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

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Keywords: acid-suppressive medications, allergy, asthma, children, H2-receptor antagonists, pregnancy, proton pump inhibitors

Running head: Prenatal acid-suppressive medications and asthma in children

Review registration: PROSPERO: CRD42015029584.

Word count: 1076

CAPSULE SUMMARY

Maternal use of acid-suppressive medications was associated with an increased risk of asthma in children. Further research is now needed to clarify if this is a true risk or if it reflects residual confounding or confounding by indication.

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 and colleagues 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 Th2-mediated conditions, such as asthma and allergy. Dehlink and colleagues therefore proposed that acid-suppressive medications could operate through one or both of these mechanisms, inducing a Th2 cytokine pattern in mothers, which could then cross the fetal membrane and induce sensitization of fetal immune cells to food and airborne allergens prior to birth.[1]

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] In order 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 sub-types 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 (i.e. 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 objectively defined asthma, atopic dermatitis/eczema, allergic rhinitis or hay fever, food allergy, urticarial and anaphylaxis; and atopic sensitization as defined either by skin prick test or raised antigen specific IgE (see description of secondary outcomes in the Online Repository).

To identify relevant studies, we searched 11 electronic databases and searched databases of ongoing studies and conference abstracts (see details in the Online Repository). We also contacted experts in the field to identify additional studies and any ongoing study. We developed a detailed search strategy in MEDLINE, which was then adapted for searching other databases (Table E1 in the Online Repository). All databases were searched from inception to the end of 2015, with no language restrictions. Two reviewers (RD and BN) 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. Any discrepancies in the process were resolved by discussion or a third reviewer (NM) 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 the Online Repository).

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 zero indicate good homogeneity across studies). Meta-analyses were undertaken using Stata 14, College Station, TX: StataCorp LP. See the Online Repository for a fuller description of our approach to data synthesis and application of the GRADE approach.

Of the 3282 records identified from our searches, eight studies[1,3-9] met our inclusion criteria (see Figure E1 in the Online Repository). Key characteristics of the studies are presented in Table E2 in the Online Repository. Six studies were graded as strong and two as moderate. In pooled analysis, use of any acid-suppressive medications (RR 1.36, 95%CI 1.16-1.61, I^2=87·6%), H2RA (HR 1.46, 95%CI 1.29-1.65, I^2=15·3%), and PPI (HR 1.30, 95%CI 1.07-1.56, I^2=45·2%) were associated with an increased risk of asthma (Figures 1 and 2). Results of sensitivity analyses are given in the Online Repository. Two studies that considered other allergic disorders both reported an increased risk amongst offspring of mothers using any acid-suppressive medications, H2RA, and PPIs compared to the offspring of non-using mothers[1,7] (see Table E2 in the 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 the Online Repository). The Egger's 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*=0.415.

Our literature search was comprehensive. We had no language restriction, reproducible search strategies, and we applied rigorous review processes, which were enhanced by publishing and registering a detailed protocol prior to undertaking the review.[10] The degree of heterogeneity between 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: lack of information about quality assessment, data extraction, or the 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 Th2 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. While 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.

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CONFLICTS OF INTEREST

The authors declare no competing interest related to this work.

AUTHORS' CONTRIBUTIONS

BN conceived the idea for this work. It was drafted by RD and BN and was then revised after several rounds of critical comments from BN, NM, and AS.

FUNDING

This work received no specific funding. BN was supported by the Institute for Advanced Social Research Fellowship, University of Tampere, Finland; School of Health Sciences, University of Tampere, Finland; and Farr Institute and Asthma UK Centre for Applied Research.

ACKNOWLEDGEMENT

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 one 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.

FIGURE LEGENDS

Figure 1:

Meta-analysis of studies investigating the association between maternal use of any acid-suppressive medication during pregnancy and the risk of asthma in the offspring. RR represents the risk ratio of association. **PANEL A**– estimates by study design; **PANEL B** – estimates by study design, excluding Yitshak-Sade 2015. Population represents the number of participants recruited into the study.

