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Acid suppressant medications and the risk of allergic diseases

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Abstract

Introduction: Acid suppressant medications, such as proton pump inhibitors and histamine-2 receptor antagonists, are used often and throughout the lifespan. These medications have been linked to the development of a variety of allergic diseases.

Areas covered: This review discusses prior studies investigating the association between acid suppressant medication exposure and the development of allergic diseases. We performed a thorough literature search to identify potentially relevant studies for inclusion. In summary, exposure to these medications prenatally, in childhood and in adulthood may increase the risk of allergic diseases. The current evidence is limited by primarily observational study design and potential bias and confounding. The mechanism of action is not yet known, but there are several proposed theories.

Expert commentary: There is a growing body of evidence to support that exposure to acid suppressant medications increases the risk of developing allergic diseases. Further research is needed to not only clarify this relationship but to define the potential mechanism of action. If further research confirms these observations, we believe that could warrant changes in the patterns of prescribing and use of acid suppressant medications.

Keywords

Acid suppressant medication; allergy; asthma; gastroesophageal reflux disease; histamine-2 receptor antagonist; prenatal and proton pump inhibitor

1. Introduction

Allergic diseases, including asthma, atopic dermatitis, food allergy and allergic rhinitis, are common and pose and a significant health burden [1]. For example, the Centers for Disease Control and Prevention in 2011 estimated rates of allergy in the United States to be 17% for

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respiratory allergy, 12.5% for skin allergy and 5.1% for food allergy [2]. Allergic diseases often develop during childhood, but can present at any age. Development occurs through complex interactions between genetic susceptibilities and environmental exposures [3]. Recent observational studies have linked exposure to acid suppressant medications (ASM) to the development of allergic diseases. The current literature suggests that exposure to ASM prenatally, in childhood and even in adulthood may increase the risk of developing allergic diseases. The objective of this review is to critically evaluate the current body of scientific literature on ASM use and the risk of allergic diseases, to identify potential mechanism(s) of action, and to discuss future directions for research.

1.1 Acid Suppressant Medications (ASM)

ASM are used commonly to treat gastroesophageal reflux disease (GERD) as well as other gastrointestinal conditions, including peptic ulcer disease, *Helicobacter pylori* infection, Barrett's esophagus and Zollinger-Ellison syndrome [4]. Medications that suppress acid include sucralfate, antacids, histamine-2 receptor antagonists (H2RA) and proton pump inhibitors (PPI) [5,6]. H2RA were first marketed in the 1970s to treat peptic ulcer disease [6]. This was followed by introduction of the more potent PPI in the 1980s [7]. Advent of these medications revolutionized the care of peptic ulcer disease and the medications quickly became integrated into clinical practice. Today, H2RA and PPI are not only among the most common prescription medications but are also some of the most frequently purchased over-the-counter medications [8].

ASM use is common among many patient populations including pregnant women and children. The use of ASM during pregnancy and childhood are pertinent to this review as immune function is developing during the prenatal and early childhood periods. GERD symptoms are common in pregnancy and affect up to 50–85% of all pregnancies [9]. While ASM are commonly used to treat GERD in pregnancy, there is little direct evidence to support their efficacy in this population and most therapy is empiric [10, 11]. Neither H2RA or PPI have been shown to be teratogenic or to increase the risk of perinatal mortality [12, 13]. In infants and children, the use of ASM has been increasing over time and is also often initiated empirically [14, 15].

1.2 Adverse effects of ASM

With widespread use of ASM, particularly H2RA and PPI, there has been increased attention on their potential adverse effects. Aside from their potential link to allergic diseases, a wide-variety of adverse effects have been reported in the literature including increased infection risk, vitamin and electrolyte deficiencies and potentially more serious consequences. Both H2RA and PPI have been associated with increased risks of pneumonia and enteric infections including *C. difficile* [16–18]. ASM also have been associated with increased risks of vitamin B12 deficiency, and PPI have been associated with increased rates of hypomagnesemia [19, 20]. In premature infants, use of H2RA has been associated with an increased risk of infection, necrotizing enterocolitis and increased overall mortality [21]. Studies have suggested that use of PPI may even increase the risk of myocardial infarction and dementia [22, 23].

