Letter to the Editor

Acid-suppressive medications during pregnancy and risk of asthma and allergy in children: A systematic review and meta-analysis

To the Editor:

Acid-suppressive medications, such as H2-receptor antagonists (H2RA) and proton pump inhibitors (PPI), are the main treatment options for dyspepsia and gastroesophageal reflux disease. These are common problems in pregnancy.[1] Recently, concerns have been raised that prenatal exposure to these medications may increase the risk of allergic disease in the offspring.[1] Dehlink et al[1] were the first to report these associations, proposing that use of acid-suppressive medications in pregnancy may increase the risk of allergic disease in the offspring through interference with maternal digestion of labile antigens, thereby increasing the amount of allergen to which the fetus is exposed. PPI use has also been linked to changes in the intestinal microbiota composition,[2] which may also increase the risk of T_H2-mediated conditions, such as asthma and allergy. Dehlink et al[1] therefore proposed that acid-suppressive medications could operate through 1 or both of these mechanisms, inducing a T_H2 cytokine pattern in mothers that could then cross the fetal membrane and induce sensitization of fetal immune cells to food and airborne allergens prior to birth.

An increasing number of studies have now investigated the impact of prenatal exposure to acid-suppressive medications on the risk of allergic disease in the offspring but with inconsistent results.[1,3-9] To obtain a clearer appreciation of the evidence base, we undertook a systematic review and meta-analysis of these studies. We were also interested in clarifying whether use of the subtypes of acid-suppressive medications, namely H2RA and PPIs, was associated with asthma/allergy and whether any associations uncovered varied by time (trimester), dose, and frequency of exposure.

We included analytical epidemiological studies (ie, cohort, case-control, and cross-sectional studies). We excluded reviews, case studies and case series, and animal studies. All women during preconception and pregnancy and their offspring who were ≤17 years were eligible for inclusion. Our primary outcomes were (1) objectively defined asthma, atopic dermatitis/eczema, allergic rhinitis or hay fever, food allergy, urticaria, and anaphylaxis and (2) atopic sensitization as defined either by skin prick test or raised antigen-specific IgE (see description of secondary outcomes in Study outcomes of this article's Online Repository at www.jacionline.org).

To identify relevant studies, we searched 11 electronic databases and searched databases of ongoing studies and conference abstracts (see details in the Information sources, search strategy, and study selection section of this article's Online Repository). We also contacted experts in the field to identify additional studies and any ongoing studies. We developed a detailed search strategy in MEDLINE, which was then adapted for searching other databases (Table E1 in this article's Online Repository at www.jacionline.org). All databases were searched from inception to the end of 2015, with no language restrictions. Two reviewers (R.E.D. and B.I.N.) independently screened all titles and/or abstracts, screened full texts of potentially eligible studies, extracted study data onto a customized data extraction form, and quality appraised all studies using the Effective Public Health Practice Project tool (Hamilton, Ontario, Canada). Any discrepancies in the process were resolved by discussion or a third reviewer (N.M.) arbitrated. We graded key components from which we derived an overall grading for each study as strong, moderate, or weak (see Tables E2 and E3 in this article's Online Repository at www.jacionline.org).

We employed random-effects meta-analysis to quantify the pooled effect estimates for reasonably homogeneous studies. Meta-analysis was possible with studies on risk of asthma but not for other outcomes due to insufficient number of studies. Dosage, trimester, and frequency of exposure to acid-suppressive medications were differentially reported across studies; hence we were unable to pool studies on these exposures. We quantified the level of heterogeneity between studies using the I^2 statistic (values near 0 indicate good homogeneity across studies). Meta-analyses were undertaken using Stata 14 (StataCorp LP, College Station, Tex). See this article's Online Repository (www.jacionline.org) for a fuller description of our approach to data synthesis and application of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Of the 3282 records identified from our searches, 8 studies[1,3-9] met our inclusion criteria (see Fig E1 in this article's Online Repository at www.jacionline.org). Key characteristics of the studies are presented in Table E2 (in this article's Online Repository at www.jacionline.org). Six studies were graded as strong and 2 as moderate. In pooled analysis, use of any acid-suppressive medications (risk ratio, 1.36; 95% CI, 1.16-1.61; I^2 = 87.6%), H2RA (hazard ratio, 1.46; 95% CI, 1.29-1.65; I^2 = 15.3%), and PPI (hazard ratio, 1.30; 95% CI, 1.07-1.56; I^2 = 45.2%) were associated with an increased risk of asthma (Figs 1 and 2). Results of sensitivity analyses are given in this article's Online Repository. Two studies that considered other allergic disorders both reported an increased risk among offspring of mothers using any acid-suppressive medications, H2RA, and PPIs compared with the offspring of nonusing mothers[1,7] (see Table E2 in this article's Online Repository). By applying the GRADE approach, we graded the evidence regarding the risk of asthma as moderate, but evidence regarding other allergic outcomes as very low (see Table E4 in this article's Online Repository at www.jacionline.org). The Egger test (to evaluate publication bias and small-study effect) for the association between use of any acid-suppressive medications and risk of asthma showed $P = .415$.

Our literature search was comprehensive. We had no language restriction, used reproducible search strategies, and applied rigorous review processes, which were enhanced by publishing and registering a detailed protocol prior to undertaking the review.[10] The degree of heterogeneity among studies was low; the only case of high heterogeneity was due to differences in the definition of the exposure. In the course of our literature search, we found a recent systematic review from Google Scholar, published in Chinese in a local journal.[11] Five studies were included in that review and were meta-analyzed. On translation to English, we found that the systematic review process was deficient in many aspects, including the following: lack of information about quality assessment, data extraction, or the

