

Prenatal exposure to acid-suppressive drugs and the risk of allergic diseases in the offspring: a cohort study

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Summary

Background Recent studies reported increased risks for the development of asthma in children after prenatal exposure to acid-suppressive drugs. As a result of common pathogenesis, associations could also be present for other allergic diseases.

Methods Using the prescription database IADB.nl, we conducted a cohort study amongst 33 536 children in the Netherlands, with a maximum follow-up of 8 years. Maternal exposure was defined as ≥ 1 dispensed prescription for proton pump inhibitors (PPIs) and/or Histamine 2-antagonists (H2As) during pregnancy. Children were considered to have a drug-treated allergic disease if they received either ≥ 2 prescriptions for dermal (atopic dermatitis), inhaled (asthma) or nasal (allergic rhinitis) steroids within a 12-month period. Clustered Cox proportional hazard regression was used to estimate crude and adjusted hazard ratios (aHR) with 95% confidence intervals (95% CI).

Results The aHR for the development of any allergic disease was 1.37 (95% CI: 1.14–1.66) for children exposed to PPIs or H2As. Prenatal exposure to PPIs and/or H2As was associated with atopic dermatitis, asthma and allergic rhinitis with aHRs of 1.32 (95% CI 1.06–1.64), 1.57 (95% CI 1.20–2.05) and 2.40 (95% CI 1.42–4.04), respectively. The aHR for the development of two or more (aHR 2.13 95% CI: 1.43–3.19) and three allergic diseases (aHR 5.18 95% CI: 2.16–12.42) were even more elevated after prenatal exposure to PPIs or H2As.

Conclusion Prenatal exposure to PPIs and H2As appeared associated with an increased risk for the development of atopic dermatitis, asthma and allergic rhinitis in the offspring, especially with the development of multiple allergic diseases. Because our study has limitations inherent to observational studies, prospective studies are now warranted to confirm our findings.

Keywords acid-suppressive drugs, atopic dermatitis, asthma, child, epidemiology, pregnancy, rhinitis

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Introduction

The prevalence of allergic diseases such as atopic dermatitis, asthma and allergic rhinitis has increased dramatically over the last decades, especially in children [1]. Because the immune system develops *in utero*, drugs that interfere with immune maturation may have long-term impact on the risk of developing allergic diseases, but research in this area has been limited [2–4].

Gastroesophageal reflux disease is common in up to 80% of the pregnancies and acid-suppressive drugs such as histamine-2 receptor antagonists (H2As), and proton pump inhibitors (PPIs) are considered effective and safe treatment [5]. Recent studies suggest that there may be a relationship between the use of these acid-suppressive drugs during pregnancy and the development of asthma in the offspring [6–10]. Prior to the current study, we conducted two case-crossover studies with data from the University of Groningen mother–

infant drug prescription database and the General Practitioner Research Database (GPRD), in which the potential for confounding influences was limited by design. These studies yielded results similar to those in the earlier studies amongst toddlers [9, 10]. However, no associations were found for the development of other allergic diseases such as allergic rhinitis or atopic dermatitis.

Multiple allergic diseases often develop as a result of common pathogenesis [11]. We therefore hypothesized that if the association between prenatal exposure to acid-suppressive drugs and the development of asthma in children is due to interference in immune maturation, associations should also be present for allergic rhinitis and atopic dermatitis. Our main objective was to assess the associations between the use of acid-suppressive medication during pregnancy and the development of allergic diseases in children.

Methods

Setting and design

This cohort study was performed with a pregnancy database that is part of the University of Groningen IADB.nl pharmacy prescription database. The IADB.nl database contains prescription data from 1994 till 2011 from approximately 600 000 patients in the Northern Netherlands. Prescription rates amongst the database population have been found to be representative of the Netherlands as a whole, and the database has been widely used for research [12]. Each prescription record contains information on the date of dispensing, the quantity dispensed, the dose regimen, the number of days the prescription is valid, the prescribing physician and the Anatomical Therapeutic Chemical code (ATC code). Each patient has a unique anonymous identifier; date of birth and gender are known. Due to the high patient pharmacy commitment in the Netherlands, the medication records for each patient are virtually complete, except for over the counter (OTC) drugs and medication dispensed during hospitalization [13].

