimester showed a stronger association with asthma, although this was not significant for PPIs (as indicated by CIs crossing 1). No association was observed between prenatal exposure to PPIs and asthma in childhood; there was a mod-

est association between prenatal exposure to H₂RAs and childhood asthma, however. The modest increase in asthma risk associated with prescription of H₂RAs should be viewed with some caution given the potential for confounding to influence the findings. Our study showed that maternal asthma, other autoimmune diseases and prescription of respiratory drugs and acetaminophen were associated with an increased risk of asthma in the infant, as was prescription of acid-suppressing drugs pre-pregnancy. Adjustments for maternal comorbidities and drug prescription during pregnancy decreased the HR estimate for asthma for both PPIs and H₂RAs in our models. Additional adjustment for unknown or unmeasured confounders, such as genetic or environmental factors, may have further reduced the HR.

A major strength of our study is the use of THIN, which allows analysis of a large sample that is representative of the UK primary care population, and which has been validated for epidemiological studies.^{16–18} The wide range of available information and the ability to link maternal and infant records and access long-term follow-up data for infants make THIN a good resource for studying associations between drug prescriptions during pregnancy and specific infant or maternal outcomes. The detailed individual records allow adjustments for a number of potential confounders, including maternal comorbidities, drug prescriptions, healthcare utilisation and smoking. Another strength of our study was the ascertainment of asthma cases. All potential asthma cases were validated via a manual review of computerised medical records, including free-text comments, providing accurate identification of cases. A further strength was the use of a validated algorithm to ascertain pregnancies and timing of pregnancy in THIN.²⁰ Limitations of our study include the possible misclassification of maternal exposure to acid-suppressing drugs. The use of prescription data to ascertain maternal drug exposure requires assumptions about the extent and timing of medication intake. In addition, the use of over-the-counter medications may have led to missed exposures, although this is likely to represent only a small proportion of acid-suppressing medication use during pregnancy in the UK.¹⁰ Pregnant women might prefer to visit their PCP rather than take medication without medical advice. Furthermore, most pregnancies are followed at least partially by the PCP, with approximately 80% of UK pregnant women choosing their PCP as the first health professional.²¹

Under most scenarios, misclassification of exposure due to lack of adherence and use of over-the-counter

drugs would result in a slight bias towards the null. On the other hand, residual confounding by unmeasured and unknown risk factors could be biasing the estimates upwards.

Several previous studies have examined the potential association between the use of acid-suppressing medication during pregnancy and the development of asthma in children, reporting an increased risk of asthma of approximately 25–50%.^{6–11} However, the observed association between maternal use of acid-suppressing medication and childhood asthma tended to lessen when adjusting for factors such as other concomitant drug use and maternal asthma.^{7–9} In studies that looked at risk by type of acid-suppressing medication, most found similar levels of risk with maternal exposure to PPIs and H₂RAs, although higher odds were observed with PPIs than H₂RAs in a study that assessed conditional odds ratios.¹⁰ As the authors of several of these studies acknowledge, the effects of confounding factors cannot be ruled out.^{7, 9} In one of the studies, maternal use of PPIs in the year after pregnancy, but not during pregnancy, was also associated with an increased asthma risk compared with non-use both during and in the year after pregnancy.⁷ The authors suggested that the findings could reflect a confounding effect of underlying maternal disease. In the current study, an increased risk of childhood asthma was associated with prescription of acid-suppressing drugs during the pre-pregnancy period only.

The findings from this and previous studies suggest that the evidence for an increased risk of childhood asthma associated with the prescription of acid-suppressing drugs during pregnancy is still unclear. Our study showed a modest increase in asthma risk with H₂RA prescription, but not with prescription of PPIs, while other studies have shown increases in risk for acid-suppressing drugs in general, for H₂RAs, and for PPIs. A general implication of our study is that physicians and clinicians need to be aware of the issues around confounding when evaluating and interpreting study results.

In conclusion, our study showed that prescription of PPIs during pregnancy was not associated with an increased risk of childhood asthma. The modest increase in risk observed with H₂RA exposure may be largely explained by underlying environmental or genetic factors, as suggested by reductions in HR estimates when maternal comorbidities and concomitant drug prescription were adjusted for, and by the association between prescription of any acid-suppressing drug prenatally and asthma in childhood.

AUTHORSHIP

Guarantor of the article: Luis A García-Rodríguez.

Author contributions: Lucia Cea Soriano, Sonia Hernández-Díaz and Luis A García-Rodríguez designed the study and performed the statistical analysis. Péter Nagy and Saga Johansson provided input on the design of the study. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. All authors were involved in analysis and interpretation of the data. All authors revised the intellectual content of the manuscript and approved the final version.

ACKNOWLEDGEMENTS

Declaration of personal interests: L. Cea Soriano and L.A. García-Rodríguez work for CEIFE, which has received research funding from AstraZeneca Gothenburg, Mölndal, Sweden and Bayer Pharma AG, Berlin, Germany. L.A. García-Rodríguez has also received honoraria for serving on scientific advisory boards for Bayer. S. Hernández-Díaz has acted as a consultant for AstraZeneca and collaborated as the epidemiologist for the North American Antiepileptic Drug Pregnancy Registry and the National Pregnancy Registry for Atypical Antipsychotics, both funded by multiple companies. The Program in Pharmacoepidemiology at the Harvard T. H. Chan School of Public Health is partially supported by training grants from Pfizer, Takeda, Bayer and the Pharmaceutical Research and Manufacturers of America (PhRMA). S. Johansson and P. Nagy are employees of AstraZeneca Gothenburg, Mölndal, Sweden, and have stock ownership or options.