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2. ASM and the development of allergic diseases

In the last decade, a growing number of studies have suggested that exposure to ASM may increase the risk of developing allergic diseases. Different periods of exposure have been assessed, including prenatal, childhood and adult exposure. A variety of allergic outcomes have been investigated including asthma, atopic dermatitis, food allergy, allergic rhinitis, eosinophilic esophagitis, medication allergy and anaphylaxis; most investigations have focused on asthma. Most of the directly relevant studies have been observational in nature. Studies were identified by a thorough search using PubMed and Google Scholar. Search terms included “acid suppressant medication” or “histamine-2 receptor antagonist” or “proton pump inhibitor” and “asthma” or “allergy” or “child” or “pregnancy.” Reference lists of selected articles were reviewed for potentially relevant citations. Studies that assessed ASM exposure and the development of allergic diseases, or the potential mechanisms of disease, were included in this review.

2.1 Prenatal exposure to ASM

As previously noted, GERD is extremely common in pregnancy and medication therapy with ASM is often utilized [11]. We identified 8 observational studies in this section (Table 1). The studies were performed mostly in Europe (Sweden, United Kingdom, Denmark, Netherlands) and Israel. In 2009, the first study linking prenatal exposure to ASM and the development of subsequent childhood asthma was published [24]. This population-based cohort study was performed in Sweden and reported that children exposed to ASM prenatally had an increased risk of developing childhood asthma (adjusted odds ratio (OR) 1.51 95% CI 1.35–1.69) [24]. Since then, 7 other observational studies on prenatal ASM exposure and the development of childhood asthma have been performed [25–31]. Only 2 assessed for allergic outcomes other than asthma. Prenatal ASM exposure was associated with increased risk of many of these other allergic outcomes (Table 2) [24, 29].

In these large observational studies, the exposure to ASM during pregnancy was largely defined by prescription for the medication during pregnancy. The outcomes were defined variably through a combination of diagnosis and prescriptions for the desired allergic disease. The specific definitions for asthma varied depending on the data available for each study.

The authors of these studies utilized a variety of methodological and statistical techniques to limit bias and confounding. An observational cohort study design was used for 4 studies and a case-control design was used for 3 studies. Beyond the case-control design, one study utilized a case-crossover design to minimize unadjusted confounding [28] and another used a nested-case control design where every subject had a control from the same biologic mother [25]. Each study used analytic methods that allowed for assessment of potential confounding, however the degree to which each study assessed for confounding was variable (Table 2).

When considering the outcome of asthma, which has been associated with many risk factors [32], it is important to assess for known and potentially important confounders. In the prenatal exposure studies, one of the most important factors to adjust for is maternal history

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of asthma. This is critically important for 2 reasons. First, maternal history of asthma increases the risk of development of childhood asthma [33]. Second, there may be increased rates of GERD and therapy with ASM in those with underlying asthma or allergic disease [34]. A variety of methods were used to adjust for maternal history of asthma. Adjusted analysis for a maternal history of asthma or allergic disease was performed in half of the studies [26, 29–31]. Two studies [26, 27] performed their analysis after excluding mothers with a history of asthma. Other potentially important factors include maternal obesity or weight gain during pregnancy and maternal smoking. These potential confounders were adjusted in some, but not all, studies (Table 2).

The two most recently published studies found less robust results than the prior studies. In 2016, a case-control study in the United Kingdom reported an increased risk of asthma development only for prenatal H2RA exposure and not for PPI exposure (adjusted hazard ratio (HR) 1.32 95%CI: 1.05–1.64 and adjusted HR 1.03 95% CI: 0.76–1.40, respectively) [30]. In 2016, an Israeli cohort study reported that prenatal exposure to ASM was associated with only a small increased risk of developing childhood asthma (adjusted relative risk (RR) 1.09 95%CI: 1.01–1.17) [31]. The reasons for these conflicting results is not clear. The study populations were geographically unique as compared to prior studies. These two studies adjusted for many potential confounders including sociodemographic factors, maternal history of allergic disease, and perinatal factors. However, further adjustment for confounding and attempts to minimize confounding by study design were utilized by several of the prior studies that reported a higher risk of childhood asthma.

Recently two comprehensive meta-analyses have been published [35,36]. These well-conducted studies were only able to assess prenatal exposure to ASM and the risk of childhood asthma as there was not enough data to assess for the risk of other allergic diseases. In both meta-analyses, the pooled results showed that prenatal exposure to any ASM, H2RA or PPI was associated with increased risk of developing asthma (Table 3). Interestingly, both of these studies report slightly higher risk estimates for H2RA than PPI, though fewer studies reported results stratified by type of ASM (PPI or H2RA). Neither study found evidence of publication bias. Using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach Devine et al. found the overall quality of evidence to be moderate [35]. These analyses strengthen inferences about the association observed in the individual studies.