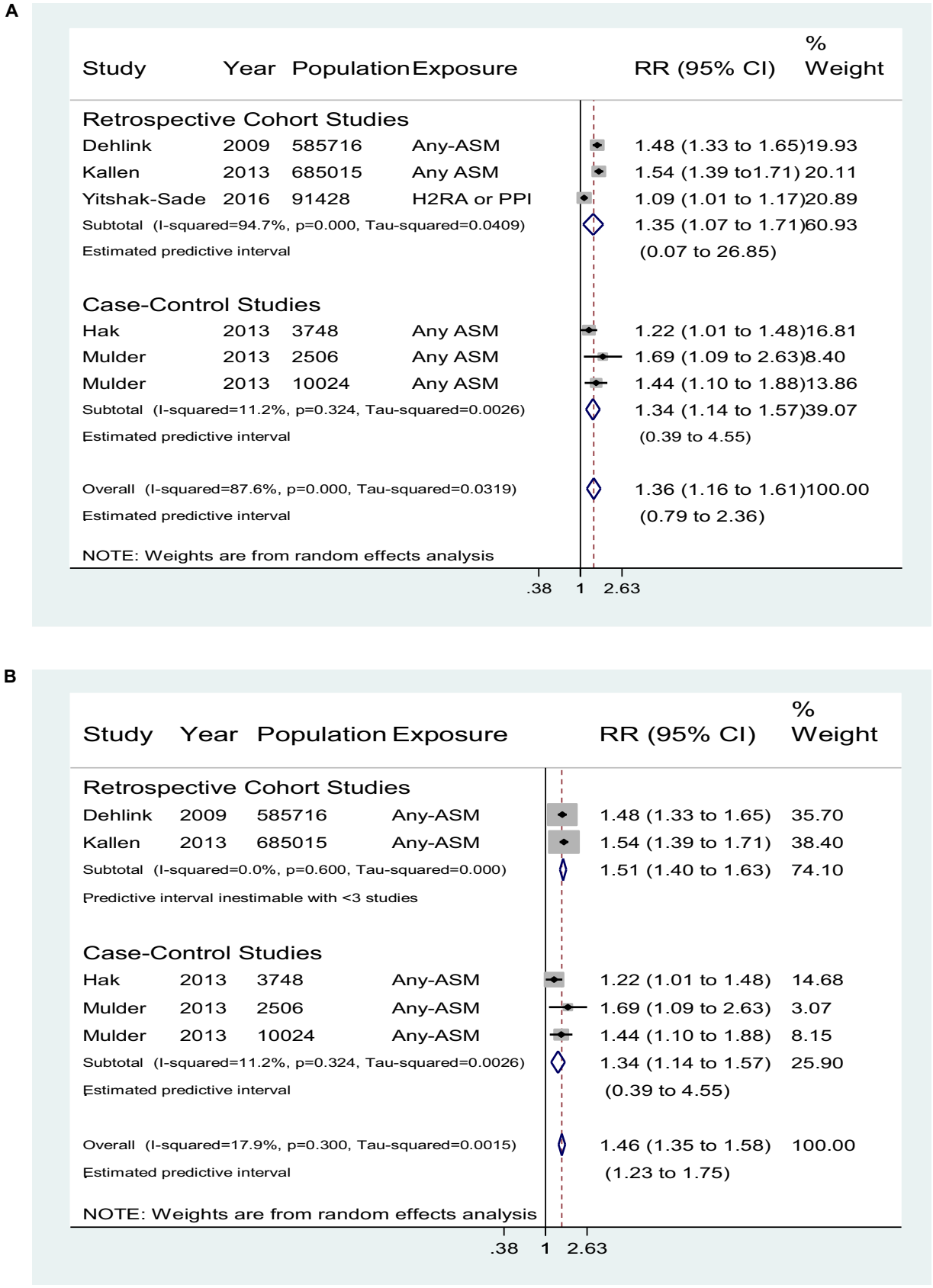

FIG 1. Meta-analysis of studies investigating the association between maternal use of any acid-suppressive medication (*ASM*) during pregnancy and the risk of asthma in the offspring. *RR* represents the risk ratio of association. **A,** Estimates by study design. **B,** Estimates by study design, excluding Yitshak-Sade 2016. Population represents the number of participants recruited into the study. *H2RA,* H2-receptor antagonists; *PPI,* proton pump inhibitors.

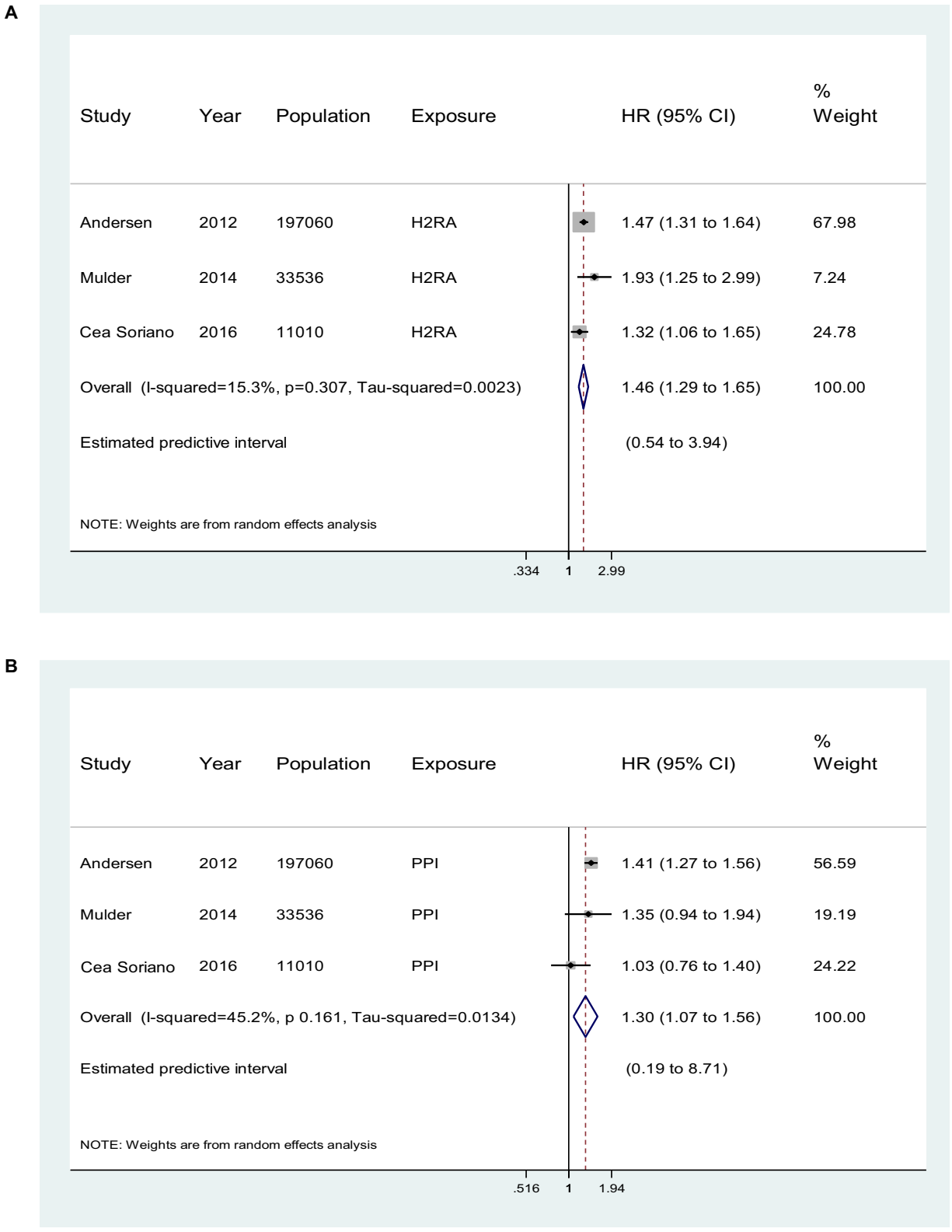

FIG 2. A and **B,** Meta-analysis of studies investigating the association between maternal use of H2-receptor antagonists (*H2RA*) and proton pump inhibitors (*PPI*) during pregnancy and the risk of asthma in the offspring. *HR* represents the hazard ratio of association. Population represents the number of participants recruited into the study.

