Acid-Suppressive Drug Use During Pregnancy and the Risk of Childhood Asthma: A Meta-analysis

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abstract

CONTEXT: The association between acid-suppressive drug exposure during pregnancy and childhood asthma has not been well established.

OBJECTIVE: To conduct a systematic review and meta-analysis on this association to provide further justification for the current studies.

DATA SOURCES: We searched PubMed, Medline, Embase, the Cochrane Database of Systematic Reviews, EBSCO Information Services, Web of Science, and Google Scholar from inception until June 2017.

STUDY SELECTION: Observational studies in which researchers assessed acid-suppressive drug use during pregnancy and the risk of childhood asthma were included.

DATA EXTRACTION: Of 556 screened articles, 8 population-based studies were included in the final analyses.

RESULTS: When all the studies were pooled, acid-suppressive drug use in pregnancy was associated with an increased risk of asthma in childhood (relative risk [RR] = 1.45; 95% confidence interval [CI] 1.35–1.56; I^2 = 0%; P < .00001). The overall risk of asthma in childhood increased among proton pump inhibitor users (RR = 1.34; 95% CI 1.18–1.52; I^2 = 46%; P < .00001) and histamine-2 receptor antagonist users (RR = 1.57; 95% CI 1.46–1.69; I^2 = 0%; P < .00001).

LIMITATIONS: None of the researchers in the studies in this meta-analysis adjusted for the full panel of known confounders in these associations.

CONCLUSIONS: The evidence suggests that prenatal, maternal, acid-suppressive drug use is associated with an increased risk of childhood asthma. This information may help clinicians and parents to use caution when deciding whether to take acid-suppressing drugs during pregnancy because of the risk of asthma in offspring.

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Dr Lai conceptualized and designed the study, drafted the initial manuscript, and interpreted the data; Dr Wu conducted the initial analyses and drafted the initial manuscript; Drs Liu, Luo, and He conducted the initial analyses; Dr Wang conducted the initial analyses and reviewed the manuscript; Prof Wu conceptualized the study and interpreted the data; Prof Ying conceptualized and designed the study and supervised the analysis; Prof Chen conducted the meta-analyses, interpreted the data, and reviewed the manuscript; Prof Li conducted the meta-analyses and interpreted the data; Prof Shen conceptualized and designed the study, supervised the analysis, and interpreted the data; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Asthma is a chronic and complex disease that is characterized by recurring expiratory dyspnea, chronic airway inflammation, airway hyperresponsiveness, and airway remodeling. It is estimated that ~300 million people worldwide have asthma, and the prevalence of asthma continues to increase.[1,2] The propensity to develop asthma or allergy is at least partially established before birth because of the interplay between environmental exposures and genetic predisposition.[3–5] Major efforts have recently focused on the identification of risk factors for the development of allergy, particularly in children.[5]

Acid-suppressive drugs are considered effective and safe to use during pregnancy to treat gastroesophageal reflux disease (GERD), a common complication that is reported with up to 80% of pregnancies.[6,7] In adults, acid-suppressive drugs may alleviate asthma in patients with GERD,[8] but the drugs are also associated with allergic sensitization. Pali-Schöll and Jensen-Jarolim[9] showed that the impairment of gastric function is a documented risk factor for sensitization against oral proteins and drugs. Schöll et al[10] showed that antiacid treatment in pregnant mice could be responsible for the increasing number of sensitizations against food allergens in their offspring. Dehlink et al[11] indicated that acid-suppressive drugs may interfere with the denaturation of food antigens in the stomach, making food proteins act like allergens and causing a T helper cell 2 cytokine dominance, which may result in subsequent sensitization of the immune system.

An increasing number of researchers in epidemiologic studies have now investigated the impact of prenatal exposure to acid-suppressive medications on the risk of childhood asthma but have gotten inconsistent results.[11–18] Dehlink et al[11] and Andersen et al[12] observed that prenatal exposure to both proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H_2RAs) was associated with an increased risk of asthma.[11–17] In contrast, Cea Soriano et al[18] observed no association between prenatal exposure to PPIs and asthma in childhood after adjusting for confounding variables. These studies were designed as retrospective cohorts or case controls. The risk of bias within studies was strong because of weaknesses in the study design, such as selection bias, confounding, exposure assessment, and outcome assessment. The limitations of each of the included articles are shown in Table 1. The confounders, such as maternal allergy or asthma, maternal smoking, and maternal antibiotic use, could be related to an increased risk of asthma in offspring. Moreover, previous studies have shown that GERD is associated with asthma in adults because of the inflammatory effects on the upper and lower airways caused by reflux material.[12,19] Asthma in the offspring could be due to GERD (eg, indication) rather than the treatment of GERD. Thus, GERD may be confounding the association of acid suppression in pregnancy and childhood asthma. Given the widespread use of gastric acid–suppressing medications during pregnancy, their role in the development of asthma and allergic disorders in the offspring raises a potential public health concern. A comprehensive synthesis of the available primary studies is required to understand the emerging evidence. Bringing together all the relevant data can clarify the underlying role of acid-suppressive medications in the development of asthma and allergy, which would eventually provide the opportunity for initiating primary prevention interventions. To comprehensively evaluate the evidence relating to these issues, we conducted a systematic review and meta-analysis of the relevant epidemiologic literature and quantified whether the use of acid-suppressive drugs during pregnancy is associated with an increased risk of childhood asthma.