Figure 2:

Meta-analysis of studies investigating the association between maternal use of H2- receptor antagonists (H2RA – **PANEL A**) and proton pump inhibitors (PPI – **PANEL B**) 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.

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Figure No. - Unmarked
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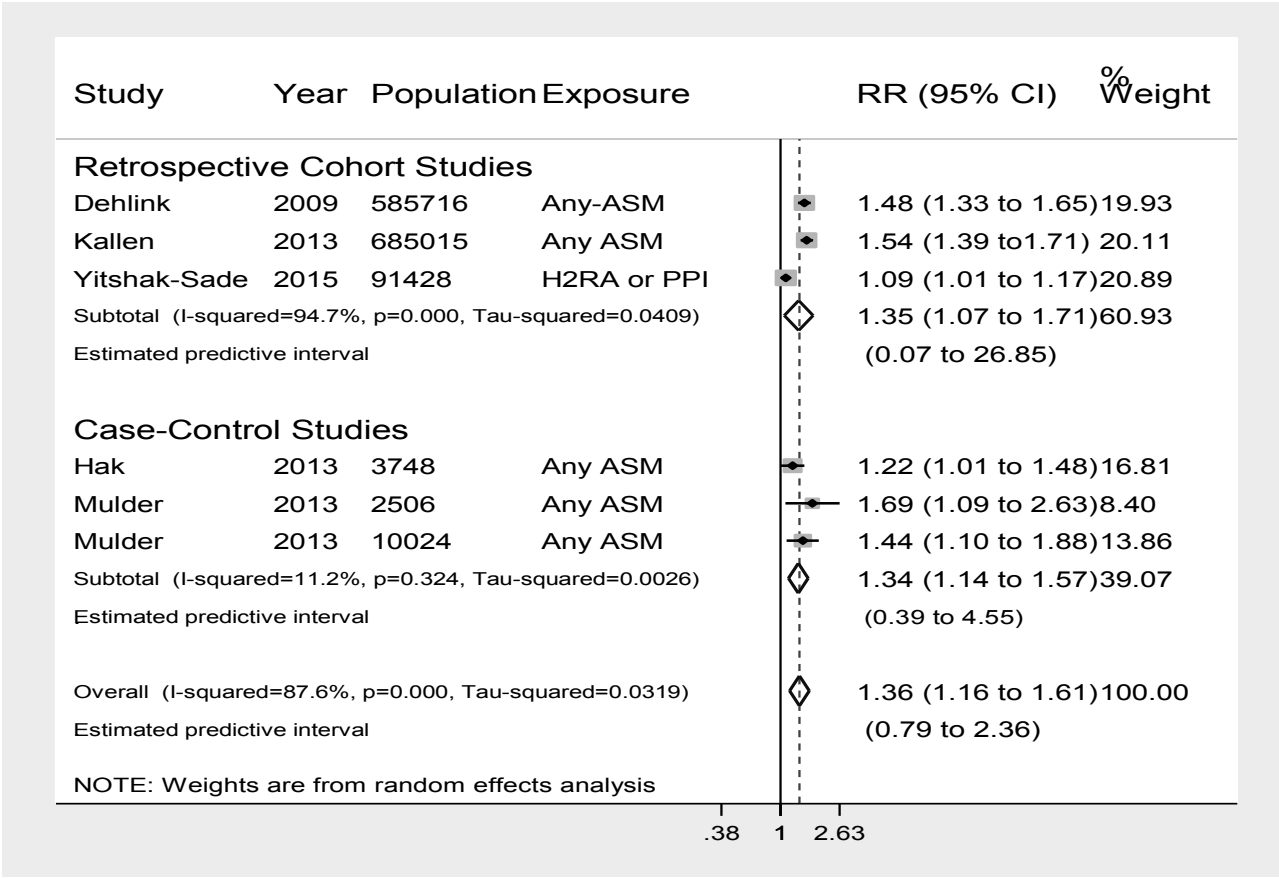
PANEL A