number of reviewers involved; unclear decisions regarding meta-analysis decisions (whether fixed-effect or random-effects meta-analysis was used) or the approach employed to evaluate heterogeneity between studies.

Animal models and studies undertaken in adults suggest that acid-suppressive medications may interfere with peptide digestion, thereby inducing a T_H2 cytokine dominance, which may result in subsequent sensitization of the immune system.[1] Such interference may increase the amount of allergen the fetus is exposed to via the placenta, thereby resulting in sensitization and subsequent development of allergic disorders and asthma.[1] Our findings of increased risk may reflect a true risk or may be explained by residual confounding and/or confounding by indication. Of note is that none of the studies adjusted for the full panel of known confounders in these associations. Although we cannot recommend any changes to the use of acid-suppressive medications by expectant mothers, further research is needed, particularly through mounting pharmacovigilance studies, which may prove more ethically acceptable and feasible than initiating randomized controlled clinical trials.

We are grateful to Marshall Dozier and Angela Nicholson, the Academic Librarians at The University of Edinburgh, for their advice on the construction of search strategies. We are grateful to Io Hui for her help in translating 1 paper from Chinese. Finally, we wish to express our sincere gratitude to the experts contacted who responded, including Eelko Hak, Edda Fiebiger, Lucia Soriano, Rafael Gorodischer, and in particular to Maaya Yitshak-Sade who provided additional data.

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METHODS

Ethics approval

We completed the University of Edinburgh's Usher Institute of Informatics and Population Health Sciences Level 1 Ethics Clearance, which revealed that no further ethics clearance is required because the study is based on published literature.

Protocol and registration

Prior to commencement of the review, we developed a detailed protocol, which was published[E1] and registered with the International Prospective Register of Systematic Reviews (PROSPERO; www.crd.york.ac.uk/prospero/, reference CRD42015029584).

Eligibility criteria

We included analytical epidemiological studies: cohort, case-control, and cross-sectional studies. We excluded reviews, case studies and case series, and animal studies. All women during preconception and pregnancy and their offspring who were ≤17 years were eligible for inclusion.

Types of exposure

We considered all studies that investigated the association between maternal use of any type of acid-suppressive medications ([ASMs], ie, H2-receptor antagonists [H2RA], proton pump inhibitors [PPIs], and antacids) during pregnancy and the risk of asthma and allergy in the offspring. We also considered the dose, frequency, and timing (trimester) of use of these medications.

Study outcomes

Our primary outcomes were objectively defined asthma, atopic dermatitis/eczema, allergic rhinitis or hay fever, anaphylaxis, food allergy, urticaria, and anaphylaxis by physician or hospital record or self-reported. Atopic sensitization as defined either by skin prick test or raised antigen-specific IgE. Secondary outcomes included objective and subjective measures of disease severity and impact on quality of life, including asthma exacerbations, use of asthma medications, hospitalization for asthma, wheeze as defined by self-report or objective diagnosis; indicators of airway function including (peak expiratory flow, forced expiratory volume in 1 second, forced vital capacity, forced expiratory flow rate or alternative age appropriate pulmonary function tests [oscillometry or exhaled nitric oxide analysis]); and measures of health-related quality of life.

Information sources, search strategy, and study selection

We searched the following international electronic databases: MEDLINE, EMBASE, Web of Science CORE, BIOSIS, CINAHL, Cochrane Library, Global Health CABI, Global Health Library, Scopus, Popline, and Google Scholar. Additional studies were retrieved by manual search of the references of eligible papers and by contacting a panel of international experts on the topic. Conference abstracts were retrieved by searching ISI Conference Proceedings Citation Index via Web of Knowledge and ZETOC (British Library). Unpublished and in-progress studies were identified by searching Current Controlled Trials, ClinicalTrials.gov, Australian and New Zealand Clinical Trials Registry. We developed a detailed search strategy in MEDLINE, which was then adapted in searching other databases (Table E1). All databases were searched from inception to the end of 2015, with no language restrictions. Identified records were exported to Endnote Library for screening. After removal of duplicate records, 2 reviewers (R.E.D. and B.I.N.) independently screened all titles and/or abstracts. Full texts of potentially eligible studies were obtained and independently screened for inclusion by the 2 reviewers. Studies that did not fulfill the inclusion criteria were excluded. Any discrepancies in the screening process were resolved by discussion.

Data extraction and quality assessment

Two reviewers (R.E.D. and B.I.N.) independently extracted study data onto a customized data extraction form. The data extraction form was piloted and revised prior to use in collecting data from all studies. Discrepancies in data extraction were resolved by discussion and arbitration by a third reviewer (N.M.). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist guided reporting.[E2]

Risk of bias in individual studies

Two reviewers (R.E.D. and B.I.N.) independently undertook the risk of bias analysis in the study using the Effective Public Health Practice Project tool (Hamilton, Ontario, Canada), which was adapted for use in this review. We graded key components of each study as strong, moderate, or weak: suitability of the study design for the research question, validity of exposure and outcome assessments, potential for selection bias, and appropriate adjustment for confounding factors. From these component-specific assessments, we derived an overall grading for each study as strong, moderate, or weak. Any discrepancies were resolved by discussion or a third reviewer (N.M.) arbitrated.