In the pregnancy database, the mother is linked to her infant using an address code. A female aged between 15 and 50 years living at the same address as the infant is identified as the mother. The male aged between 18 and 50 years living at the same address as the infant is identified as the father. Approximately 65% of the infants in the main IADB.nl database could be linked to their mother, and validation of the identified mothers showed 99% accuracy [14]. The pregnancy period was estimated by subtracting 273 days (3 trimesters of 91 days) from each child's date of birth.

Study population

The study population was restricted to all children born between 1995 and 2011 whose mothers had at least 12 months of maternal data present prior to the birth date. Children those were part of twins/multiple births were excluded from the study population.

Exposure and reference group

Exposure was defined as one or more maternal prescriptions for a PPI (ATC A02BC) or a H2A (ATC A02BA) dispensed during pregnancy. Exposure during first trimester was defined as a prescription received between 181 and 273 days prior to the delivery date, for the second trimester between 91 and 180 days, and for the third trimester between 0 and 90 days. We also stratified exposure by the total amount dispensed of the study drug during pregnancy (≤ 15 or >15 defined daily doses (DDDs)). Because all first prescriptions in the Netherlands are prescribed for 2 weeks, this categorization will distinguish short-term use from prolonged use. Exposure was further grouped into H2As and PPIs separately. We defined the reference group as children non-exposed to H2As and PPIs during the entire pregnancy.

In addition, we also analysed paternal exposure to H2A's and PPIs during pregnancy in a subset of children where paternal data were present [15].

Outcome

We determined case status by identifying drugs received to treat each allergic disease according to Dutch General Practitioner Guidelines [16–18], atopic dermatitis, asthma or allergic rhinitis. A child was considered to have atopic dermatitis when he/she had at least two prescriptions for an ointment containing either steroids (ATC-group D07) or calcineurin-inhibitors: Tacrolimus and Pimecrolimus (ATC codes *D11AH 01/02*) within a 12-month period [18, 19]. A child who received at least two prescriptions for an inhaled corticosteroid (ATC codes R03BA, R03AK06/07) within a 12-month period was considered to have asthma [20–22]. Making an asthma diagnosis in toddlers before the age of 5 is difficult; hence, we performed a subanalysis in which asthma was defined as receiving two prescriptions for an inhaled corticosteroid after the age of 5. A child who received at least two prescriptions for nasal steroids (ATC R01AD) within a 12-month period was considered to have allergic rhinitis [19, 23]. The index date, the date at which the child becomes a case, was defined as the date at which the first prescription of the qualifying drugs was dispensed. If a child has multiple allergic diseases, the index date is the date of the first qualifying prescription of the first developed disease.

Covariates

Covariates that could potentially confound the association between acid-suppressive drugs during pregnancy and allergic diseases in the offspring were year of birth, sex of the child, the use of acid-suppressive drugs (ATC A02B) by the child prior to the index date, the age of the mother at delivery, maternal use of systemic antibiotics (ATC J01) during pregnancy and allergic disease in the mother or father [3, 24–27]. Allergic diseases in the mother or father were defined similarly as for the child (see section ‘Outcome’).