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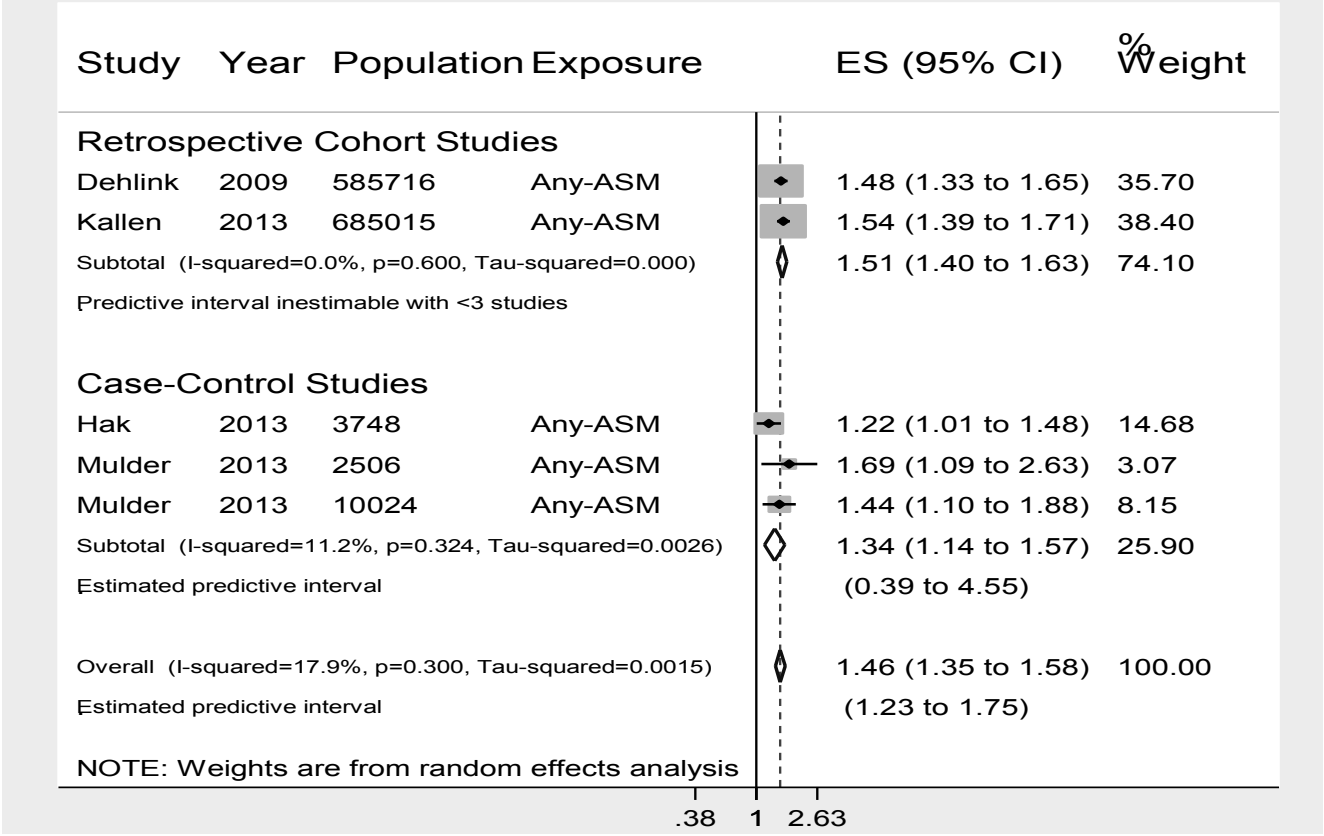