Declaration of funding interests: The study was funded in part by AstraZeneca Gothenburg, Mölndal, Sweden. Two of the study authors are employees of AstraZeneca. Medical writing support was provided by Dr Rowan Pearce of Oxford PharmaGenesis, Oxford, UK, and was funded by AstraZeneca Gothenburg, Mölndal, Sweden.

REFERENCES

1. Richter JE. Review article: the management of heartburn in pregnancy. *Aliment Pharmacol Ther* 2005; **22**: 749–57.
2. Richter JE. Gastroesophageal reflux disease during pregnancy. *Gastroenterol Clin North Am* 2003; **32**: 235–61.
3. Ali RA, Egan LJ. Gastroesophageal reflux disease in pregnancy. *Best Pract Res Clin Gastroenterol* 2007; **21**: 793–806.
4. Pasternak B, Hviid A. Use of proton-pump inhibitors in early pregnancy and the risk of birth defects. *N Engl J Med* 2010; **363**: 2114–23.
5. Gill SK, O'Brien L, Einarson TR, Koren G. The safety of proton pump inhibitors (PPIs) in pregnancy: a meta-analysis. *Am J Gastroenterol* 2009; **104**: 1541–5.
6. Dehlink E, Yen E, Leichtner AM, Hait EJ, Fiebigler E. First evidence of a possible association between gastric acid

- suppression during pregnancy and childhood asthma: a population-based register study. *Clin Exp Allergy* 2009; **39**: 246–53.
7. Andersen AB, Erichsen R, Farkas DK, Mehnert F, Ehrenstein V, Sorensen HT. Prenatal exposure to acid-suppressive drugs and the risk of childhood asthma: a population-based Danish cohort study. *Aliment Pharmacol Ther* 2012; **35**: 1190–8.
8. Kallen B, Finnstrom O, Nygren KG, Otterblad Olausson P. Maternal drug use during pregnancy and asthma risk among children. *Pediatr Allergy Immunol* 2013; **24**: 28–32.
9. Mulder B, Schuiling-Veninga CC, Bos HJ, De Vries TW, Jick SS, Hak E. Prenatal exposure to acid-suppressive drugs and the risk of allergic diseases in the offspring: a cohort study. *Clin Exp Allergy* 2014; **44**: 261–9.
10. Hak E, Mulder B, Schuiling-Veninga CC, de Vries TW, Jick SS. Use of acid-suppressive drugs in pregnancy and the risk of childhood asthma: bidirectional crossover study using the general practice research database. *Drug Saf* 2013; **36**: 1097–104.
11. Mulder B, Schuiling-Veninga CC, Bos JH, de Vries TW, Hak E. Acid-suppressive drug use in pregnancy and the toddler's asthma risk: a crossover, case-control study. *J Allergy Clin Immunol* 2013; **132**: 1438–40.
12. Andersen AB, Farkas DK, Mehnert F, Ehrenstein V, Erichsen R. Use of prescription paracetamol during pregnancy and risk of asthma in children: a population-based Danish cohort study. *Clin Epidemiol* 2012; **4**: 33–40.
13. Yuan W, Fonager K, Olsen J, Sorensen HT. Prenatal factors and use of anti-asthma medications in early childhood: a population-based Danish birth cohort study. *Eur J Epidemiol* 2003; **18**: 763–8.
14. Murk W, Risnes KR, Bracken MB. Prenatal or early-life exposure to antibiotics and risk of childhood asthma: a systematic review. *Pediatrics* 2011; **127**: 1125–38.
15. Benn CS, Thorsen P, Jensen JS, *et al*. Maternal vaginal microflora during pregnancy and the risk of asthma hospitalization and use of antiasthma medication in early childhood. *J Allergy Clin Immunol* 2002; **110**: 72–7.
16. Blak BT, Thompson M, Dattani H, Bourke A. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. *Inform Prim Care* 2011; **19**: 251–5.
17. 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.
18. Lewis JD, Schinnar R, Bilker WB, Wang X, Strom BL. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. *Pharmacoepidemiol Drug Saf* 2007; **16**: 393–401.
19. First Databank. MULTILEX for primary care. 2010. Available at: <http://www.fdbhealth.co.uk/multilex-overview/> (accessed 18 December 2014).
20. Cea-Soriano L, Garcia Rodriguez LA, Fernandez Cantero O, Hernandez-Diaz S. Challenges of using primary care electronic medical records in the UK to study medications in pregnancy. *Pharmacoepidemiol Drug Saf* 2013; **22**: 977–85.
21. Redshaw M, Heikkila K. Delivered with care: a national survey of women's experience of maternity care 2010. The National Perinatal Epidemiology Unit, Oxford, 2010. Available at: <https://www.npeu.ox.ac.uk/downloads/files/reports/Maternity-Survey-Report-2010.pdf> (accessed 6 Oct 2015).