Statistical analysis

Children were followed from their date of birth until the index date, the end of the record, or their 8th birthday, whichever occurred first. The end of the record was defined as the date of the last prescription received by the child or the mother, whichever resulted in the longest follow-up. We calculated incidence rates of any drug-treated allergic disease as the number of children identified with atopic dermatitis, asthma and/or allergic rhinitis divided by the total follow-up time. Clustered Cox proportional hazards regression was used to compute crude and adjusted hazard ratios (HRs) with 95% confidence intervals (95% CI) for the development of any allergic disease and the development of the allergic diseases separately after exposure to acid-suppressive drugs during pregnancy. Children from the same mother were clustered to control for correlation between them. Adjustments were made for the covariates gender, use of acid-suppressive drugs by the child, age of the mother at giving birth, maternal use of systemic antibiotics during pregnancy and the presence of allergic disease in mother to compute adjusted HRs for the development of any allergic disease. Allergic disease in the father was also assessed for possible confounding. The assumption of proportional hazards was assessed graphically. To examine whether the association varied by the number of allergic diseases, we also performed analyses restricted to children with two or more allergic diseases and to children with three allergic diseases. All analyses were conducted using R [28].

Results

There were 33 536 children from 22 856 different mothers included in the analysis. Data on paternal exposures were present for 18 619 (55.5%) children (figure 1). Of all children, 51.8% were boys. A total of 489 (1.5%) children were exposed to PPIs or H2As during pregnancy. The mean maternal age at delivery was 31.4 and 30.0 years for mothers of exposed and non-exposed children, respectively. The presence of allergic

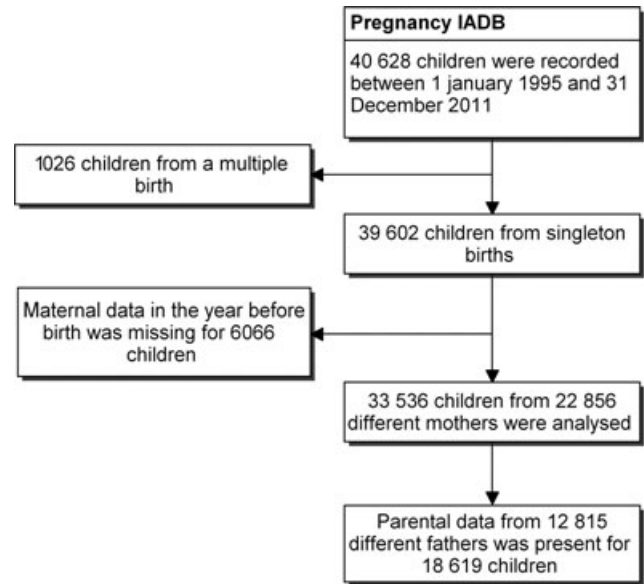


Fig. 1. Flow diagram of the in- and exclusion criteria of the study population.

Table 1. Distribution of covariates between exposed and non-exposed pregnancies

	<i>n</i> (%) Exposed during pregnancy (<i>N</i> = 489)	<i>n</i> (%) Non-exposed during pregnancy (<i>N</i> = 33 047)	<i>P</i> -value
Child characteristics			
Male gender	263 (53.8)	17 131 (51.8)	0.393
Mean age at index date first allergic disease (years)	1.8 ± 0.16	2.0 ± 0.02	NA
Use of acid-suppressive drugs	25 (5.1)	549 (1.7)	<0.001
Mother characteristics			
Mean age in years	31.4 ± 0.26	30.0 ± 0.03	<0.001
Presence of allergic disease	80 (16.4)	3097 (9.4)	<0.001
Atopic dermatitis	38 (7.8)	1854 (5.6)	0.040
Asthma	31 (6.3)	794 (2.4)	<0.001
Allergic rhinitis	25 (5.1)	732 (2.2)	<0.001
Use of antibiotics during pregnancy	187 (38.2)	6628 (20.1)	<0.001
Father characteristics			
Data present*	279 (57.1)	18 340 (55.5)	0.491
Presence of allergic disease	37 (13.3)	2114 (11.5)	0.368
Atopic dermatitis	17 (6.1)	1095 (6.0)	0.932
Asthma	9 (3.2)	554 (3.0)	0.843
Allergic rhinitis	13 (4.7)	686 (3.7)	0.423

*Data on fathers were missing for 14 917 pregnancies.

diseases in the mother, maternal use of antibiotics and the use of acid-suppressive drugs in the child were higher amongst exposed compared to non-exposed chil-