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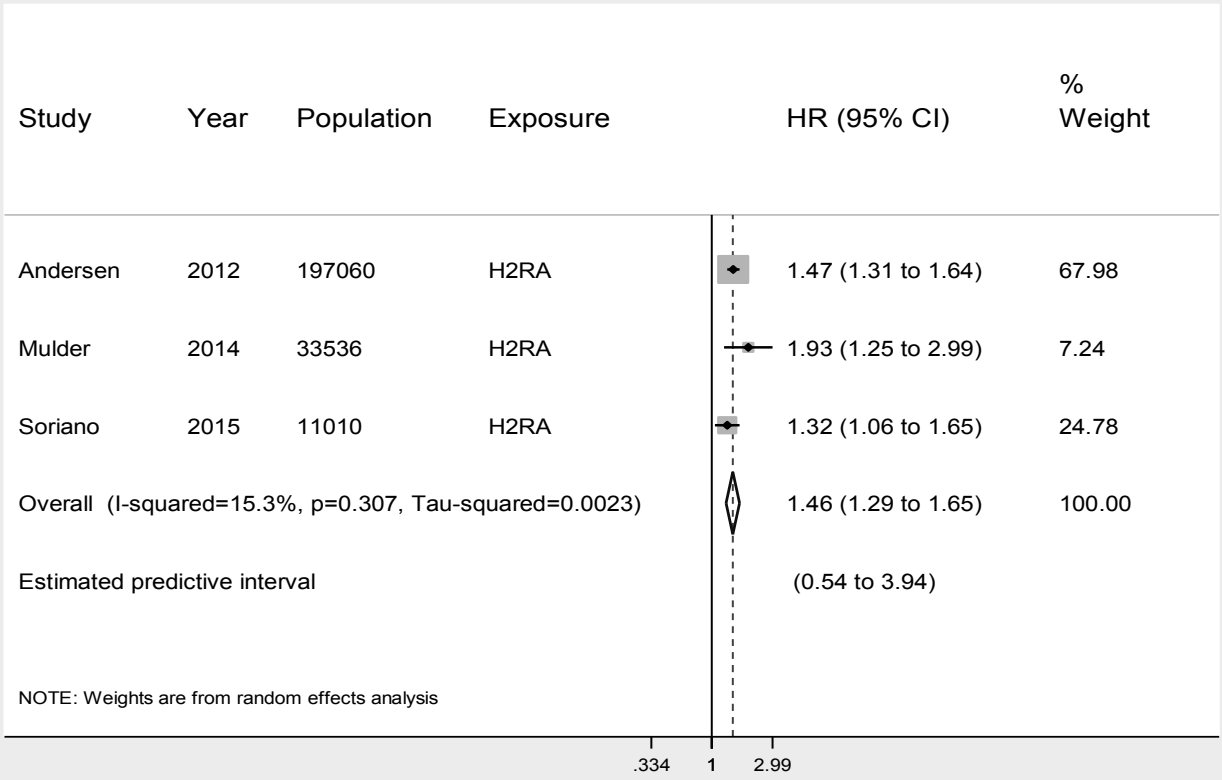
PANEL A



