

Letter to the Editor

Acid-suppressive drug use in pregnancy and the toddler's asthma risk: A crossover, case-control study

To the Editor:

Acid-suppressive drugs (ASDs) are considered effective and safe to use during pregnancy to treat gastroesophageal reflux disease. Three recent studies reported a causal relation between prenatal exposure to ASDs and the development of childhood asthma, but unmeasured confounding could not be ruled out.¹⁻³ We applied a bidirectional case-crossover design to minimize time-invariant confounding influences using siblings from the same mother as control subjects and compared our findings with those of a case-control design.

The studies were performed with data from a pregnancy database as part of the University Groningen IADB.nl pharmacy prescription database (for more information, see the [Methods](#) section in this article's Online Repository at www.jacionline.org).⁴ Because case-crossover designs can be vulnerable to time trends, we first examined the time trend in exposure to ASDs (Anatomical Therapeutic Chemical [ATC] code A02B) among all registered singleton pregnancies in the database between 1995 and 2006. For both the bidirectional case-crossover and case-control designs, the study population was restricted to toddlers of singleton birth between 1995 and 2006 who could be followed in the database for at least 5.5 years since birth. In both analyses 1253 toddlers who started a minimum of 2 prescriptions for asthma medication (ATC code R03) during a 6-month period before their fifth birthday were selected as cases.^{5,6} In the case-crossover and case-control study, 1253 siblings of the cases and 8771 toddlers born to different mothers than the cases without any asthma prescriptions before their fifth birthday were selected as control subjects, respectively. Control subjects were matched to cases on birth date and maternal age at delivery. Maternal exposure was defined as receiving at least 1 prescription for an ASD (ATC group A02B) during pregnancy. Exposure was also examined as 14 defined daily doses (DDDs) or less or greater than 14 DDDs.

We applied conditional logistic regression to obtain odds ratios (ORs) and their corresponding 95% CIs. Potential confounders were the age of the mother at birth, maternal asthma, sex of the child, sequence of birth, and use of ASDs by the child. Covariates were treated as confounders in a multivariable conditional logistic regression model in cases of a significant ($P < .05$) association with the outcome and exposure status.⁷

The time-trend analysis over the study period 1995-2006 showed no appreciable trends, with an average exposure to ASDs of 3.1% in 30,955 pregnancies (range, 2.5% in 2004 to 4.5% in 1998; [Fig 1](#)), and data were similar for control pregnancies in both analyses (data on file). In the case-crossover study none of the measured covariates were confounders, and prenatal exposure to ASDs was associated with a statistically significant increased odds of having toddler's asthma of 85% (1.85; 95% CI, 1.07-3.19; [Table I](#)). Exposure to more than 14 DDDs of any ASD increased the odds of having toddler's asthma by 156% (OR, 2.56; 95% CI, 1.18-5.52). The mean duration of ASD exposure in the group with greater than 14 DDDs was 40 ± 5.5 days. In the case-control study only the covariate of maternal

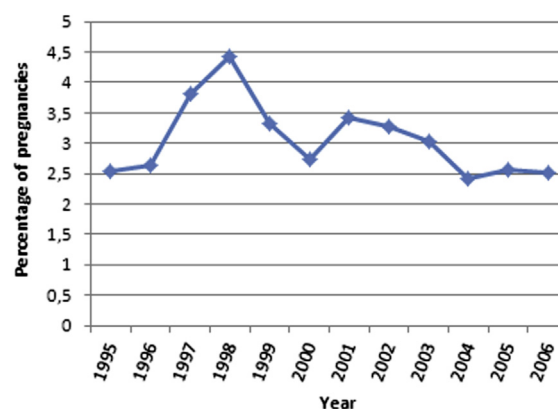


FIG 1. Percentage of pregnancies exposed to any ASD during pregnancy over the study years (1995-2006).

age at birth was a confounder. After adjustment for this covariate, prenatal exposure to ASDs statistically significantly increased the odds of having toddler's asthma by 52% (adjusted OR, 1.52; 95% CI, 1.11-2.09). Exposure to more than 14 DDDs of any ASD increased the odds of having toddler's asthma to 89% (adjusted OR, 1.89; 95% CI, 1.24-2.88).

Prenatal exposure to ASDs appeared to be associated with a substantially increased risk of toddler's asthma in both the bidirectional case-crossover (85%) and case-control (52%) analysis. A major strength of the present study is the consistency of findings in both applied study designs. The case-crossover design minimizes the potential influence of time-invariant confounders that are potentially strong risk factors for asthma development, such as smoking behavior or genetic predisposition for asthma or other comorbid conditions that might increase the child's risk of asthma. Primary results from both the case-crossover and case-control studies showed largely overlapping CIs, indicating that the influence of potential confounding is likely small. Data were obtained from a widely researched prescription database with proved accuracy of prescription rates and high accuracy of the identification of mother-infant pairs, which reduced the potential for information bias. Selection bias during follow-up of the toddlers is also unlikely because the study population was restricted to toddlers who could be followed in the database for at least 5.5 years.