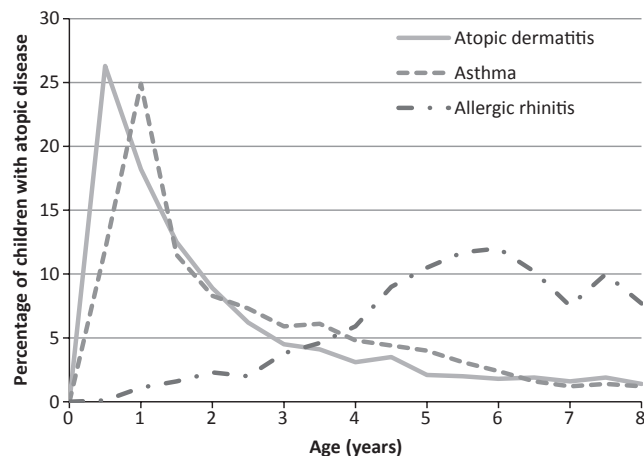


Fig. 2. Age distribution of case children when first identified with the atopic diseases atopic dermatitis, asthma or allergic rhinitis.

dren. Gender of the child and allergic disease in the father was similarly distributed between exposed and non-exposed children. (Table 1) The maximum follow-up time was 8 years, with a median follow-up of 4.9 years. During follow-up, 8603 (25.7%) children suffered from a medically treated allergic disease, 5679 (16.9%) had atopic dermatitis, 3702 (11.0%) had asthma, 690 (2.1%) had allergic rhinitis and 1348 (4.0%) had more than one medically treated allergic disease. The age distribution of children when first identified with atopic diseases atopic dermatitis, asthma or allergic rhinitis is presented in figure 2. The distribu-

tion of the covariates between children with and without an allergic disease is described in Appendix I.

Amongst the children with PPI or H2A exposure during pregnancy, 30.1% developed an allergic disease vs. 25.6% of the children without exposure. After adjustments for other potential risk factors, the risk for the development of any allergic disease was 37% higher (aHR: 1.37 95% CI: 1.14–1.66) in children exposed to PPIs or H2As than in unexposed children. Analysis according to H2A exposure showed an increased risk of developing any allergic disease amongst exposed children (aHR: 1.52 95% CI: 1.11–2.09). Although confidence intervals were overlapping, the risk of developing an allergic disease was lower after PPI exposure than after H2A exposure (aHR: 1.25 95% CI: 0.98–1.59). The risk of any allergic disease was approximately the same after exposure to more or less than 15 DDDs of PPIs and/or H2As during pregnancy. When examining the risk of allergic disease for the different trimesters of exposure, the risk was higher for children exposed in third trimester compared with children exposed in first and/or second trimester (table 2).

The presence of allergic diseases in the mother was twice as high amongst exposed pregnancies than unexposed pregnancies (Table 1), but adjustment of the crude HR [1.51 (95% CI 1.25–1.82)] for allergic disease in the mother showed little effect [aHR 1.46 (95%CI 1.46 (1.21–1.76)].

After adjustment for allergic disease in the father in the subset of children where paternal data were present ($N = 18\ 619$), the crude HR for the development of any

Table 2. Risks of allergic disease in children according to mother's exposure to acid-suppressive drugs (H2A and PPI's) during pregnancy

	N	Children with outcome n (%)	IR (per 1000 PY)	HR (95% CI)	aHR (95% CI) [†]
Non-exposed (Reference)	33 047	8456 (25.6)	52.4	1.00	1.00
Exposure to acid-suppressive drug (H2A and PPI)	489	147 (30.1)	84.9	1.51 (1.25–1.82)	1.37 (1.14–1.66)
H2As*	150	53 (35.3)	83.6	1.57 (1.14–2.15)	1.52 (1.11–2.09)
PPI*	319	85 (26.6)	84.6	1.42 (1.12–1.81)	1.25 (0.98–1.59)
Number of DDDs					
0–15 DDD	151	49 (32.5)	84.0	1.57 (1.13–2.17)	1.42 (1.03–1.93)
>15 DDD	338	98 (29.0)	85.5	1.49 (1.18–1.87)	1.36 (1.08–1.71)
Time of exposure					
Trimester 1 + 2	208	66 (31.7)	80.1	1.46 (1.10–1.93)	1.34 (1.02–1.77)
Trimester 3	156	48 (30.8)	101.2	1.71 (1.24–2.38)	1.58 (1.14–2.19)