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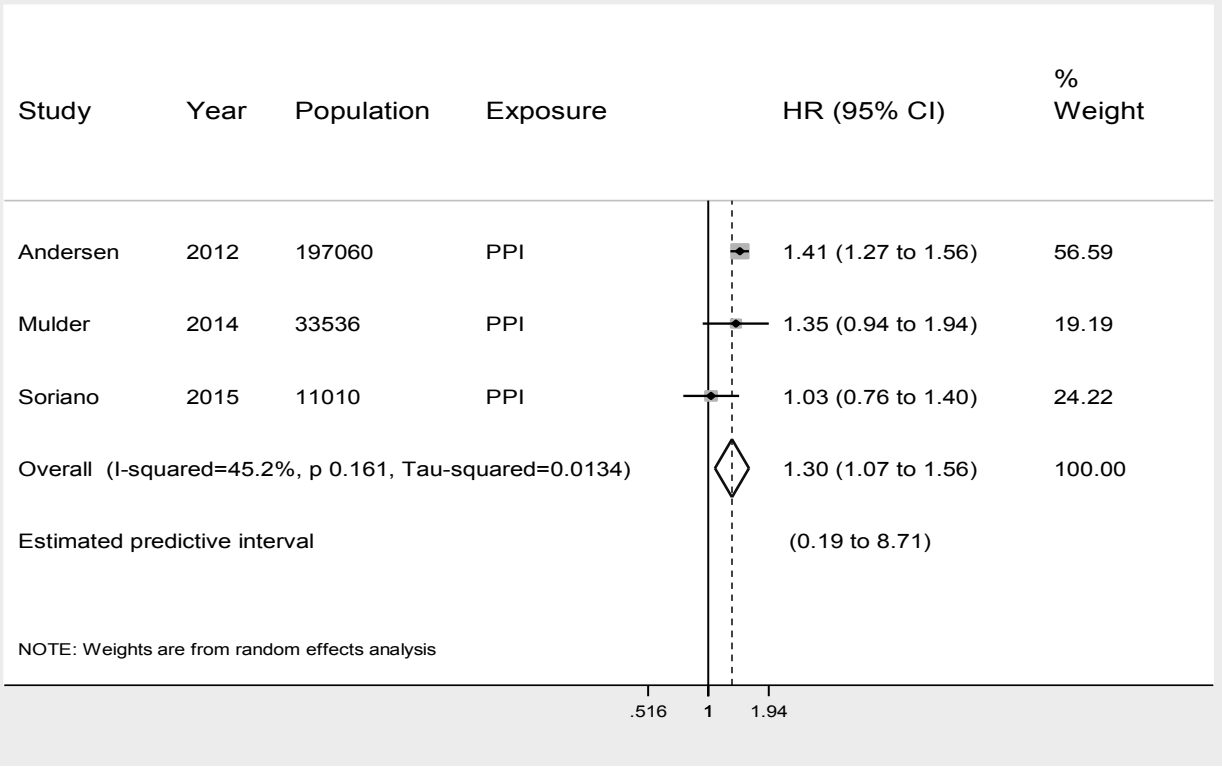

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TABLE E1: MEDLINE Search Strategies used to Identify Studies and Adapted in Searching other Databases

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 acid-suppressive medications during pregnancy and risk of asthma and allergy in the offspring