A limitation of this study is that it is unknown whether the prescribed drugs were actually taken, which risks the misclassification of exposure. Also, because the actual conception date was not known, misclassification of exposure might have resulted in an overestimation of actual use. No information about the use of over-the-counter drugs is present in the database, which might have led to an underestimation of actual use. However, we believe that these potential misclassifications of exposure are likely random, which might have biased our findings toward a null finding. Another limitation is the lack of diagnostic information. Making an asthma diagnosis in toddlers is difficult, and we therefore defined toddlers as having toddler's asthma based on their prescribed drugs.^{5,6}

The validity of previous reported results are supported by our study because we showed the minimal influence of confounding

TABLE I. Conditional ORs for the development of toddler's asthma after exposure to ASDs during pregnancy in the case-crossover and case-control analysis

	Case-crossover study			Case-control study			
	Cases, no. (%) n = 1253	Control subjects, no. (%) n = 1253	Conditional OR (95% CI)	Cases, no. (%) n = 1253	Control subjects, no. (%) n = 8771	Conditional OR (95% CI)	Adjusted conditional OR (95% CI)*
Exposure to ASDs†	48 (3.8)	31 (2.5)	1.85 (1.07-3.19)	48 (3.8)	225 (2.6)	1.51 (1.10-2.08)	1.52 (1.11-2.10)
No. of DDDs							
0-14	20 (1.6)	17 (1.4)	1.19 (0.61-2.31)	20 (1.6)	120 (1.4)	1.17 (0.73-1.89)	1.18 (0.73-1.91)
>14	28 (2.2)	14 (1.1)	2.56 (1.18-5.52)	28 (2.2)	105 (1.2)	1.88 (1.24-2.87)	1.89 (1.24-2.88)

*Adjusted for age of the mother when giving birth.

†ASDs include proton pump inhibitors, histamine 2 antagonists, prostaglandins, combinations for eradication of *Helicobacter pylori*, and other drugs for peptic ulcer and gastroesophageal reflux disease.

in these associations. Although the mechanism behind the association is not entirely clear, ASDs can interfere with denaturation of food antigens, resulting in allergic sensitization and possibly asthma.⁸ This hypothesis is supported by a study in pregnant mice showing a T_H2-dominant immune response in the offspring caused by gastric acid suppression.⁹ This condition might predispose to allergies and asthma. This hypothesis seems likely given our results that the associations were significant, especially during later trimesters in which the immune system is particularly developing. However, more study, for example of the mechanism or development of other atopic conditions in relation to ASD, is now warranted, and the benefit-risk balance of such drugs should be reconsidered in pregnancy.

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METHODS

Description of the IADB.nl pregnancy database

The University Groningen IADB.nl pharmacy prescription database contains prescription data from 1994 until 2011 from approximately 55 community pharmacies and covers an estimated population of 600,000 patients. Registration in the database is irrespective of health care insurance, and age, sex, and prescription rates among the database population have been found to be representative for The Netherlands as a whole. In addition, the database is widely researched. 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 ATC code. Each patient has a unique anonymous identifier; date of birth and sex are known. Because of the high patient-pharmacy commitment in The Netherlands, the medication records for each patient are virtually complete, except for over-the-counter drugs and medication dispensed during hospitalizations.

For the present study, data were obtained from a large mother-infant subset extracted from the main IADB.nl database and referred to as the pregnancy IADB database. The pregnancy IADB database contains the prescription data from nearly 40,000 infants born between 1995 and 2011 and their mothers. The mother is linked to her infant by using an address code. A female subject between 15 and 50 years of age and living at the same address as the infant is identified as the mother. Infants could not be linked to their mothers if the mother had a separate address registration number than the infant or the mother was registered with another pharmacy. If 2 female subjects within this age range were living at the same address, no mother was selected, and the mother-infant pair was not registered in the pregnancy database. Also, all found mothers who registered later than 50 weeks before the birthday of the child were excluded because registration of possible drug use would not be complete for the period of interest.

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. Validation of the method used to link infants to their mothers is

extensively described in the study by Schirm et al.^{E1} Pregnancies could not be identified if these resulted in a spontaneous or induced abortion, a stillbirth, or an early neonatal death; if the infant was (still) unregistered within a participating pharmacy; or if 2 or more women between the ages of 15 and 40 years lived at the same address. Because the actual duration of the pregnancy was unknown, the theoretic conception date was determined as the date of birth minus 273 days. Therefore the length of pregnancy is standardized at 39 weeks or 3 trimesters of 13 weeks each.

Subgroup analysis

In the case-crossover analysis we examined the numbers of pregnant women who only used the drugs during pregnancy and women who used these drugs before, during, and after pregnancy. Only 5 women were exposed to ASDs 3 months before and during pregnancy. Exposure to ASDs before and during pregnancy resulted in an imprecise lower OR of 0.667 (95% CI, 0.111-3.990) for the development of asthma in the offspring. Information of drug use in the 3 months before pregnancy was missing for 259 pregnancies. Seventy-four pregnancies were exposed only during pregnancy. Exposure only during pregnancy resulted in an OR of 2.000 (95% CI, 1.136-3.522) for the development of asthma in the offspring, which agrees with the main result. Only 3 women were exposed to ASDs during and 3 months after pregnancy. Exposure to ASDs during and after pregnancy resulted in an OR of 0.500 (95% CI, 0.045-5.514) for the development of asthma in the offspring. Exposure to ASDs only in the 3 months after pregnancy resulted in an OR of 1.200 (95% CI, 0.366-3.932). Therefore we can conclude that the effect is due to the drug and not some underlying condition or health behavior.

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