IR, Incidence rate; HR, hazard ratio; aHR, adjusted hazard ratio, H2A; histamine-2-antagonists; PPI, proton pump inhibitor; DDD, defined daily dose.

*In some pregnancies, more than one subgroup of drugs was prescribed.

[†]Adjusted for birth year, gender, use of acid-suppressive drugs by the child, age of the mother at giving birth, maternal use of systemic antibiotics during pregnancy and allergic disease in the mother.

allergic disease was 1.35 (95% CI: 1.06–1.71) and the aHR was 1.34 (1.06–1.70) after exposure to PPIs and/or H2As during pregnancy. The analysis of paternal exposure during pregnancy showed no increase in the risk of the development of any allergic disease (HR 1.04 95% CI 0.91–1.19).

The aHRs for the development of the separate allergic diseases after prenatal exposure to PPIs and/or H2As were 1.32 (95% CI 1.06–1.64), 1.57 (95% CI 1.20–2.05) and 2.40 (95% CI 1.42–4.04) for atopic dermatitis, asthma and allergic rhinitis, respectively. The aHR for having asthma after the age of 5 after prenatal exposure to PPIs and/or H2As was even higher 2.59 (95% CI 1.69–3.95). When examining exposure to different amounts of DDDs, only the risks for developing asthma were elevated amongst children exposed to more than 15 DDDs compared with children exposed to 15 DDDs or less. When we examined the trimesters of exposure, the risks for the development of atopic dermatitis and allergic rhinitis were elevated amongst children exposed in third trimester compared with children exposed in first and/or second trimester. Analysis according to sub-type of acid-suppressive drugs yielded higher risks for the development of atopic dermatitis and asthma in children exposed to H2As compared with children exposed to PPIs during pregnancy (Table 3).

In the analyses where we restricted the outcome to children with two or more allergic diseases and to children with three allergic diseases, the aHRs were 2.13 (95% CI: 1.43–3.19) and 5.18 (2.16–12.42), respectively (data not shown).

Discussion

In this prescription-based cohort study, prenatal exposure to acid-suppressive drugs such as PPIs and H2As was associated with an increased risk of the development of any allergic disease in the offspring. Comparable increases in risk were also found for the development of the separate allergic diseases after prenatal exposure to PPI and/or H2As. Associations between acid-suppressive drugs and the development of atopic diseases were even stronger in children who developed multiple atopic diseases.

Our study has strengths and limitations. The data were obtained from a widely researched prescription database with proven accuracy of prescription rates amongst community-dwelling adults and high accuracy of the identification of mother–infant pairs, hence potential influence of information bias is likely minimal [14]. Recall bias with respect to maternal use of medication is not present because medication was measured by dispensed prescriptions. Apart from these strengths, potential limitations that are inherent to observational studies with prescription databases need

to be considered when interpreting these findings. The database contains information on the dispensing of drugs, including information about the dose and the dispensing date. However, whether these drugs were actually taken by the mothers is unknown and may have led to misclassification of exposure status. Furthermore, because information on the conception date was unavailable to the researchers, in accordance with other pregnancy studies [29], we applied a standardized period of 273 days to define the pregnancy duration.