Reference, country; and 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 2012; Denmark; Retrospective Cohort Study	197060; Population recruited from the Danish Medical Birth Registry	197060	Maximum follow-up of 14 years; median 6.8 years	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 (1st; 2nd & 3rd combined) of exposure. Also considered pre-conception and post-pregnancy exposures	***Asthma***: having a record of a hospitalization, out-patient visit, emergency room visit plus asthma diagnosis OR dispensations record for of anti-asthmatic 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 (IRR) for the associations using Cox proportional hazards regression. As the Cox model estimates the hazard function, the correct measure here should be hazard ratio (HR). Adjusted for year of birth, county, gender, gestational age, birth order, maternal age, maternal smoking, maternal asthma, delivery mode, and maternal use of antibiotics during pregnancy	*(HR, 95% CI)); reference is non-use.* **PPI**: (1.41, 1.27 to 1.56); ≤28 pills (1.20, 1.01 to 1.43); >28 pills (1.54 , 1.36 to 1.75) **H2RA**: (1.47, 1.32 to 1.65); ≤20 pills (1.44, 1.06 to 1.95); >20 pills (1.48, 1.31 to 1.67) **Trimester (i.e. use of PPI or H2RA)**: 1st trimester (1.46, 1.27 to1.67); 2nd/3rd trimester (1.34, 1.15 to1.56)	Strong
Dehlink et al 2009; Sweden; Retrospective Cohort Study	860215; Linkage of the Medical Birth Register, the Hospital Discharge Register, and the Swedish Prescribed Drug Register	585716	Maximum follow-up of 11 years	Ascertained from the Medical Birth Register. Studied use of any ASM, including PPI, H2RA, and other drugs used for peptic ulcer and gastro-esophageal reflux disease. Also considered the trimester of exposure (1st trimester; late pregnancy)	***Allergy***: ever hospitalized for an allergic disease (food allergy, atopic dermatitis, allergic rhinitis, anaphylaxis) or received two 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	Odds ratio (OR) using the Mantel-Haenszel procedure; 95% CI confidence intervals calculated using the Miettinen's test method. Adjusted for year of birth, parity, maternal age, maternal smoking, maternal BMI	*(OR, 95% CI)); reference is non-use.* **Any ASM and allergy**: (1.43, 1.29 to 1.59); 1st trimester (1.38, 1.22 to 1.57); Later pregnancy (1.34, 1.11 to 1.63) **Any ASM and asthma**: (1.51, 1.35 to 1.69) **H2RA and allergy**: (1.41, 1.16 to 1.70) **PPI and allergy**: (1.46, 1.27 to 1.66) **Other ASM**: (1.29, 1.04 to 1.60)	Strong
Hak et al 2013; United Kingdom; Case-Control Study	Cases: 1874; Controls (siblings of cases): 1874 Population recruited from the Clinical Practice Research Datalink (CPRD)	Cases: 1874; Controls: 1874	Maximum 14 years of follow-up. Mean age at diagnosis of asthma 3.6 years	Ascertained from the CPRD database. Studied use of any ASM, including PPI, H2RA, and use of other antacids. Also considered the trimester of exposure (1st/2nd trimester; 3rd trimester)	***Asthma***: received a diagnosis of asthma and was prescribed any asthma medications at least 3 times within 12 months after the firs diagnosis date	Ascertained from the CPRD database. Asthma cases coded using the Read coding system	OR using conditional logistic regression. Adjusted for gender, 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 to 1.51); 1st/2nd trimester (1.01, 0.79 to 2.08); 3rd trimester (1.29, 1.03-1.62) **PPI or H2RA**: (1.72, 1.00 to 2.07); **PPI**: (2.76, 0.93 to 8.17) **H2RA**: (1.56, 0.85-2.90) **Other ASM**: (1.16, 1.95 to 1.42)	Strong

Källén et al 2013; Sweden; Retrospective Cohort Study	685015; Linkage of the Swedish Medical Birth Register and the Swedish Prescribed Drug Register	685015	2-6 years	Ascertained from the Swedish Medical Birth Register. Studied use of any ASM during the 2nd or 3rd trimester	***Asthma***: having at least 5 prescription events for anti-asthmatic drugs during follow-up	Ascertained from the Swedish Prescribed Drug Register	OR using the Mantel-Haenszel procedure; 95% CI confidence intervals calculated using the Miettinen's test method. Adjusted for year of birth, maternal age, parity, smoking, BMI, and use of other drugs during pregnancy	*(OR, 95% CI)); reference is non-use.* **Any ASM during 2nd or 3rd trimester of pregnancy**: (1.60, 1.40 to 1.76)	Moderate
Mulder et al 2013; The Netherlands; Case-Control Study	Two sets of case-control analyses: 1.Sibling-based controls (cases: 1253; controls: 1253) 2.Non-sibling-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 years	Ascertained from the University of Groningen IADB.nl pharmacy prescription database using ATC codes. Studied use of any ASM and dosage (defined daily doses [DDD]) of use – 0-14 DDD; >14 DDD	***Asthma***: having at least 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 non-sibling 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 were not adjusted in the analyses	*(OR, 95% CI)); reference is non-use.* **1.Sibling case-control analysis:** **Any ASM**: (1.85, 1.07 to 3.19) 0-14 DDD: (1.19, 0.61 to 2.31) >14 DDD: (2.56, 1.18 to 5.52) **2.Non-sibling case-control analysis:** **Any ASM**: (1.52, 1.11 to 2.10) 0-14 DDD: (1.18, 0.73 to 1.91) >14 DDD: (1.89, 1.24 to 2.88)	Moderate
Mulder et al 2014; The Netherlands; Retrospective Cohort Study	40628; From The University of Groningen IADB.nl pharmacy prescription database	33536	Maximum of 8 years follow-up. Median follow-up 4.9 years	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 (1st/2nd trimester, 3rd trimester)	***Asthma***: ≥2 inhaled steroid prescription within 12 months ***Atopic dermatitis***: ≥2 prescriptions for ointment containing either steroid or calcineurinhibitors 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 non-use.* **Results for use of ASM and asthma** (*results for atopic dermatitis and allergic rhinitis are given in the paper*) **H2RA or PPI**: (1.57, 1.20 to 2.05) 0-15 DDD: (1.37, 0.84 to 2.25) >15 DDD: (1.68, 1.21 to 2.32) 1st/2nd trimester: (1.64, 1.12 to 2.41) 3rd trimester: (1.32, 0.77 to 2.25) **H2RA**: (1.93, 1.25 to 3.00) **PPI**: (1.35, 0.94 to 1.94)	Strong
Soriano et al 2015; United Kingdom; Retrospective Cohort Study	14522; From The Health Improvement Network database	11010	Maximum of 6 years follow-up	Ascertained from The Health Improvement Network database using Read codes. At least one prescription of ASM (PPI, H2RA) during pregnancy. Also	***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 pre and during pregnancy, maternal asthma, maternal comorbidities, maternal use of nonsteroidal anti-inflammatory drugs, antibiotics,	*(HR, 95% CI)); reference is non-use.* **H2RA**: Anytime (1.32, 1.05 to 1.64); 1st trimester (1.15, 0.77 to 1.72); 2nd trimester (1.75, 1.25 to 2.47); 3rd trimester (1.20, 0.93 to 1.54); all three trimesters (1.26,	Strong