2.2 Childhood exposure to ASM and allergic diseases

Fewer studies have investigated the risk of exposure to ASM in infancy and early childhood (Table 1). The 3 observational studies included were performed in the United States. The first, a cross-sectional study published in 2013, specifically looked at the risk of developing food allergy after exposure to ASM in childhood [37]. The authors reported that childhood exposure to ASM was associated with increased risk of food allergy (adjusted prevalence ratio (PR) 1.70 95%CI: 1.10–2.50) [37]. A smaller case control study was performed looking for risk factors in the development of eosinophilic esophagitis (EE) [38]. Among those exposed to ASM during infancy, there was a significantly increased risk of subsequent development of EE (adjusted OR 6.05 95%CI: 2.55–14.0) [38]. More recently, a large

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observational cohort study was conducted assessing childhood exposure to ASM and the risk of multiple allergic disease (asthma, atopic dermatitis, food allergy, allergic rhinitis, allergic conjunctivitis, mediation allergy, urticaria, contact dermatitis, anaphylaxis and other allergy). Exposure to either H2RA or PPI increased the risk of developing all of these allergic disease outcomes (Table 2) [39].

The smaller cross-sectional and case-control studies gathered exposure and outcome information directly from the subject's parents likely decreasing misclassification bias [37, 38]. However, their sample sizes were relatively small. In the study of EE patients, they attempted to adjust for confounding by indication by only looking at ASM exposure during infancy in children who had reported EE symptoms developing after 3 years of age. These results may still be affected by confounding by indication as we do not yet know if GERD in early childhood often precedes EE [38]. Due to the nature of the data in the large cohort study, exposure and outcome were defined by pharmacy records and diagnosis codes, respectively. Some of the allergic disease categories, like "other allergy," seem overly broad and are of uncertain relevance [39]. Analytic adjustment for potential confounders was generally limited in these studies (Table 2).

2.3 Adult exposure to ASM and allergic diseases

Only one observational study, a case-control study performed in Spain, investigated the association between ASM exposure in adults and risk of allergic diseases [40]. This 2012 publication examined hospitalized patients and found that those taking PPI were more likely to develop a drug hypersensitivity reaction (adjusted OR 4.35 95% CI: 2.00–9.45) [40]. This study is unique in that the exposure and outcome occurred during the same hospitalization and were verified by direct record review. Moreover, the time frame between exposure and outcome was shorter than seen in previous studies.

2.4 Potential mechanisms

The mechanism(s) by which ASM exposure may lead to an increase in allergic disease is not known. Several potential mechanisms have been suggested including an increase in allergic sensitization, a propensity to alter the cytokine profile to a pro-allergic Th2 profile, and alternation in the microbiome.

Before publication of the first human cohort study [24], work in mouse models provided the initial basis for inquiry. These first studies established that the digestion of some dietary proteins is pH dependent and can be altered by exposure to ASM [41]. Feeding of dietary antigens to mice in combination with ASM lead to an increase in IgE formation toward the dietary antigen as well as evidence of clinical food allergy [41,42]. Subsequent studies in pregnant mice fed a combination of ASM and food antigen developed not only increased levels of sensitization to the food antigen, but the offspring showed a Th2 dominant cytokine profile [43]. Similar increases in sensitization were seen when the mice were given ASM in conjunction with a non-steroidal anti-inflammatory medication [44].

Further proof of concept studies were performed in humans. In an observational cohort study, 152 subjects with no clinical history of atopic disease were enrolled in a gastroenterology clinic prior to planned treatment with 3 months of either H2RA or PPI for

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dyspepsia or chronic gastritis. Total IgE and specific IgE levels for common allergens, including foods, were obtained before and after therapy. After completion of therapy total IgE levels in patients treated with ASM were significantly higher than baseline. Additionally, 15% of the subjects developed *de novo* allergen sensitization to foods. Five months after completion of ASM therapy food-specific IgE remained detectable in 6% of subjects [45]. In a follow up study, a small subset of these original patients (5/152 or 3.3%) whom developed hazelnut specific IgE after ASM therapy underwent further evaluation for clinical food allergy by skin prick testing and oral food challenge. True clinical food allergy was confirmed in in 3/5 (60%) of the sensitized patients by oral food challenge [42].