Such standardization may also have led to some misclassification of exposure, especially in the first trimester that may have resulted in an overestimation or underestimation of actual use. Furthermore, no information about the use of OTC drugs that are not dispensed on prescription is present in the database, which may have led to an underestimation of actual use. A recent study from Verstappen et al. [30] showed that only 12.5% of pregnant women use OTC medication and only 2.7% use gastrointestinal tract medication without a prescription. This includes acid-suppressive drugs like H2As and PPIs but mainly consists of the use of antacids. So missing information on OTC use of acid-suppressive drugs should not have materially affected the results of our study.

Another limitation of the prescription database is the lack of the clinical indications for which the drugs are prescribed. Case status was determined by drugs prescribed for allergic diseases according to Dutch General Practitioner Guidelines [16–18]. Validation studies have shown that defining allergic diseases like asthma with the aid of prescriptions results in an accurate and reliable selection of asthma cases [19]. We decided for reasons of causality assessments to only include prescriptions for corticosteroids to contrast with controls who had no drugs for allergic diseases. Because of these specific measurements, some mild cases may have been missed, but that should not have materially affected the results of our study. In addition, the study of TW de Vries et al. used the same criteria for the identification of children with allergic diseases [19]. This study also showed that these criteria detect especially children with more severe symptoms that need drug treatment.

Inherent to observational studies, those mothers who received prescriptions for acid-suppressive drugs may have been different in their risks of having a child who develops an allergic diseases than those who were unexposed, which may have led to confounding. Prior to the present study, we obtained information on important risk factors from the literature [3, 24–27]. Although we adjusted the analyses for measured risk factors for the development of allergic diseases and adjustments led to only relatively small changes in the effect esti-

Table 3. Hazard ratios for the development of atopic dermatitis, asthma and allergic rhinitis in children after exposure to acid-suppressive drugs (PPI's and/or H2As) during pregnancy

	<i>N</i>	Children with outcome <i>n</i> (%)	IR (per 1000 PY)	HR (95% CI)	aHR (95% CI) [†]
Atopic dermatitis					
Reference	33 047	5581 (16.9)	31.9	1.00	1.00
Exposure to acid-suppressive drugs (H2A and PPI)	489	98 (20.0)	50.0	1.47 (1.18–1.83)	1.32 (1.06–1.64)
H2As*	150	34 (22.7)	46.8	1.45 (1.00–2.10)	1.42 (0.98–2.06)
PPI*	319	59 (18.5)	52.4	1.46 (1.10–1.93)	1.24 (0.94–1.65)
Number of DDDs					
0–15 DDDs	151	34 (22.5)	52.3	1.57 (1.08–2.27)	1.42 (0.98–2.05)
>15 DDDs	338	64 (18.9)	48.8	1.42 (1.08–1.85)	1.27 (0.97–1.66)
Time of exposure					
Trimester 1 + 2	208	40 (19.2)	42.4	1.29 (0.92–1.80)	1.17 (0.83–1.64)
Trimester 3	156	36 (23.1)	68.1	1.87 (1.30–2.70)	1.68 (1.17–2.41)
Asthma					
Reference	33 047	3630 (11.0)	19.9	1.00	1.00
Exposure to acid-suppressive drugs (H2A & PPI)	489	72 (14.7)	36.0	1.67 (1.27–2.19)	1.57 (1.20–2.05)
H2As*	150	29 (19.3)	39.3	1.99 (1.28–3.09)	1.93 (1.25–3.00)
PPI*	319	39 (12.2)	33.7	1.46 (1.02–2.08)	1.35 (0.94–1.94)
Number of DDDs					
0–15 DDDs	151	21 (13.9)	30.3	1.50 (0.91–2.45)	1.37 (0.84–2.25)
>15 DDDs	338	51 (15.1)	39.0	1.77 (1.28–2.45)	1.68 (1.21–2.32)
Time of exposure					
Trimester 1 + 2	208	36 (17.3)	37.6	1.76 (1.20–2.59)	1.64 (1.12–2.41)
Trimester 3	156	17 (10.9)	29.4	1.33 (0.78–2.29)	1.32 (0.77–2.25)
Allergic rhinitis					
Reference	33 047	672 (2.0)	3.4	1.00	1.00
Exposure to acid-suppressive drugs (H2A and PPI)	489	18 (3.7)	7.9	2.79 (1.65–4.70)	2.40 (1.42–4.04)
H2As*	150	6 (4.0)	7.0	2.11 (0.88–5.04)	1.88 (0.78–4.51)
PPI*	319	12 (3.8)	9.2	3.73 (1.94–7.15)	3.13 (1.63–6.00)
Number of DDDs					
0–15 DDDs	151	8 (5.3)	10.4	3.48 (1.59–7.61)	2.87 (1.31–6.29)
>15 DDDs	338	10 (3.0)	6.6	2.39 (1.21–4.73)	2.12 (1.06–4.24)
Time of exposure					
Trimester 1 + 2	208	8 (3.8)	7.2	2.25 (1.06–4.76)	1.94 (0.91–4.14)
Trimester 3	156	5 (3.2)	7.8	2.91 (1.10–7.66)	2.62 (0.99–6.95)