METHODS

Data Sources and Search Strategy

A systematic review of published studies and a meta-analysis of retrospective cohort studies was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.[20] We conducted a search for journal studies published in English, which included all studies until June 2017, by using the medical databases PubMed, Medline, Embase, EBSCO Information Services, Web of Science, Google Scholar, and the Cochrane Database of Systematic Reviews. The following search terms were applied in the search for eligible studies: ("Proton pump inhibitor" or "H2 blockers" or "H2 receptor antagonist" or "acid-suppressive drugs") and "child asthma" and "pregnancy." To ensure a complete review of the available studies, we scanned the reference lists of eligible articles as well as the relevant systematic review articles returned in the search and examined the abstracts of relevant scientific meetings. We also made efforts to contact authors in cases in which relevant data were unclear.

Selection Criteria

We included case control studies, case-crossover studies, and cohort studies in which researchers investigated the association between the use of acid-suppressive drugs during pregnancy and the risk of childhood asthma, which reported an adjusted odds ratio (OR) or relative risk (RR) and the corresponding 95% confidence interval (CI). We only selected articles that were written in English and excluded studies with no available data for outcome measures.

TABLE 1 The Limitations of Each of the Included Articles

Source	Limitations
Dehlink et al[11]	The study did not show a change in the OR for developing allergy in allergic mothers on acid-suppressive treatment. The no. cases for subanalysis might have been too small to reach statistical significance. The study lacked information on the subsequent social and medical histories of the children. The study did not address GERD and may be confounding the association.
Andersen et al[12]	The study cannot remove the potential effect of exposure through breastfeeding because such data are not recorded in the routine registries in Denmark. The study did not address GERD and may be confounding the association.
Mulder et al[13]	The database contains information on the dispensing of drugs, including information about the dose and dispensing date. However, whether these drugs were actually taken by the mothers is unknown and may have led to a misclassification of exposure status. The prescription database lacked the clinical indications for which the drugs are prescribed. The authors had no information about potential risk factors, such as maternal smoking in pregnancy, birth order and/or parity, or perinatal factors, such as gestational age and/or birth wt. They cannot rule out unknown and unmeasured confounding. The study did not address GERD and may be confounding the association.
Källén et al[15]	Some nonasthmatic children may have been included, although antiasthmatic drugs had been prescribed. The use of antibiotics and cough medicines gave increased risk estimates, which declined when indicators of maternal asthma were considered. It may involve incomplete identification of concomitant drug use or maternal asthma. The study did not address GERD and may be confounding the association.
Yitshak-Sade et al[14]	The main possible bias in the study was confounding by indication, which was supported by a statistically significant association between maternal consumption of the medications 2 y after delivery and childhood asthma. Residual confounding factors associated with asthma could exist in their databases. There was a possibility of misclassification of the outcome at study.
Cea Soriano et al[18]	The possible misclassification of maternal exposure to acid-suppressing drugs; Residual confounding by unmeasured and unknown risk factors could be biasing the estimates upward.
Hak et al[16]	Although ORs were materially elevated for PPIs and H_2RAs, the OR was smaller overall, which suggests a class effect, but the study had inadequate statistical power to formally test this. It is possible that the study missed some children who had undiagnosed asthma because some children did not seek medical attention or had mild asthma not treated chronically, as was required by the study definition including drug treatment. The study did not address GERD and may be confounding the association.
Mulder et al[17]	It is unknown whether the prescribed drugs were actually taken, which risks the misclassification of exposure. 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. There was a lack of diagnostic information. The study did not address GERD and may be confounding the association.

Quality Assessment

Methodological quality was evaluated by using the Newcastle-Ottawa scale (NOS) for quality assessment for the included studies.[21] In this study, we assigned scores of 0 to 3, 4 to 6, and 7 to 9 for low, moderate, and high quality of studies, respectively. A star system (a score range from 0 to 9) was developed for quality assessment according to the NOS.

Data Extraction

We independently evaluated all the studies that were retrieved from the databases and bibliographies and met the inclusion criteria described above. Titles and abstracts were independently reviewed by 2 reviewers (T. W. L. and M. D. W.) to determine their potential relevance. Any disagreements were resolved by consensus with a third reviewer when necessary. For each study, we extracted data by using a data extraction form that included author, year, study design, country, study period, sample size, and database.