In addition to these proposed mechanisms, it is important to note that ASM, particularly PPIs, have been shown to alter the human gastrointestinal microbiome. Alterations in the microbiome related to PPI have been described throughout the entire gastrointestinal tract including the esophagus, stomach, small intestine and colon [46]. Changes described include a decrease in commensal bacteria and lower microbial diversity [47]. The effect of H2RA on the gastrointestinal microbiome has not been well studied, but one small study in premature infants suggests that these medications also change the fecal microbiome [48]. The microbiome is being increasingly recognized for its potential role in the development of allergic diseases [49]. To our knowledge, no studies have assessed if the changes in the microbiome seen with ASM therapy are related to the development of allergic disease.

3. Summary

A growing body of evidence links exposure to ASM medications throughout the life span to the development of allergic diseases. The increased risk for multiple allergic diseases (after exposure to ASM) suggests that the medications may increase the propensity to develop atopy. The current evidence, derived from observational studies, shows a modest increase in risk, thus bias and confounding may play a role and causation cannot be proven definitively. However, the increasing number of similar results, in diverse populations using different analytic approaches and study designs, strengthens casual inferences about the observed associations. The potential mechanism of action remains unclear. Clearly, further research is warranted to better define the relationship between ASM and allergic diseases.

4. Expert commentary

We believe that this area of research is critically important as ASM are used during all stages of life and use the of ASM is modifiable. ASM are not only some of the most commonly prescribed medications but in the United States but they are readily available over-the-counter without a prescription [8]. While these medications certainly serve an important role in treating serious gastrointestinal disease, ASM are being overused and overprescribed to treat less serious ailments with little evidence to support their efficacy (e.g., empiric therapy and treatment of minor gastrointestinal complaints) [50]. With this pattern of overuse there is abundant exposure during immunologically critical time periods including during pregnancy and childhood. Based on our review of the scientific literature, we can see a pattern suggestive of increased risk for development of a wide variety of allergic diseases. There is currently the most evidence for prenatal exposure to ASM and a modestly increased risk of

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developing childhood asthma. The estimates of risk are potentially even larger for childhood exposure and other allergic diseases, such as food allergy. Due to the nature of the data and the relatively small increases in risk reported in most studies we cannot exclude that the results could be related to unaccounted for bias and confounding.

Based on the current findings, we encourage researchers to focus in two main areas. The first area is to clearly elucidate the risks of exposure to ASM for the development of allergic diseases in different populations, ideally with different methods of study. Research may continue to focus on the prenatal exposures but it would be helpful to expand into other allergic diseases beyond asthma. Populations of interest may include not only all age ranges of exposure, but also include those who are at high risk of allergic disease due to other factors such as family history of allergic disease and key environmental exposures. We anticipate that most of these studies in children and pregnant women will be observational, but we challenge investigators to perform prospective cohort studies, and even randomized controlled trials, when feasible. We encourage future observational studies to focus on study design and analytic methods that minimize bias and confounding. Special attention should be paid to known and potential risk factors for developing allergic diseases, including family history of allergic disease. As previously noted by Lai and colleagues in the recent meta-analysis [36], most studies have not controlled for maternal diagnosis of GERD and thus there is a possibility of confounding by indication as many adult patients with asthma are concomitantly treated for GERD either as a co-morbid condition or as an adjunct therapy for asthma or cough [51]. Certainly, confounding by indication may also be important in childhood and adult populations since the early manifestations of some allergic diseases may mimic GERD. Randomized controlled trials would be the most effective at controlling for confounding by indication but other analytic approaches, such as propensity scoring, may also be employed.

The second area of focus would be to elucidate the mechanisms by which ASM increases the propensity for allergic diseases. There are surprisingly few mechanistic studies currently and most are focused on allergic sensitization to food allergens. These studies show that in mice and probably humans, that therapy with ASM in conjunction with acid-labile food antigens can increase the risk of sensitization and even true clinical food allergy [41–45]. Allergic sensitization is certainly important in the pathogenesis of most allergic diseases; however, it is not yet known if the increased rates of sensitization occur only with acid-labile food allergens or with other allergens, such as aeroallergens. Since ASM have been linked to such a wide range of allergic diseases, it seems likely that the underlying mechanism of action may be related to a common step in allergic pathogenesis. Although there appears to be an elevated risk of allergic disease with any ASM the risk estimates for H2RA and PPI vary slightly with several studies reporting an higher risk for H2RA than PPI. As these classes of medications have distinct mechanisms of action and cause different degrees of acid suppression it will be important to determine if true risk differences exist between these medication classes in order to investigate potential mechanisms of action.