Summary measures

Eligible studies reported 1 of the following effect measures: hazard ratio (HR), risk ratio (RR), or odds ratio (OR). Although Andersen et al[E3] stated that they estimated incidence rate ratios using Cox proportional hazard regression, we took these estimates as HR in the pooled analysis because the Cox model estimates the hazard function. Mulder et al[E4] and Soriano et al[E5] also reported HR. Yitshak-Sade et al[E6] reported RR; estimates of studies reporting OR[E7-E10] were converted to RR using the formulae by Grant[E11] and then pooled with the Yitshak-Sade et al[E6] study. The formula for conversion is given as follows: $RR = OR/[1 - p_0 + (p_0 \times OR)]$, where p0 is the baseline risk. The baseline risks for Dehlink et al[E7] and Källén et al[E8] were taken from the respective papers. The baseline risk for Mulder et al (2013)[E9] was taken from Mulder et al (2014),[E4] which was based on the same study population. For Hak et al,[E10] we used the prevalence estimate (4.2%) reported elsewhere but based on a similar primary care database.[E12] The RR derived from these calculations are presented in Table E5.

Data synthesis

Of the 8 studies, 6 were retrospective cohort studies,[E3-E8] and 2 were case-control studies.[E9,E10,E13,E14] We summarized the overall evidence both narratively and quantitatively. For the quantitative synthesis, we employed random-effects meta-analysis to quantify the pooled effect estimates for sufficiently clinically, methodologically, and statistically homogeneous studies. Mulder et al (2013)[E9] analyzed 2 sets of control populations that were compared with the same asthma cases: sibling-based controls and non-sibling-based controls. In the analysis, we treated these sets of case-control populations independently. This was applicable for use of any ASMs, H2RA only, and PPIs only; there were no data on use of antacids. Dosage of ASMs and trimester of exposure were differentially reported across studies; hence we were unable to pool studies on these exposures. Meta-analysis was possible only with studies on asthma and not for other outcomes as an insufficient number of studies were available for other allergic outcomes. In the meta-analysis, studies reporting HR and RR were separately pooled. We quantified the level of heterogeneity between studies using the I^2 statistic. In addition to the overall summary effect estimate, we also estimated the 95% prediction interval, which takes into account the overall uncertainty surrounding the summary effect and heterogeneity across studies to provide a range for which we are 95% confident that the effect of ASMs on the risk of asthma in new studies would lie.[E13] Given that the number of studies for each meta-analysis was small, thus lacking the required power (ie, less than the recommended minimum of 10 studies),[E14] we were unable to graph the funnel plots to evaluate possible publication bias or small study effect; hence we performed the Begg and Egger tests for this purpose.[E15] Meta-analyses were undertaken using Stata statistical software (release 14; StataCorp LP, College Station, Tex).

Sensitivity analyses

Given observed high heterogeneity across studies in the meta-analysis of the association between use of any ASMs or H2RA/PPIs, we undertook the following steps to explore possible reasons for the heterogeneity. First, we stratified the analysis by study design (cohort vs case-control studies). Second, given that within the cohort studies, in comparison to other studies, the study by Yitshak-Sade et al (2015) studied use of H2RA or PPIs rather than use of any ASMs, we excluded that study to assess its impact on the heterogeneity across studies.

Grading the quality of the overall body of evidence

Using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, we first identified all potentially relevant outcomes and rated their relative clinical importance: asthma was considered a critical outcome; atopic dermatitis/eczema, allergic rhinitis, and other allergic disorders were considered as important outcomes. Second, we appraised the quality of the overall evidence for each outcome and presented this information using the GRADE evidence profiling table template.[E16]

RESULTS

Study selection

We identified 3282 records, of which 3057 were included for screening by title and/or abstract after deduplication. Of these, 3033 were excluded for not meeting the inclusion criteria, leaving 24 papers for full text screening. A further 16 papers were excluded, leaving 8 papers that met our inclusion criteria (Fig E1).[E3-E10]

Study characteristics

All studies were either based on a primary care database or population-based prescription or dispensing database. Two studies each were undertaken in The Netherlands,[E4,E9] Sweden,[E7,E8] and United Kingdom,[E5,E10] whereas 1 study each was undertaken in Denmark[E3] and Israel.[E6] All studies considered asthma as an outcome and 2 additionally considered other allergic disorders, including atopic dermatitis/eczema and allergic rhinitis.[E4,E7] Whereas most studies considered use of any ASMs or H2RA/PPIs,[E4,E7-E10] the independent role of H2RA and PPIs were examined in 3 studies,[E3,E4,E6] but no study examined the role of antacids alone. Seven of the studies also considered the trimester of exposure to ASMs, and 3 examined the dosage of use, commonly defined as defined daily doses; however, marginally different definitions of trimester and dosage were used across studies.

Risk of bias within studies

Based on overall risk of bias assessment in the studies, 6 studies were graded as strong and 2 as moderate. The overall quality grading was derived from the grading for the different components of the studies. Apart from Mulder et al,[E9] which was graded weak for confounding adjustment, all other studies were graded moderate or strong for all components (Table E3).

Use of ASMs and risk of asthma

Across individual studies, offspring of mothers who used any ASMs during pregnancy were at an increased risk of asthma compared with offspring of nonusers (Table E2). The results were similar when H2RA and PPIs were examined separately, except for imprecise estimates from 2 studies.[E4,E5] Higher dosage of ASMs appeared to show a greater risk compared with lower dosage (Table E2). Whereas use of ASMs during any trimester of pregnancy was associated with an increased risk of asthma, there was no clear indication that any specific trimester was associated with greatest risk (Table E2). The high heterogeneity in the analysis of the use of any ASMs was reduced in further exploration, as explained in the sensitivity analysis section.

Use of ASMs and risk of other allergic disorders

The association between use of ASMs and other allergic disorders was investigated by 2 studies,[E4,E7] both reporting an increased risk among offspring of mothers using any ASMs, H2RA, and PPIs, compared with those of nonusing mothers (Table E2). Mulder et al,[E4] in addition, reported an increased risk of atopic dermatitis/eczema and allergic rhinitis with use of ASMs, although estimates were imprecise in some cases for the independent roles of H2RA and PPIs (data not shown). Given the different effect measures used by Dehlink et al[E7] (OR) and Mulder et al[E4] (HR), and considering that only Mulder et al (2014)[E4] examined atopic dermatitis/eczema and allergic rhinitis, we could not calculate pooled estimates of the association between ASMs and risk of allergic disorders other than asthma.

Sensitivity analyses

By stratifying the association between use of any ASMs or H2RA/PPIs by study design, the results showed that the high heterogeneity was specific to the cohort studies (Fig 1). Further exclusion of the study by Yitshak-Sade et al[E6] reduced the heterogeneity in all studies from the initial 87% to 18% and the heterogeneity in the cohort studies from 95% to 0% (Fig 1). Stratification of the results by study design and exclusion of the Yitshak-Sade et al[E6] study did not dramatically change the pooled relative effect estimates, but did result in a more precise predictive interval (1.23-1.75) (Fig 1).