Statistical Analysis

We used RRs and 95% CIs for the meta-analysis to analyze the association between the use of acid-suppressive drugs during pregnancy and the risk of childhood asthma. Heterogeneity across the studies was assessed by using the I^2 statistic. I^2 values of 25%, 50%, and 75% represent low, moderate, and high heterogeneity, respectively. When heterogeneity was found, we conducted sensitivity analyses by removing each study from the analysis to assess the changes in the I^2 values and determine which studies contributed most significantly to the heterogeneity.[22] We used Egger's test and Begg's test for publication bias. All analyses were performed by using Review Manager version 5.3 (The Cochrane Collaboration, London, United Kingdom) and Stata/SE 12.0 (StataCorp, College Station, TX). A P value of <.05 was considered to be statistically significant.

RESULTS

Identification of Relevant Studies

A total of 556 studies were identified from searching the electronic database by using keywords and

relevant bibliographies. We first excluded 191 duplications after screening on the basis of the abstract and title. Another 357 studies were excluded for the relative outcome or because they were review articles, commentaries, letters, author replies, or had no full text. After a full-text, detailed review, 8 studies were included in our systematic review and meta-analysis.[11–18] The detailed steps of the study selection process are shown in Fig 1.

The main characteristics of the included studies are summarized in Table 2. Researchers in 7 studies evaluated the association between acid-suppressive drug use and the risk of childhood asthma,[11,13–18] and researchers in 6 studies assessed the association between the use of PPIs or H_2RAs and the risk of childhood asthma.[11–13,16–18] Countries where the studies were conducted were as follows: Sweden (n = 2), the United Kingdom (n = 2), the Netherlands (n = 2), Israel (n = 1), and Denmark (n = 1). The confounders, such as maternal asthma and GERD, could be related to an increased risk of childhood asthma.

Maternal asthma is considered to be a main confounder in these studies. Only 1 study by Mulder et al[13] showed that mothers without any asthma prescriptions before their own fifth birthday were selected. Researchers in 3 studies tried to assess maternal GERD.[12,14,18] We summarized the confounders in the studies during the meta-analysis (Table 3). The methodological quality of the 8 studies was assessed according to the NOS (Table 4).

Overall Use of Acid-Suppressive Drugs During Pregnancy and the Risk of Childhood Asthma

Of the studies identified, 7 reported the overall use of acid-suppressive drugs.[11,13–18] The analysis showed

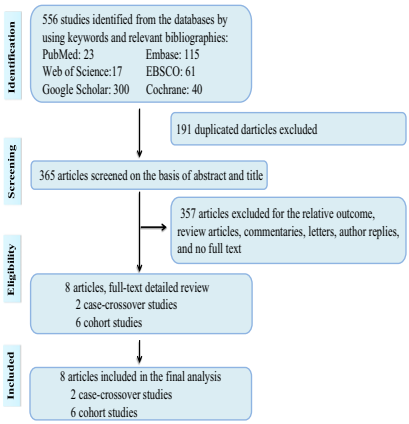

FIGURE 1
Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram for the database search of studies in which researchers investigated the association between acid-suppressive drug use during pregnancy and the risk of childhood asthma.

that the overall use of acid-suppressive drugs during pregnancy was associated with an increased risk of childhood asthma (RR = 1.31; 95% CI 1.15–1.49; P < .0001) by using a random-effects model. Statistical heterogeneity was observed (I^2 = 84%; P < .00001; Fig 2). In a sensitivity analysis (Supplemental Fig 6), the total RR of the 7 studies was 1.24 (95% CI 1.18–1.30). The 95% CI of all the studies crosses 1.0, suggesting that these studies were of poor stability, and they require caution when discussing and drawing conclusions. We further assessed heterogeneity by using the sensitivity analyses and removing each study from the analysis to assess the changes in the I^2 values and determine which studies contributed most significantly to the heterogeneity. The number of patients in the study by Hak et al[16] was lower compared with other studies, and Yitshak-Sade et al[14] investigated the use of H_2RA or PPIs rather than the use of any acid-suppressive drug. We found that when the studies by Yitshak-Sade et al[14] and Hak et al[16] were removed, the I^2 values decreased from 88% to 0% (P = .68), but the effect remained significant (RR = 1.45; 95% CI 1.35–1.56; P < .00001; Fig 3).

Subgroup Meta-analysis

Overall acid-suppressive drug use included maternal use of any type of acid-suppressive drug (eg, H_2RAs and PPIs) during pregnancy. The type of use of these medications was different across studies and may contribute to the heterogeneity in overall acid-suppressive drug use. Thus, we stratified the analysis by subgroup analyses (PPIs and H_2RAs) in the meta-analysis. In a subgroup meta-analysis for use of PPIs and the risk of childhood asthma, 5 studies were included.[11–13,16–18] The result showed that the use of PPIs during pregnancy was associated with an increased childhood asthma risk (RR = 1.34; 95% CI 1.18–1.52; P < .00001). There was some statistical heterogeneity (I^2 = 46%; P = .10; Fig 4). Compared with other studies, the number of patients in the study by Hak et al[16] was lower. We found that excluding the study by Hak et al[16] reduced the heterogeneity in all studies from the initial 46% to 38%.