While sensitization is certainly a candidate, Th2 function should also be investigated further as this could be an important factor. As our understanding of the human microbiome begins to grow, it is becoming clearer that alterations in the microbiome can predispose to allergic

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disease [49]. There is abundant evidence that ASM alter the composition of the microbiome [46,47]. As previously mentioned, alterations in the microbiome seen after exposure to ASM have not yet been associated with developing allergic disease, but these studies may be critically important. In respiratory diseases, such as bronchiolitis and asthma, there are changes in the respiratory microbiome [52]. It is not known if ASM use has any impact on the respiratory microbiome, but this merits investigation. There remains uncertainly about the impact of microbiome in early infancy to affect long term changes, but this could be an interesting field of study as well.

Further work in the field will shed light on the true risk of exposure to ASM for the development of allergic diseases, as well as the underlying mechanisms. If future studies continue to report an increased risk of allergic disease with ASM exposure, we believe that care providers would do well to adjust their prescribing patterns. Depending on the impact of the results of future research, there may even be a need to implement patient education programs or policy changes in order to decrease recognized over-use of widely available ASM [8, 49].

5. Five-year view

In the next five-years we anticipate more investigations into the association between ASM and allergic diseases that will shed light on many of the remaining questions in the field, including potential mechanisms of action. If the current pattern holds true in future studies, we anticipate that more resources will be devoted to studying the mechanism(s) by which ASM increases allergic diathesis. Furthermore, if ASM exposure continues to confer an increased risk of allergic disease, we anticipate shifts in the prescribing practices of ASM, especially in more at-risk populations such as pregnant women and children. Changing the culture of over-use of these medications may occur not only due to the increase risk of allergic disease but also in response to concerns over other adverse effects of the medications. Use of these medications in general may require more stringent diagnostic criteria rather than initiation of empiric therapy.

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Abbreviations:

ASM	acid suppressant medications
GERD	gastroesophageal reflux disease
H2RA	histamine-2 receptor anatagonist
PPI	proton pump inhibitor

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HR	hazard ratio
RR	relative risk
PR	prevalence ratio
EE	eosinophilic esophagitis
OR	odds ratio

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Key Issues

- Acid suppressant medications (ASM), such as histamine-2 receptor antagonists and proton pump inhibitors, are commonly used medications throughout the lifespan.
- In observational studies, ASM use during both pregnancy and childhood have been linked to a modestly increased risk of developing allergic diseases, including asthma, atopic dermatitis, food allergy, allergic rhinitis and eosinophilic esophagitis.
- The mechanisms of action are not yet known, but ASM have been shown to predispose to allergic sensitization and are known to alter the gastrointestinal microbiome.
- More research is warranted to further elucidate the risk of exposure to these medications and the development of allergic diseases, as well as the underlying mechanisms of pathogenesis.

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Table 1.

Acid suppressant medications and allergic diseases: observational study design

A. Prenatal exposure to ASM									
Author (year), Location	**Study Design**	**Sample Size**	**Excluded**	**Exposure**	**Outcome- Asthma**	**Outcome- Atopic Dermatitis (AD)**	**Outcome – Food Allergy (FA)**	**Outcome- - Allergic Rhinitis (AR)**	**Outcome- Other Allergic Disease**
Dehlink (2009), Sweden [24]	Cohort	585,716	<37 weeks GA, infertility, C-section, single parent household	Use of H2RA, prostaglandins, PPI, *H. pylori* treatment, or sucralfate during pregnancy identified by medication code in birth registry	Ever hospitalized for asthma (over age 2 or multiple hospitalizations) or received 2 or more prescriptions for asthma medication	AD by discharge diagnosis or 2 or more prescriptions to treat an allergic condition *	FA by discharge diagnosis or 2 or more prescriptions to treat an allergic condition *	AR by discharge diagnosis or 2 or more prescriptions to treat an allergic condition *	Unspecified allergic reaction or anaphylaxis: by a discharge diagnosis or 2 or more prescriptions to treat an allergic condition Allergic disease: if ever hospitalized for an allergic disease (asthma, FA, AD or unspecified allergic reaction/ anaphylaxis) or if received 2 or more prescription allergy medications *
Hak (2013), United Kingdom [25]	Nested cross-over	1874 cases 1874 controls	Congenital birth defects, chromosomal anomaly, known teratogen exposure, <12 months of pre-pregnancy follow up or < 3 years follow up after birth	Prescription of any acid suppressive therapy during pregnancy	Diagnosis from birth to age 14 years and prescription for 3 asthma medications in the 12 months after diagnosis	-	-	-	-
Andersen (2012), Denmark [26]	Cohort	197,060	Twins or other multiple births	Prescription for H2RA or PPI during pregnancy	Diagnosis at hospitalization, outpatient visit, or ED visit or dispended anti-asthma medications †	-	-	-	-