Grading quality of the overall body of evidence

By applying the GRADE system (Table E4), we graded the evidence regarding risk of asthma as moderate. None of the studies assessed the possible influence of confounding by indication or unmeasured confounding, and ASMs data were based on either prescribed or dispensed medication without information on actual use. It is therefore possible that the results could be partly explained by these factors. Given very few studies, we graded the evidence regarding atopic dermatitis/eczema, allergic rhinitis, and other allergic outcomes as very low.

Assessment of publication bias

We calculated the Egger test for the association between use of any ASMs and risk of asthma, and the result showed $P = .415$ (Table E5), indicating that publication bias or small study effect was unlikely to have influenced our results.

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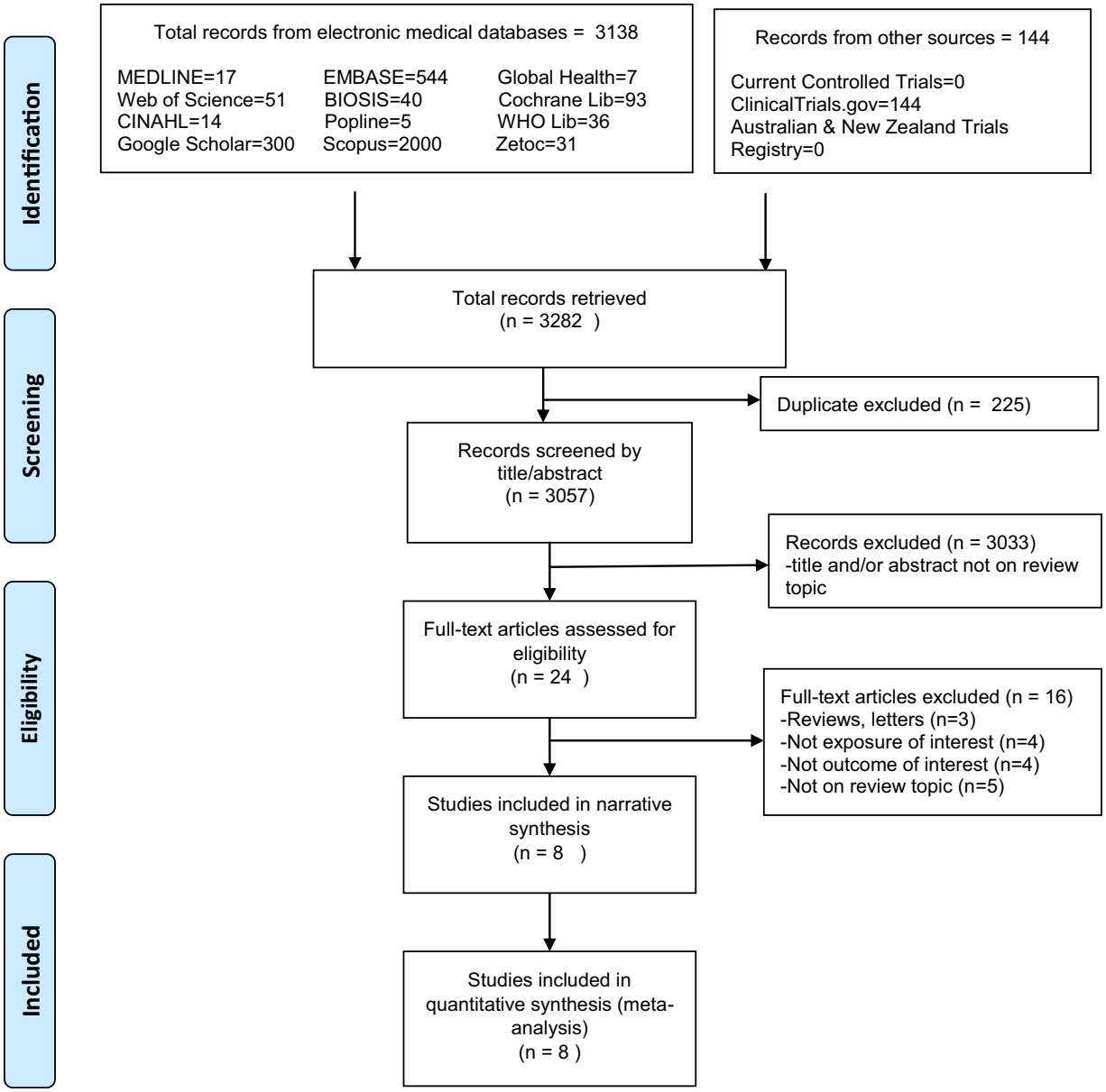

FIG E1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for database search of studies investigating the association between maternal use of acid-suppressive medications during pregnancy and risk of asthma and allergy in the offspring.

TABLE E1. MEDLINE search strategies used to identify studies and adapted in searching other databases

1.	exp Proton Pump Inhibitors/OR *Gastroesophageal Reflux/OR exp Anti-Ulcer Agents/OR exp Histamine H2 Antagonists/OR *Helicobacter Infections/
2.	exp Antacids/OR antacid.mp.
3.	exp Aluminum Hydroxide/ae, tu [Adverse Effects, Therapeutic Use]
4.	magnesium carbonate.mp.
5.	magnesium trisilicate.mp.
6.	hydrotalcite.mp.
7.	Alginates.mp. OR exp Alginates/
8.	Omeprazole/
9.	Lansoprazole/
10.	Esomeprazole/
11.	Rabeprazole/
12.	pantoprazole.mp.
13.	Cimetidine/
14.	Famotidine/
15.	Nizatidine/
16.	Ranitidine/
17.	OR/1-16
18.	exp pregnancy trimesters/
19.	pregnancy/
20.	antenatal.mp
21.	Pregnancy Trimester, Third/or exp Pregnancy/or Pregnancy Trimester, First/or Pregnancy Trimester, Second/or Pregnancy Trimesters/or pregnancy.mp.
22.	exp Asthma/
23.	asthma.mp.
24.	wheez*.mp.
25.	exp Bronchial Hyperreactivity/
26.	airway hyperreactivity.mp.
27.	bronchial disorder.mp.
28.	lung function.mp.
29.	respiratory function.mp.
30.	ventilatory function.mp.
31.	airway function.mp.
32.	Vital Capacity/
33.	Forced Expiratory Volume/
34.	Peak Expiratory Flow Rate/
35.	peak expiratory flow.mp.
36.	exp hypersensitivity/
37.	exp dermatitis, allergic contact/
38.	exp hypersensitivity, immediate/
39.	anaphylaxis/
40.	conjunctivitis, allergic/
41.	dermatitis, atopic/
42.	exp food hypersensitivity/
43.	exp respiratory hypersensitivity/
44.	exp rhinitis, allergic/
45.	exp urticaria/
46.	angioedema/
47.	eczema/
48.	allergy.mp.
49.	atopy.mp.
50.	OR/22-49
51.	Limit 50 to “all child (0-18 years)”
52.	OR/18-21
53.	17 AND 51 AND 52