Researchers in 5 studies assessed the use of H_2RAs during pregnancy and the risk of childhood asthma.[11–13,16–18] The data showed that the use of H_2RAs during pregnancy was associated with an increased risk of asthma in the offspring (RR = 1.57; 95% CI 1.46–1.69; P < .00001). Statistical heterogeneity was not observed (I^2 = 0%; P = .48; Fig 5).

Collectively, the data suggest that prenatal exposure to both PPIs and H_2RAs was associated with an increased risk of asthma.

Publication Bias

We used Egger's test and Begg's test for publication bias. Funnel plots of the studies used to evaluate the outcomes (overall acid-suppressive drug use, PPIs, and H_2RAs) appeared to be symmetrical by visual examination. The data suggested that

TABLE 2 The Characteristics of the Studies Included

Source	No. Analyzed	Study Period	Age Range of Children, Follow-up in Years[a]	Exposure Assessment	Asthma Assessment	Database
Cohort studies						
Dehlink et al[11] (Sweden)	585 716	1995–2004 2005–2006	>2 y	The trimester of exposure: first trimester (OR 1.38; 95% CI 1.22–1.57), later pregnancy (OR 1.34; 95% CI 1.11–1.63)	Hospitalized or received prescription for medication for asthma	The Swedish Hospital Discharge Register, The Swedish Prescribed Drug Register, and The Swedish Medical Birth Register
Andersen et al[12] (Denmark)	197 060	1996–2008	The maximum follow-up time was 14 y with a median follow-up of 6.8 y	Trimester of exposure: first trimester (HR 1.46; 95% CI 1.27–1.67), second and/or third trimester (HR 1.34; 95% CI 1.15–1.56), preconception and postpregnancy exposures	Asthma diagnosis or dispensations record for of antiasthmatic medication	Danish medical registries, The Aarhus University Prescription Database, and the Danish National Registry of Patients
Mulder et al[13] (Netherlands)	33 536	1995–2011	The maximum follow-up time was 8 y with a median follow-up of 4.9 y	Trimester of exposure: first and/or second trimester (HR 1.64; 95% CI 1.12–2.41); third trimester (HR 1.32; 95% CI 0.77–2.25)	>2 inhaled steroid prescriptions within 12 mo	The pregnancy IADB database
Källén et al[15] (Sweden)	685 015	1999–2007 2005–2009	2–6 y	During the second or third trimester (OR 1.60, 95% CI 1.40–1.76)	>5 prescription events for antiasthmatic drugs	The Swedish Medical Birth Register and The Swedish Prescribed Drug Register
Yitshak-Sade et al[14] (Israel)	91 428	1999–2008	3–13 y	Trimester of exposure: first trimester (RR 1.08; 95% CI 0.97–1.21), second trimester (RR 1.11; 95% CI 0.93–1.32), third trimester: (RR 0.99; 95% CI 0.82–1.20)	Hospitalization for asthma diagnosis	Clalit health services (health maintenance organization)
Cea Soriano et al[18] (United Kingdom)	11 010	1996–2010	Maximum of 6 y follow-up	Trimester of exposure (RR, 95% CI)[b]. Model A: first trimester (PPI: 1.16 [0.88–1.52], H_2RA: 1.16 [0.84–1.61]); second trimester (PPI: 1.39 [0.89–2.18], H_2RA: 1.77 [1.34–2.33]); third trimester (PPI: 1.04 [0.68–1.60], H_2RA: 1.38 [1.14–1.68]). Model E: first trimester (PPI: 1.07 [0.76–1.51], H_2RA: 1.15 [0.77–1.72]); second trimester (PPI: 1.11 [0.60–2.05], H_2RA: 1.75 [1.25–2.47]); third trimester (PPI: 0.69 [0.36–1.30], H_2RA: 1.20 [0.93–1.54])	According to general practitioner, recorded clinical asthma events	The health improvement network database[c]
Case-crossover studies						

TABLE 2 Continued

Source	No. Analyzed	Study Period	Age Range of Children, Follow-up in Years[a]	Exposure Assessment	Asthma Assessment	Database
Hak et al[16] (United Kingdom)	3748	1996–2010	Mean age at diagnosis of asthma 3.6 y	The trimester of exposure. H_2RA: first trimester (HR 1.15; 95% CI 0.77–1.72), second trimester (HR 1.75; 95% CI 1.25–2.47), third trimester (HR 1.20; 95% CI 0.93–1.54); PPI: first trimester (HR 1.07; 95% CI 0.76–1.51), second trimester (HR 1.11; 95% CI 0.60–2.05), third trimester (HR 0.69; 95% CI 0.36–1.30)	Prescribed any asthma medications >3 times within 12 mo after the first diagnosis date	United Kingdom General Practitioners Research Database
Mulder et al[17] (Netherlands)	12 530	1995–2011	≥5.5 y	After adjustment for maternal age at birth, prenatal exposure to acid-suppressive drugs. Statistically significantly increased the odds of toddler having asthma by 52% (adjusted OR, 1.52; 95% CI 1.11–2.09)	>2 prescriptions for asthma medications during follow-up	The pregnancy IADB database

IADB, InterAction Database; NA, not available.