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A. Prenatal exposure to ASM									
Author (year), Location	**Study Design**	**Sample Size**	**Excluded**	**Exposure**	**Outcome- Asthma**	**Outcome- Atopic Dermatitis (AD)**	**Outcome – Food Allergy (FA)**	**Outcome- - Allergic Rhinitis (AR)**	**Outcome- Other Allergic Disease**
Kallen (2013), Sweden [27]	Cohort	685,015	Not born in Sweden, twins or other multiple births, additional analysis excluding women with history of asthma	Prescription or recommendation for use of GERD medications and other medications during pregnancy	5 or more prescriptions for asthma medications in child > 2 years of age	-	-	-	-
Mulder (2013), Netherlands [28]	Case-Control	1253 cases 1253 controls	< 5.5 years of follow up after birth	1 or more prescription(s) for H2RA, PPI, prostaglandin, *H. pylori* therapy or GERD medication during pregnancy	2 or more prescriptions for asthma medications in a 6-month period prior to age 5	-	-	-	-
Mulder (2014), Netherlands [29]	Cohort	33,536	Twins or other multiple births, mothers with <12 months of follow up prior to pregnancy	1 or more prescription(s) for H2RA or PPI during pregnancy	Receiving two prescriptions for an inhaled corticosteroid within a 12 month period after age 5	2 or more prescriptions for steroid or calcineurin inhibitor ointment in 12 months	-	2 or more prescriptions for nasal steroids within a 12 month period	Allergic disease: combined outcome of asthma, AD, or AR as defined
Cea Soriano (2016), United Kingdom [30]	Case Control	2371 exposed 7745 un-exposed	< 12 months follow up prior to pregnancy or < 1 year of follow up after birth	1 or more prescription(s) for PPI or H2RA during pregnancy	Diagnosis codes for asthma then confirmed by manual chart review	-	-	-	-
Yitshak-Sade (2016), Israel [31]	Cohort	91,428	Unknown personal information for follow up, childhood diagnoses of cystic fibrosis, bronchiolitis, bronchitis, heart failure, chronic airway obstruction, other pulmonary disease, GERD or heart defects	Purchase of H2RA or PPI during pregnancy	Hospitalization with diagnosis of asthma or recurrent wheeze between the ages of 2-13 years or dispensed at least 2 or a combination of asthma medications[≠]	-	-	-	-

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B. Childhood exposure to ASM

Author (year), Location	Study Design	Sample Size	Excluded	Exposure	Outcome- Asthma	Outcome – AD	Outcome- FA	Outcome- AR	Outcome- Other Allergic Disease
DeMuth (2013), United States [37]	Cross-sectional	104	Chronic conditions other than atopic disease	Parent report by questionnaire of use of any ASM during childhood	-	-	Food Allergy: By parent report with a reaction consistent with anaphylaxis and elevated food specific IgE or positive skin prick test	-	-
Jensen (2018), United States [38]	Case Control	136 cases 125 controls	Age > 18, symptoms of EOE started prior to age 3 years	Parental report by survey of ASM use during infancy	-	-	-	-	EOE: ≥15 eosinophils per high power field on endoscopy
Mitre (2018), United States [39]	Cohort	792,130	Initial birth hospital stay > 7 days, diagnosed with any allergic outcome by 6 months of age	Prescription for H2RA or PPI	Diagnosis code for asthma	Diagnosis code for atopic dermatitis	Diagnosis code for food allergy	Diagnosis code for allergic rhinitis	Allergic conjunctivitis: Diagnosis code Anaphylaxis: Diagnosis code Medication allergy: Diagnosis code Urticaria: Diagnosis code Contact dermatitis: Diagnosis code Other allergy: Diagnosis code