TABLE E2. Main characteristics, key results, and overall risk of bias assessment of the studies investigating the association between maternal use of ASMs during pregnancy and risk of asthma and allergy in the offspring

Reference, country; study design	Study population N (maternal-child; source of study population)		Age of children/ follow-up years	Exposure assessment	Outcome studied and assessment method		Occurrence measure(s) and approach to statistical analysis	Key results	Overall risk of bias assessment
	Number recruited	Number analyzed			Outcome(s) studied and definition	Method of outcome assessment			
Andersen et al[E3] (2012); Denmark; retrospective cohort study	197,060; Population recruited from the Danish Medical Birth Registry	197,060	Maximum follow-up of 14 y; median 6.8 y	Ascertained from the Aarhus University Prescription Database. Studied use of PPI, H2RA; their dosages (PPI: ≤28 pills, >28 pills; H2RA: ≤20 pills, >20 pills); and trimester (first, second, and third combined) of exposure. Also considered preconception and postpregnancy exposures	Asthma: having a record of a hospitalization, out-patient visit, emergency room visit plus asthma diagnosis OR dispensations record for of antiasthmatic medication	Ascertained from records of inpatient, outpatient, and emergency room visits from the Danish National Registry of Patients. Coded using ICD-10	The authors stated they estimated incidence rate ratio for the associations using Cox proportional hazards regression. As the Cox model estimates the hazard function, the correct measure here should be HR. Adjusted for year of birth, county, sex, gestational age, birth order, maternal age, maternal smoking, maternal asthma, delivery mode, and maternal use of antibiotics during pregnancy	(HR, 95% CI); reference is nonuse. PPI: (1.41, 1.27-1.56), ≤28 pills (1.20, 1.01-1.43), >28 pills (1.54, 1.36-1.75) H2RA: (1.47, 1.32-1.65), ≤20 pills (1.44, 1.06-1.95), >20 pills (1.48, 1.31-1.67) Trimester (ie, use of PPI or H2RA): first trimester (1.46, 1.27 to1.67); second/third trimester (1.34, 1.15-1.56)	Strong
Dehlink et al[E7] (2009); Sweden; retrospective cohort study	860,215; Linkage of the Medical Birth Register, the Hospital Discharge Register, and the Swedish Prescribed Drug Register	585,716	Maximum follow-up of 11 y	Ascertained from the Medical Birth Register. Studied use of any ASM, including PPI, H2RA, and other drugs used for peptic ulcer and gastroesophageal reflux disease. Also considered the trimester of exposure (first trimester; late pregnancy)	Allergy: ever hospitalized for an allergic disease (food allergy, atopic dermatitis, allergic rhinitis, anaphylaxis) or received 2 or more prescriptions for allergy medication Asthma: hospitalized or received prescription for medication for asthma	Ascertained from the Hospital Discharge Register and the Prescribed Drug Register. Outcomes coded using the ICD-9 and 10	OR using the Mantel-Haenszel procedure; 95% CI calculated using the Miettinen test method. Adjusted for year of birth, parity, maternal age, maternal smoking, maternal BMI	(OR, 95% CI); reference is nonuse. Any ASM and allergy: (1.43, 1.29-1.59); first trimester (1.38, 1.22-1.57); later pregnancy (1.34, 1.11-1.63) Any ASM and asthma: (1.51, 1.35-1.69) H2RA and allergy: (1.41, 1.16-1.70) PPI and allergy: (1.46, 1.27-1.66) Other ASM: (1.29, 1.04-1.60)	Strong

(Continued)

TABLE E2. *(Continued)*

Reference, country; study design	Study population N (maternal-child; source of study population)		Age of children/ follow-up years	Exposure assessment	Outcome studied and assessment method		Occurrence measure(s) and approach to statistical analysis	Key results	Overall risk of bias assessment
	Number recruited	Number analyzed			Outcome(s) studied and definition	Method of outcome assessment			
Hak et al[E10] (2013); United Kingdom; case-control study	Cases: 1874; Controls (siblings of cases): 1874 Population recruited from the CPRD	Cases: 1874; Controls: 1874	Maximum 14 y of follow-up. Mean age at diagnosis of asthma 3.6 y	Ascertained from the CPRD database. Studied use of any ASM, including PPI, H2RA, and use of other antacids. Also considered the trimester of exposure (first/second trimester; third trimester)	Asthma: received a diagnosis of asthma and was prescribed any asthma medications ≥3 times within 12 months after the first diagnosis date	Ascertained from the CPRD database. Asthma cases coded using the Read coding system	OR using conditional logistic regression. Adjusted for sex, birth order, maternal age at birth, and number of GP visits during pregnancy	(OR, 95% CI); reference is non-use. Any ASM: (1.23, 1.01-1.51); first/second trimester (1.01, 0.79-2.08); third trimester (1.29, 1.03-1.62) PPI or H2RA: (1.72, 1.00-2.07); PPI: (2.76, 0.93-8.17) H2RA: (1.56, 0.85-2.90) Other ASM: (1.16, 1.95-1.42)	Strong
Källén et al[E8] (2013); Sweden; retrospective cohort study	685,015; Linkage of the Swedish Medical Birth Register and the Swedish Prescribed Drug Register	685,015	2-6 y	Ascertained from the Swedish Medical Birth Register. Studied use of any ASM during the second or third trimester	Asthma: having ≥5 prescription events for antiasthmatic drugs during follow-up	Ascertained from the Swedish Prescribed Drug Register	OR using the Mantel-Haenszel procedure; 95% CI calculated using the Miettinen test method. Adjusted for year of birth, maternal age, parity, smoking, BMI, and use of other drugs during pregnancy	(OR, 95% CI); reference is nonuse. Any ASM during second or third trimester of pregnancy: (1.60, 1.40-1.76)	Moderate
Mulder et al[E9] (2013); The Netherlands; case-control study	Two sets of case-control analyses: 1. Sibling-based controls (cases: 1253; controls: 1253) 2. Nonsibling-based controls (cases: 1253; controls: 8771). From The University of Groningen IADB.nl pharmacy prescription database	1. Cases: 1253; controls: 1253; 2. Cases: 1253; controls: 8771	≤5.5 y	Ascertained from the University of Groningen IADB.nl pharmacy prescription database using ATC codes. Studied use of any ASM and dosage (DDD) of use – 0-14 DDD; >14 DDD	Asthma: having ≥2 prescriptions for asthma medication during 6 months of follow-up	Ascertained from the University of Groningen IADB.nl pharmacy prescription database and coded using the ATC coding system	OR using conditional logistic regression. Adjusted for maternal age at birth in the nonsibling case-control analysis, but not in the sibling case-control analysis as that variable was not a confounder in the latter analysis. Other factors—maternal asthma, sex of child, sequence of birth, and use of ASM by child were tested *a priori* as confounders but did not indicate any confounding role; hence they were not adjusted in the analyses	(OR, 95% CI); reference is nonuse. 1. Sibling case-control analysis: any ASM: (1.85, 1.07-3.19) 0-14 DDD: (1.19, 0.61-2.31) >14 DDD: (2.56, 1.18-5.52) 2. Nonsibling case-control analysis: any ASM: (1.52, 1.11-2.10) 0-14 DDD: (1.18, 0.73-1.91) >14 DDD: (1.89, 1.24-2.88)	Moderate