[a] The minimum age of children and minimum medication dispensing when defining asthma.

[b] Model A: Cox proportional hazard model adjusted for the number of maternal primary care physician visits and referrals during the year before the last menstrual period date and year of delivery. Model E shows the Cox proportional hazard model adjusted for number of maternal primary care physician visits and referrals during the year before the last menstrual period date and year of delivery; maternal comorbidities (asthma, allergies, GERD, and peptic ulcer); maternal use of nonsteroidal anti-inflammatory drugs, antacids, antibiotics, and antihistamine medications during pregnancy; and sex of the infant.

[c] Automated computer search, manual confirmation, and secondary validation by questionnaire.

there was no evidence of publication bias ($P > .05$; Supplemental Fig 7).

DISCUSSION

Our aim with this systematic review was to provide an overview of the literature describing associations between acid-suppressive drug use during pregnancy and the risk of childhood asthma. Our meta-analysis showed that prenatal exposure to acid-suppressive drugs, such as H_2RAs and PPIs, is associated with an increased risk of childhood asthma. On the basis of this study, researchers in future studies examining the early origins of childhood asthma need to account for the impact of prenatal, maternal, acid-suppressive drug use.

Asthma is characterized by chronic bronchial inflammation, airway hyperresponsiveness, and reversible bronchial obstruction. Prenatal exposures, such as the use of antibiotics, paracetamol, folic acid, acid-suppressive drugs, and maternal smoking and/or passive smoking, are some of the speculated causes that contribute to asthma.[23–25] In adults, the use of acid-suppressive drugs may alleviate asthma in patients with GERD, but the drugs are also associated with allergic sensitization. Although little is known about acid-suppressive drug exposure and the risk of childhood asthma, researchers in animal and human studies proposed some hypotheses. Acid-suppressive drugs may interfere with the denaturation of food antigens in the stomach, making food proteins act like allergens and thereby causing allergic sensitization, which could lead to food-specific immunoglobulin-E induction and the development of T helper cell-2–biased hypersensitivities in pregnant women.[9,10]

Potential confounding as a result of genetic and environmental factors shared by the mother, father, and offspring during and after gestation

TABLE 3 The Details of Maternal Asthma and Other Factors in Included Studies

Source	Maternal Asthma	Confounders
Dehlink et al[11]	Among nonallergic mothers (n = 551 234), maternal acid-suppressive drug use remained a risk factor, with an OR of 1.43 for developing childhood allergic disease (95% CI 1.28–1.59). Analysis of allergic mothers (n = 34 482) revealed that acid-suppressive drug use had no significant effect on the development of childhood allergic disease (OR 1.25; 95% CI 0.84–1.87).	Year of birth, parity, maternal age, maternal smoking, and maternal BMI
Andersen et al[12]	Maternal asthma was more frequent among PPI-exposed children than among unexposed children.	Year of birth, county, birth order, sex, gestational age, maternal age, maternal smoking, maternal asthma, delivery mode, and maternal use of antibiotics during pregnancy
Mulder et al[13]	The presence of allergic diseases in the mother was twice as high among those exposed during pregnancy than those who were unexposed, but adjustment of the crude HR (1.51 [95% CI 1.25–1.82]) for allergic disease in the mother showed little effect (adjusted HR 1.46 [95% CI 1.21–1.76]).	Year of birth, sex of child, use of acid-suppressive drugs by child, maternal age at birth, maternal allergy, and maternal use of systemic antibiotics during pregnancy
Källén et al[15]	Prescription of antiasthmatics during 2005–2011 did not identify all women with asthma during pregnancy. Among 11 300 women who had used antiasthmatics during pregnancy, 2527 (23%) were not identified as asthmatic on the basis of prescriptions during 2005–2011.	Maternal age, year of birth, smoking, parity, BMI, and use of other drugs during pregnancy
Yitshak-Sade et al[14]	The prevalence of maternal allergies did not differ substantially by exposure to H2Bs or PPIs. Mothers in the group exposed to H2Bs or PPIs were characterized by a higher proportion of asthma as compared with nonexposed mothers.	Maternal allergy or asthma, maternal age, maternal use of antibiotics, infertility treatment, prenatal care, gestational age at birth, cesarean delivery, birth wt, child sex, year of birth, child use of acid-suppressive drugs at <2 y old, metoclopramide, nonsteroidal anti-inflammatory drugs, and insulin
Cea Soriano et al[18]	One hundred seventy-one (19.3%) women were identified as asthmatic. The adjusted HR for preexisting maternal asthma was 1.55 (95% CI 1.21–2.00), and for those diagnosed during pregnancy, it was 0.99 (95% CI 0.76–1.28).	Sex of child, maternal asthma, maternal comorbidities, maternal use of nonsteroidal anti-inflammatory drugs, antacids, antibiotics or antihistamine medications during pregnancy, maternal primary care physician visits before and during pregnancy
Hak et al[16]	The presence of maternal asthma was similar among those exposed during pregnancy and those not exposed to acid-suppressive drugs.	Sex, maternal age at birth, birth order, and no. general practitioner visits during pregnancy. Paracetamol use, smoking status, presence of migraine, preeclampsia, or the prescription of paracetamol or nonsteroidal anti-inflammatory drugs during pregnancy
Mulder et al[17]	Mothers without any asthma prescriptions before their own fifth birthday were selected.	The age of the mother at birth, maternal asthma, sex of the child, sequence of birth, and use of acid-suppressive drugs by the child