HR, hazard ratio; aHR, adjusted hazard ratio; H2A, histamine-2-antagonists; PPI, proton pump inhibitor; DDD, defined daily dose.

*In few pregnancies, more than one subgroup of drugs was prescribed.

†Adjusted for birth year, gender, use of acid-suppressive drugs by the child, age of the mother at giving birth, maternal use of systemic antibiotics during pregnancy and allergic disease in the mother.

mates, we had no information about other potential risk factors like socio-economic status, maternal smoking in pregnancy, birth order/parity or perinatal factors such as gestational age/birth weight. So we cannot rule out unknown and unmeasured confounding.

Recent publications from our group described the association between prenatal exposure to acid-suppressive drugs and the development of childhood asthma using a crossover design [9, 10]. In these studies, children with asthma were compared with their own siblings without asthma, to control for potential confounding influences. Both studies showed that the influences of potential confounding had minimal impact on the association between acid-suppressive drugs and childhood asthma.

Causality of these associations needs to be further supported by prospective studies and studies looking at the potential mechanisms.

The observed associations between prenatal exposure to acid-suppressive drugs and asthma are consistent with previous conducted studies [6–10]. The associations between prenatal exposure to acid-suppressive drugs and the development of atopic dermatitis and allergic rhinitis however have not been previously established. The mechanisms by which acid-suppressive drugs may actually cause allergic diseases are not known. It has been suggested that acid-suppressive drugs interfere with normal digestion of peptides in the adult stomach, resulting in the preservation of antigens [31–33]. If transferred to the fetus, these anti-

gens could induce a Th2-dominant immune response and allergic sensitization of the fetus [34]. The development of the fetal immune system is also influenced by the allergic state of the mother. Maternal IgE can cross fetal membranes, and a Th2-dominant phenotype of the mother could promote an allergy-prone phenotype in the fetus [35]. The fetal immune systems start early with its development but matures mainly in later trimesters, which corresponds with our results, except for the association with asthma [36]. It would be expected that the risk for allergic diseases would be higher when children are exposed to larger amounts or long-term use of the drugs, but this was not found for any of the allergic diseases. The fact that there was no difference in risk measured between the different doses of H2As and PPIs does not necessarily mean that there is no dose-response effect. These analyses were considered explorative, and statistical power for these subgroup analyses was inadequate to detect potential differences between the two groups; 95% CIs were largely overlapping.

Although gastroesophageal reflux disease is common in up to 80% of the pregnancies, the use of H2As and/or PPIs is low in this study (1.5%). It is likely that these exposed cases were the more severe cases of reflux disease.

Paternal exposure to acid-suppressive drugs showed no increase in risk for the development of allergic diseases in children. With a causal intrauterine effect, no independent association should be observed between paternal exposure to PPIs and H2As during pregnancy and the development of any allergic disease [15]. If the association was due to confounding factors as genetic, social environmental or household-level confounders, the risk of the development of allergic diseases could be increased after paternal exposure during pregnancy.