(Continued)

TABLE E2. *(Continued)*

Reference, country; study design	Study population N (maternal-child; source of study population)		Age of children/ follow-up years	Exposure assessment	Outcome studied and assessment method		Occurrence measure(s) and approach to statistical analysis	Key results	Overall risk of bias assessment
	Number recruited	Number analyzed			Outcome(s) studied and definition	Method of outcome assessment			
Mulder et al[E4] (2014); The Netherlands; retrospective cohort study	40,628; From The University of Groningen IADB.nl pharmacy prescription database	33,536	Maximum of 8 y follow-up. Median follow-up 4.9 y	Ascertained from the University of Groningen IADB.nl pharmacy prescription database using ATC codes. Studied use of PPI or H2RA, PPI only, H2RA only, dosages (0-15, >15 DDD); trimester of exposure (first/second trimester, third trimester)	Asthma: ≥2 inhaled steroid prescription within 12 months Atopic dermatitis: ≥2 prescriptions for ointment containing either steroid or calcineurin inhibitors Tacrolimus or pimecrolimus Allergic rhinitis: ≥2 prescriptions for nasal steroids within a 12-month period	Ascertained from the University of Groningen IADB.nl pharmacy prescription database and coded using the ATC coding system	HR using Cox proportional hazard regression. Adjusted for year of birth, sex of child, use of ASM by child, maternal age at birth, maternal use of systemic antibiotics during pregnancy, and maternal allergy	(HR, 95% CI); reference is nonuse. Results for use of ASM and asthma (results for atopic dermatitis and allergic rhinitis are given in Mulder et al 2014) H2RA or PPI: (1.57, 1.20-2.05) 0-15 DDD: (1.37, 0.84-2.25) >15 DDD: (1.68, 1.21-2.32) first/second trimester: (1.64, 1.12-2.41) third trimester: (1.32, 0.77-2.25) H2RA: (1.93, 1.25-3.00) PPI: (1.35, 0.94-1.94)	Strong
Cea Soriano et al[E5] (2016); United Kingdom; retrospective cohort study	14,522; From the Health Improvement Network database	11,010	Maximum of 6 y follow-up	Ascertained from the Health Improvement Network database using Read codes. At least 1 prescription of ASM (PPI, H2RA) during pregnancy. Also considered trimester of exposure (first, second, third, all 3 trimesters).	Asthma: based on GP-recorded clinical asthma events suggestive of asthma symptoms	Ascertained from the Health Improvement Network database using Read codes	HR using Cox proportional hazard regression. Adjusted for maternal primary care physician visits before and during pregnancy, maternal asthma, maternal comorbidities, maternal use of nonsteroidal anti-inflammatory drugs, antibiotics, antihistamines during pregnancy, sex of child	(HR, 95% CI); reference is nonuse. H2RA: anytime (1.32, 1.05-1.64); first trimester (1.15, 0.77-1.72); second trimester (1.75, 1.25-2.47); third trimester (1.20, 0.93-1.54); all 3 trimesters (1.26, 0.51-3.08) PPI: anytime (1.03, 0.76-1.40); first trimester (1.07, 0.76-1.51); second trimester (1.11, 0.60-2.05); third trimester (0.69, 0.36-1.30); all 3 trimesters (0.73, 0.23-2.31)	Strong

(Continued)

TABLE E2. *(Continued)*

Reference, country; study design	Study population N (maternal-child; source of study population)		Age of children/ follow-up years	Exposure assessment	Outcome studied and assessment method		Occurrence measure(s) and approach to statistical analysis	Key results	Overall risk of bias assessment
	Number recruited	Number analyzed			Outcome(s) studied and definition	Method of outcome assessment			
Yitshak-Sade[E6] et al (2016); Israel; retrospective cohort study	91,459; From the "Clalit" Health Services HMO database	91,428	3-13 y follow-up	Ascertained from the "Clalit" Health Services HMO medication dispensing registry. Maternal use of H2RA or PPI 2 months prior to and during pregnancy. Studied use of H2RA, PPI, trimester of exposure, and DDD	Asthma: hospitalization for asthma or had recurrent wheeze diagnosis. Classified using ICD-9	Ascertained from the "Clalit" Health Services HMO medication dispensing registry	RR using generalized estimating equations. Adjusted for maternal allergy or asthma, maternal age, infertility treatment, prenatal care, gestational age at birth, cesarean section birth, birth weight, child sex, year of birth, child use of ASM ≤2 years, maternal use of antibiotics, nonsteroidal anti-inflammatory drugs, metoclopramide and insulin	(RR, 95% CI); reference is nonuse. H2RA or PPI: anytime (1.09, 1.01-1.17) <10 DDD: (1.05, 0.94-1.17) 10-20 DDD: (1.07, 0.96-1.18) >20 DDD: (1.12, 1.06-1.18) first trimester: (1.08, 0.97-1.21) second trimester: (1.11, 0.93-1.32) third trimester: (0.99, 0.82-1.20) H2RA: (1.06, 0.97-1.15) PPI: (1.10, 0.98-1.22)	Strong

ASM, Acid-suppressive medication; *ATC*, Anatomical Therapeutic Chemical; *BMI*, body mass index; *CPRD*, Clinical Practice Research Datalink; *DDD*, defined daily doses; *GP*, general practitioner; *H2RA*, H2-receptor antagonist; *HMO*, health maintenance organization; *HR*, hazard ratio; *IADB.nl*, InterAction Database Netherlands; *PPI*, proton pump inhibitor; *RR*, risk ratio.