H2B, H2 blockers.

presents a further challenge for researchers examining true associations.[16] Because all the results in the included studies were based on the population register database, it is imperative to eliminate this confounding variable, which is not always easy to accomplish. Andersen et al[12] adjusted the maximum range of risk factors, and their results also showed an increased RR in childhood asthma. Källén et al[15] showed that the association still existed even after they adjusted for confounding factors by excluding women who used specified drug categories and antiasthmatic drugs. Moreover, researchers in 2 studies minimized the potential confounding factors by using the case-crossover method.[17,18]

Residual confounding by unmeasured and unknown risk factors could be biasing the estimates upward, which can occur in register-based studies. GERD is associated with asthma in adults, and asthma in the offspring could be due to GERD (eg, indication) rather than the treatment of GERD.[26] Of the 8 studies identified in the meta-analysis, researchers in only 3 tried to assess this issue.[12,14,18] Andersen et al[12] reported that maternal GERD could explain the association observed for maternal postnatal use of PPIs. Although they adjusted the analysis for maternal asthma, maternal GERD may be associated with asthma in offspring also, but this has not yet been investigated.

Yitshak-Sade et al[14] showed that the main possible bias in a study of this kind is confounding by indication. This finding raises a question of the causality of the effect at study. They were not able to retrieve the exact indication for administering the PPIs or H_2RAs from their databases. However, these medications can be taken for a variety of reasons, which possibly explains why the propensity score method failed to distinguish between the exposed and unexposed subjects. In the study by Cea Soriano et al,[18] different Cox regression models were used to adjust for various confounding factors, and 1 model was maternal comorbidities at any time before delivery (allergies, GERD, peptic ulcer; model C).

TABLE 4 Methodological Quality Assessment According to the NOS

	Representativeness of the Exposed Cohort	Selection of the Non-exposed Cohort	Ascertainment of Exposure	Demonstration That Outcome of Interest Was Not Present at Start of Study	Comparability of Cohorts on the Basis of the Design or Analysis	Assessment of Outcome	Follow-up Was Long Enough for Outcomes to Occur	Adequacy of Follow-up of Cohorts
Andersen et al,[12]	—	a	a	a	b	c	c	c
Cea Soriano et al,[18]	—	a	a	a	b	c	c	c
Dehlink et al,[11]	—	a	a	a	b	c	c	c
Källén et al,[15]	a	a	a	a	b	c	c	—
Mulder et al,[13]	—	a	a	a	b	c	c	c
Yitshak-Sade et al,[14]	—	a	a	a	b	c	c	—
Hak et al,[16]	—	a	a	a	b	c	c	c
Mulder et al,[17]	a	a	a	a	b	c	c	c

—, not applicable.
[a] Selection.
[b] Comparability.
[c] Outcomes.

The adjusted hazard ratios (HRs) for GERD that was preexisting and diagnosed during pregnancy were 1.07 (95% CI 0.79–1.44) and 1.17 (95% CI 0.92–1.48), respectively. It is a strength that researchers in these studies actually addressed this real issue and supported GERD disease as an alternative explanation to GERD treatment as a risk factor for childhood asthma. However, we don't know; these types of studies can't really answer that question unless we can find a population of women with GERD who did not take medication. Therefore, the association between acid-suppressive drug use in pregnancy and the risk of childhood asthma should be interpreted cautiously. The current results suggest that a cohort study in which all mothers are assessed for GERD by severity and drug use and all children are assessed for asthma by lung function testing or by a doctor is required.