C. Adult exposure to ASM

Author (year), Location	Study Design	Sample Size	Excluded	Exposure	Outcome- Asthma	Outcome- AD	Outcome- FA	Outcome- AR	Outcome- Allergic Disease
Ramirez (2012), Spain [40]	Case Control	161 cases 318 controls	Allergic contact dermatitis, receipt of less than 1 systemic drug during admission	Receipt of PPI during admission	-	-	-	-	Drug Hypersensitivity: Cases identified by consultations to the allergy department and verified as drug hypersensitivity reaction based on record review

Abbreviations: AD: atopic dermatitis, ASM: acid suppressant medication, C-section: cesarean section, ED: emergency department, EOE: eosinophilic esophagitis, FA: food allergy, GA: gestational age, GERD: gastroesophageal reflux disease, H2RA: histamine-2 receptor antagonist, PPI: proton pump inhibitor, AR: allergic rhinitis.

*Medications included asthma medications, antihistamines, steroid ointments or epinephrine auto injector.

†Anti-asthmatic medications: Beta–agonist or inhaled glucocorticoid.

‡6 categories of medications including inhaled beta agonists, oral corticosteroids, inhaled corticosteroids, combined inhalers, montelukast, ipratropium bromide or cromoglycate.

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Table 2.

Results of observational studies assessing acid suppressant medications and development of allergic diseases

Author (year), Location	Confounders Included in Adjusted Analysis	Exposure	Outcome	Result
Prenatal exposure				
Dehlink (2009), Sweden [24]	Year of birth, maternal age, maternal parity, maternal smoking, maternal BMI	Any ASM Any ASM	Asthma Allergic Disease *	aOR 1.51 (1.35-1.69) aOR 1.43 (1.29-1.59)
Hak (2013), United Kingdom [25]	Sex, birth order, maternal age, number of general practice visits	H2RA or PPI PPI Only	Asthma Asthma	aOR 1.72 (1.00-2.07) aOR 2.76 (0.98-8.17)
Andersen (2012), Denmark [26]	Year of birth, sex, birth order, country of birth, maternal age, maternal smoking, maternal asthma, mode of delivery, maternal antibiotics during pregnancy, gestational age	H2RA Only PPI Only	Asthma Asthma	aIRR 1.47 (1.32-1.65) aIRR 1.41 (1.27-1.56)
Kallen (2013), Sweden [27]	Year of birth, maternal age, maternal parity, maternal smoking, maternal BMI	Any ASM	Asthma	aOR 1.32 (1.18-1.54)
Mulder (2013), Netherlands [28]	Maternal age	Any ASM	Asthma	aOR 1.52 (1.11-2.09)
Mulder (2014), Netherlands [29]	Sex, maternal age, maternal use of antibiotics during pregnancy, maternal history of allergic disease, childhood use of ASM	Any ASM Any ASM Any ASM Any ASM H2RA Only PPI Only	Asthma Atopic Dermatitis Allergic Rhinitis Allergic Disease † Allergic Disease † Allergic Disease †	aHR 1.57 (1.20-2.05) aHR 1.32 (1.06-1.64) aHR 2.40 (1.42-4.04) aHR 1.37 (1.14-1.66) aHR 1.52 (1.11-2.09) aHR 1.25 (0.98-1.59)
Cea Soriano (2016), United Kingdom [30]	Sex, maternal asthma, maternal comorbidities (GERD, allergic disease), maternal use of NSAIDs during pregnancy, maternal use of antacids, antibiotics, antihistamines during pregnancy, maternal primary care visits and referrals in the year prior to pregnancy ‡	H2RA Only PPI Only	Asthma Asthma	aHR 1.32 (1.05-1.64) aHR 1.03 (0.76-1.40)
Yitshak-Sade (2016), Israel [31]	Sex, year of birth, maternal age, maternal asthma, maternal allergies, maternal use of antibiotics or NSAIDs, maternal use of metoclopramide or insulin, history of infertility, lack of parental care, preterm delivery, low birth weight, delivered by C-section, child H2RA or PPI exposure	Any ASM	Asthma	aRR 1.09 (1.01-1.17)
Childhood Exposure				
DeMuth (2013), United States [37]	Age, sex, history of atopic dermatitis	Any ASM	Food Allergy	aPR 1.70 (1.10-2.50)
Jensen (2018), United States [38]	Maternal education	Any ASM	Eosinophilic Esophagitis	aOR 6.05 (2.55-14.40)
Mitre (2018), United States [39]	Sex, preterm delivery, delivery by C-section, other medication exposure in childhood	H2RA PPI	Asthma Atopic dermatitis Food allergy Allergic rhinitis Allergic conjunctivitis Anaphylaxis Medication allergy Urticaria Contact dermatitis Other Allergy	aHR 1.25 (1.21-1.29) aHR 1.12 (1.09-1.14) aHR 2.18 (2.04-2.33) aHR 1.50 (1.46-1.54) aHR 1.48 (1.35-1.62) aHR 1.51 (1.38-1.66) aHR 1.70 (1.60-1.80) aHR 1.30 (1.24-1.35) aHR 1.25 (1.22-1.28) aHR 1.63 (1.55-1.71)