TABLE E3. Quality assessment of the studies investigating the association between maternal use of ASMs during pregnancy and risk of asthma and allergy in the offspring

Reference; country	Overall risk of bias assessment	Risk of bias assessment for study components				
		Study design	Exposure assessment	Outcome assessment	Selection bias	Confounding
Andersen et al[E3] (2012); Denmark	Strong	Strong	Strong	Strong	Strong	Strong
Dehlink et al[E7] (2009); Sweden	Strong	Strong	Strong	Strong	Strong	Moderate
Hak et al[E10] (2013); United Kingdom	Strong	Strong	Strong	Strong	Strong	Moderate
Källén et al[E8] (2013); Sweden	Moderate	Strong	Moderate	Moderate	Moderate	Moderate
Mulder et al[E9] (2013); The Netherlands	Moderate	Strong	Strong	Moderate	Moderate	Weak
Mulder et al[E4] (2014); The Netherlands	Strong	Strong	Strong	Moderate	Strong	Strong
Cea Soriano et al[E5] (2016); United Kingdom	Strong	Strong	Moderate	Strong	Strong	Moderate
Yitshak-Sade et al[E6] (2016); Israel	Strong	Strong	Strong	Moderate	Moderate	Strong

The overall risk assessment was based on the component risk assessments (ie, on the suitability of the study design for the research question, validity of exposure and outcome assessments, potential for selection bias, adjustment for confounding factors).
ASM, Acid-suppressive medication.

TABLE E4. GRADE evidence profile for systematic review and meta-analysis of observational analytic epidemiologic studies on the association between maternal use of ASMs during pregnancy and risk of asthma and allergy in the offspring

		Quality assessment							Summary of findings		
Outcome	No. of studies (no. of participants)	Study design	Study limitations	Consistency	Directness	Precision	Publication bias (*P* value for Egger test)	Other potential factors	Relative effect (95% CI)	Quality of the evidence (GRADE)	Importance of outcome
Asthma	8 (1,620,043)	Observational cohort and case-control studies	No serious limitations*	No important inconsistency†	Direct	Estimates precise	Unlikely‡ ($P = .415$)	Very likely§	Any ASM (RR, 1.36; 95% CI, 1.16-1.61), H2RA (HR, 1.46; 95% CI, 1.29-1.65), PPI (HR, 1.30; 95% CI, 1.07-1.56)	Moderate	Critical
Atopic dermatitis	1 (33,536)	Observational cohort study	No serious limitations*	Only 1 study‖	Direct	Only 1 study‖	Unlikely‡	Very likely§	Not estimated‖	Very low	Important
Allergic rhinitis	1 (33,536)	Observational cohort study	No serious limitations*	Only 1 study‖	Direct	Only 1 study‖	Unlikely‡	Very likely§	Not estimated‖	Very low	Important
Other or any allergic disorders	2 (619,252)	Observational cohort studies	No serious limitations*	Some inconsistencies¶	Direct	Estimates precise#	Unlikely‡	Very likely§	Not estimated¶	Very low	Important

ASM, Acid-suppressive medications; *GRADE*, Grading of Recommendations Assessment, Development and Evaluation; *H2RA*, H2-receptor antagonists; *HR*, hazard ratio; *PPI*, proton pump inhibitor; RR, risk ratio.

*All studies were registry-based studies derived from population-based health care registers or general practitioner database.

†Overall, estimates of the test of heterogeneity across studies was low. The initial observed high heterogeneity in the pooled estimates was explained by pooling together studies on any ASM and H2RA/PPI, but the heterogeneity was removed after excluding studies on H2RA/PPI from the pooled data.

‡It is unlikely that we had missed any eligible study for inclusion: with highly sensitive search strategies, we searched 11 leading medical electronic databases, contacted experts in the field, and searched abstract and ongoing studies databases for additional references. Egger test for small-study effect for the pooled estimate was statistically nonsignificant.

§It is plausible that confounding by indication, residual confounding, or other unmeasured confounding factors could have influenced these observations. Data on use of ASM across studies were based on either prescription or dispensed medication; hence actual use was not ascertained. Given some inconsistency in reporting dosage and trimester of exposure to ASM, dose-response gradients of effect could not be evaluated in a pooled analysis.

‖Only 1 study evaluated this outcome; hence consistency across studies and precision of the pooled overall estimated could not be evaluated.

¶Each study calculated the risk estimate using different measures (hazard or odds ratios), which did not allow pooling of the studies.

#Although pooled estimates could not be calculated from the studies because of different measures used to estimate risk effects across studies, the estimates provided in each study were precise.

TABLE E5. Conversion of ORs to RRs to aid calculation of pooled estimates*

Reference	Exposure	Outcome	Baseline risk of outcome (proportion)	Source of baseline risk	OR (95% CI)	Formula for conversion	Converted RR (95% CI)
Dehlink et al[E7] (2009)	Any ASM	Asthma	0.037	Reported in the same paper	1.51 (1.35-1.69)	RR = OR/[1 − p_0 + (p_0 × OR)], where p_0 is the baseline risk	1.48 (1.33-1.65)
Hak et al[E10] (2013)	Any ASM	Asthma	0.042	Based on Simpson and Sheikh[E12] (2010)	1.23 (1.01-1.51)		1.22 (1.01-1.48)
Källén et al[E8] (2013)	Any ASM	Asthma	0.063	Reported in the same paper	1.60 (1.40-1.76)		1.54 (1.37-1.68)
Mulder et al[E9] (2013a)†	Any ASM	Asthma	0.11	Based on Mulder et al[E4] (2014)	1.85 (1.07-3.19)		1.69 (1.06-2.57)
Mulder et al[E9] (2013b)†	Any ASM	Asthma	0.11	Based on Mulder et al[E4] (2014)	1.52 (1.11-2.10)		1.44 (1.10-1.87)

ASM, Acid-suppressive medications; *OR*, odds ratio; *RR*, risk ratio.

*Guddat et al[E13] (2012). The same formula was used for converting the lower and upper 95% CIs as suggested by Robert Grant in an electronic correspondence.

†Mulder et al[E9] (2013) undertook 2 sets of analysis using the same asthma cases but different controls in the same study and compared estimates from analyses: in 2013a, they used siblings of the cases as the controls, and in 2013b, they used nonsiblings as controls. Hence each analysis was regarded as independent on its own right given the different control populations.