Our meta-analysis has several strengths. First, it is the most comprehensive meta-analysis to date on the association between the use of acid-suppressive drugs during pregnancy and the risk of childhood asthma. Second, it examines the associations in greater detail by stratifying by the type of agent (PPIs or H_2RAs). Heterogeneity was observed for overall acid-suppressive drug use but not for the subgroup analyses (PPIs and H_2RAs). This may be a result of potential confounders. Overall acid-suppressive drug use included maternal use of any type of acid-suppressive drug (eg, PPIs and H_2RAs) during pregnancy. The type, dose, frequency, and timing (trimester) of the use of these medications were different across studies, and they may contribute to heterogeneity in overall acid-suppressive drug use. Thus, we stratified the analysis by subgroup (PPIs and H_2RAs) in the sensitivity analysis. After controlling for confounding factors,

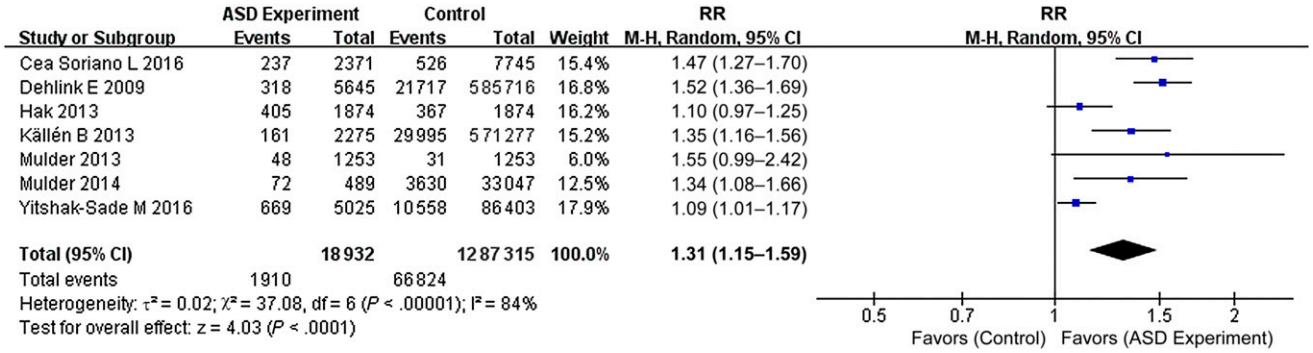

FIGURE 2

Forest plot of the association between maternal use of overall acid-suppressive drugs during pregnancy and the risk of childhood asthma by using Review Manager 5.3. ASD, acid-suppressive drug; df, degree of freedom; M-H, Mantel Haenszel.

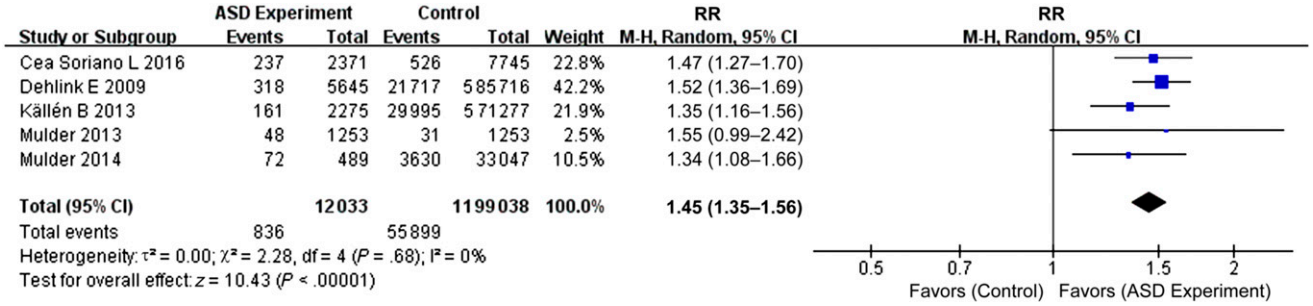

FIGURE 3

Forest plot of the association between maternal use of overall acid-suppressive drugs during pregnancy and the risk of childhood asthma after sensitivity analysis, which excluded 2 studies by Hak et al[16] and Yitshak-Sade et al.[14] ASD, acid-suppressive drug; df, degree of freedom; M-H, Mantel Haenszel.