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Author (year), Location	Confounders Included in Adjusted Analysis	Exposure	Outcome	Result
Prenatal exposure				
			Asthma Atopic dermatitis Food allergy Allergic rhinitis Allergic conjunctivitis Anaphylaxis Medication allergy Urticaria Contact dermatitis Other Allergy	aHR 1.41 (1.31-1.52) aHR 1.12 (1.07-1.17) aHR 2.59 (2.25-3.00) aHR 1.44 (1.36-1.52) aHR 1.15 (1.04-1.27) aHR 1.45 (1.22-1.73) aHR 1.84 (1.56-2.17) aHR 1.27 (1.17-1.38) aHR 1.21 (1.15-1.28) aHR 1.62 (1.45-1.80)
Adult Exposure				
Ramirez (2012), Spain [40]	Age, sex and hospitalization ward	PPI Only	Drug Hypersensitivity	aOR 4.35 (2.00-9.45)

Abbreviations: ASM: acid suppressant medications, aOR: adjusted odds ratio, aHR: adjusted hazard ratio, aRR: adjusted relative risk, aIRR: adjusted incidence rate ratio, aPR: adjusted prevalence ratio, BMI: body mass index, C-section: cesarean section, GERD: gastroesophageal reflux disease, H2RA: histamine-2 receptor antagonist, NSAIDs: non-steroidal anti-inflammatory drugs, PPI: proton pump inhibitor.

[*] Includes asthma, atopic dermatitis, food allergy, allergic rhinitis, and unspecified allergic reaction/anaphylaxis.

[†] Includes asthma, atopic dermatitis or allergic rhinitis.

[‡] Multiple models reported with additive adjustment for confounding.

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Table 3.

Prenatal exposure to acid suppressant medications and the development of asthma: meta-analysis results

Author (year)	# of Studies Included	Author (year) of studied included	Publication bias (P value for Egger test)	Asthma*		
				Prenatal Exposure	Result	Heterogeneity
Devine (2017) [35]	8	Dehlink (2009), Kallen (2013), Hak (2013), Mulder (2013), Mulder (2014), Andersen (2012), Cea Soriano (2016), Yitshak-Sade (2016)	Unlikely (P=0.415)	Any ASM H2RA PPI	RR 1.36 (1.16 −1.61) RR 1.46 (1.29-1.65) RR 1.30 (1.07-1.56)	I^2 = 87.6% I^2= 15.3% I^2= 42.5%
Lai (2018) [36]	8	Dehlink (2009), Kallen (2013), Hak (2013), Mulder (2013), Mulder (2014, Andersen (2012), Cea Soriano (2016), Yitshak-Sade (2016)	Unlikely (P>0.05)	Any ASM H2RA PPI	RR 1.31 (1.15-1.49) RR 1.57 (1.46-1.69) RR 1.34 (1.18-1.52)	I^2 = 84% I^2= 0% I^2= 46%
	5	Dehlink (2009), Kallen (2013), Mulder (2013), Mulder (2014), Andersen (2012), Cea Soriano (2016)	Unlikely (P>0.05)	Any ASM**	RR 1.45 (1.35-1.56)	I^2 = 0%

Abbreviations: ASM: acid suppressant medications, BMI: body mass index, GRADE: Grading of Recommendations, Assessment, Development and Evaluation, H2RA: histamine-2 receptor antagonist, PPI: proton pump inhibitor, NOS: Newcastle-Ottowa Sclae.

*Other allergic diseases included atopic dermatitis, food allergy, allergic rhinitis, eosinophilic esophagitis, drug hypersensitivity reaction or other allergic reactions. However, there was insufficient data for analysis of these outcomes.

**Results of sensitivity analysis.