Recent studies suggested a potential relationship between prenatal exposure to antibiotics and subsequent development of asthma [3]. In the current study, antibiotic use was classified as either present or not present. We did not refine antibiotic use into specific drug classes or duration of use because the majority of the antibiotics prescribed were nitrofurantoin and amoxicillin (77.5%) and were prescribed for short-term use (79%), and the addition of antibiotic use to the multivariate regression model did not materially change the result (aHRs changed <5%).

In conclusion, we found an increased risk of allergic diseases in the offspring of women after prenatal exposure to acid-suppressive drugs, such as PPIs and H2As compared to non-exposed children. The association was strongest in children who developed allergic rhinitis or multiple allergic diseases. Because our study has limitations inherent to the design,

prospective studies are now warranted to confirm our findings.

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Authors' contributions

BM participated in the design of the study, performed the study, analysed and interpreted the data and drafted the manuscript; CCMSV participated in the design of the study as an expert in pharmaceutical research and reviewed the analyses and manuscript; JHB was responsible for the data retrieval from the IADB.nl database and reviewed the manuscript; TWdV participated in the design of the study as an expert in paediatric asthma and reviewed the manuscript; SSJ reviewed the manuscript; EH initiated and designed the study, and supervised the data collection, analysis and report. All authors commented on the manuscript and approved the final manuscript.

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Competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: they had support from the department of Pharmacy, University Groningen, for the submitted work; no financial relationships with any organization that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval

Ethical approval for observational studies with anonymized data from IADB.nl is waived in the Netherlands. The University Groningen IADB.nl prescription database collects and stores data according to the Dutch law on privacy.

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Appendix 1. Distribution of covariates between children with allergic diseases and children without an allergic disease

	n (%)				
	Any allergic disease [‡] N = 8603	Atopic dermatitis N = 5679	Asthma N = 3702	Allergic rhinitis N = 690	No allergic disease N = 24 933
Child characteristics					
Male gender	4884 (56.8) [†]	3091 (54.4) [†]	2309 (62.4) [†]	430 (62.3) [†]	12 510 (50.2)
Use of acid-suppressive drugs	133 (1.5)	80 (1.4)	81 (2.2)	10 (1.4)	441 (1.8)
Mother characteristics					
Mean age in years	29.8 [†]	29.8 [†]	29.7 [†]	30.2	30.0
Presence of allergic disease	1097 (12.8) [†]	720 (12.7) [†]	506 (13.7) [†]	101 (14.6) [†]	2080 (8.3)
Atopic dermatitis	655 (7.6) [†]	471 (8.3) [†]	260 (7.0) [†]	55 (8.0) [†]	1237 (5.0)
Asthma	302 (3.5) [†]	172 (3.0) [†]	178 (4.8) [†]	27 (3.9) [†]	523 (2.1)
Allergic rhinitis	252 (2.9) [†]	146 (2.6) [†]	127 (3.4) [*]	35 (5.1) [†]	505 (2.0)
Use of antibiotics during pregnancy	2072 (24.1) [†]	1324 (23.3) [†]	962 (26.0) [†]	189 (27.4) [†]	4743 (19.0)
Father characteristics					
Data present	5311 [†]	3404 [†]	2391 [†]	435 [†]	13 308
Presence of allergic disease	737 (13.9) [†]	487 (14.3) [†]	351 (14.7) [†]	70 (16.1) [†]	1414 (10.6)
Atopic dermatitis	376 (7.1) [†]	264 (7.8)	156 (6.5) [†]	32 (7.4)	736 (5.5)
Asthma	230 (4.3) [†]	148 (4.3) [†]	126 (5.3) [†]	20 (4.6) [†]	333 (2.5)
Allergic rhinitis	236 (4.4) [†]	151 (4.4) [†]	117 (4.9) [†]	28 (6.4) [†]	463 (3.5)

^{*}P-value <0.05.

[†]P-value <0.01.

[‡]Children can have multiple allergic diseases.