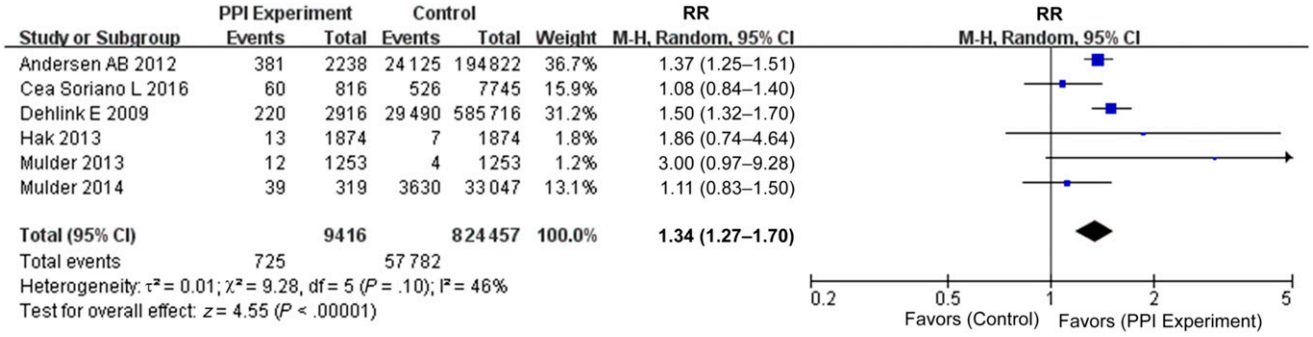

FIGURE 4

Forest plot of studies in which researchers investigated the association between maternal use of H_2RAs during pregnancy and the risk of asthma in the offspring. df, degree of freedom; M-H, Mantel Haenszel.

heterogeneity was not observed in the subgroup analyses. Third, we included analytical epidemiologic studies: cohort, case control, and cross-sectional studies, which included a large number of studies and participants. Fourth, there was no publication bias in this study, which was assessed for by using Egger's test and Begg's test. Fifth, a sensitivity analysis was conducted, and it confirmed the robustness of our results. It minimized the recall bias and selection bias to the fullest extent.[27] Even if adjustments for confounding factors have been made in the analysis, residual confounding remains a potentially serious problem in observational research. Residual confounding arises when a confounding factor cannot be measured with sufficient precision, which often occurs in epidemiologic studies. The main assessments in a sensitivity analysis include changing the inclusion criteria (especially in controversial studies), excluding low-quality studies, and using different statistical methods and/or models to analyze the same data. If the results remain unchanged, this indicates that the sensitivity is low, and the results are robust and

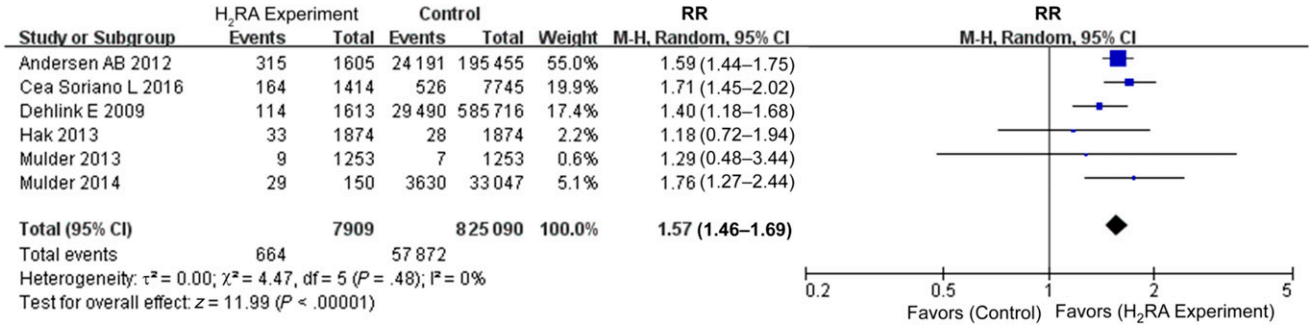

FIGURE 5

Forest plot of studies in which researchers investigated the association between maternal use of PPIs during pregnancy and the risk of asthma in the offspring. df, degree of freedom; M-H, Mantel Haenszel.

trustworthy. However, if the results changed or opposite conclusions can be drawn, this indicates that the sensitivity is high, and the robustness of the results is relatively low. These results should be interpreted, and conclusions should be made, with caution.

Our meta-analysis also had some limitations. First, most of the studies in our meta-analysis were observational studies. As discussed above, observational studies may reduce the quality of the meta-analysis and are considered to have greater potential for bias. To compensate for this limitation, we conducted subgroup analysis according to the type of agent (PPIs or H_2RAs). Observational studies have limitations inherent to their design, and variant confounders include maternal characteristics, genetic predisposition for asthma, and other comorbid conditions that might increase a child's risk of asthma. The type and dose of these medications were different across studies and may contribute to heterogeneity in overall acid-suppressive drug use. Confounding is the most important threat to the validity of the results from cohort studies. In the sensitivity analysis of the subgroups (PPIs and H_2RAs), the confounding factor (type of acid-suppressive drug) was controlled, and heterogeneity was not observed in the subgroup analyses. Second, we could not evaluate individual data on dose-response relationships that may have affected gastric acid production because these data were not available in each study.

CONCLUSIONS

In this study, we show that prenatal, maternal, acid-suppressive drug use plays a negative role in the development of asthma in offspring. Clinicians and parents need to exercise caution when deciding whether to take acid-suppressing drugs during pregnancy because of the risk of asthma in offspring.

ABBREVIATIONS

CI: confidence interval
GERD: gastroesophageal reflux disease
H_2RA: histamine-2 receptor antagonist
HR: hazard ratio
NOS: Newcastle-Ottawa scale
OR: odds ratio
PPI: proton pump inhibitor
RR: relative risk

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