				considered trimester of exposure (1st, 2nd, 3rd, all three trimesters).			antihistamines during pregnancy, sex of child	0.51 to 3.08) **PPI**: Anytime (1.03, 0.76 to 1.40); 1st trimester (1.07, 0.76 to 1.51); 2nd trimester (1.11, 0.60 to 2.05); 3rd trimester (0.69, 0.36 to 1.30); all three trimesters (0.73, 0.23 to 2.31)	
Yitshak-Sade et al 2015; Israel; Retrospective Cohort Study	91459; From the "Clalit" Health Services HMO database	91428	3-13 years follow-up	Ascertained from the "Clalit" Health Services HMO medication dispensing registry. Maternal use of H2RA or PPI 2 months prior and during pregnancy. Studied use of H2RA; PPI; trimester of exposure; and DDD	***Asthma***: hospitalization for asthma or had recurrent wheeze diagnosis. Classified using the ICD-9	Ascertained from the "Clalit" Health Services HMO medication dispensing registry	Risk ratio (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 non-use.* **H2RA or PPI**: Anytime (1.09, 1.01 to 1.17) <10 DDD: (1.05, 0.94 to 1.17); 10-20 DDD: (1.07, 0.96 to 1.18); >20 DDD: (1.12, 1.06 to 1.18) 1st trimester: (1.08, 0.97 to 1.21) 2nd trimester: (1.11, 0.93 to 1.32) 3rd trimester: (0.99, 0.82 to 1.20) **H2RA**: (1.06, 0.97 to 1.15) **PPI**: (1.10, 0.98 to 1.22)	Strong

Abbreviations: ASM – Acid-suppressive medications; ATC – Anatomical Therapeutic Chemical; GP – General Practitioner; ICD-10; - International Classification of Diseases [version 9, 10]; H2RA – H2- receptor antagonists; PPI – Proton pump inhibitors

Table E3: Quality assessment of the studies investigating the association between maternal use of acid-suppressive medications 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 2012; Denmark	Strong	Strong	Strong	Strong	Strong	Strong
Dehlink et al 2009; Sweden	Strong	Strong	Strong	Strong	Strong	Moderate
Hak et al 2013;United Kingdom	Strong	Strong	Strong	Strong	Strong	Moderate
Källén et al 2013; Sweden	Moderate	Strong	Moderate	Moderate	Moderate	Moderate
Mulder et al 2013; The Netherlands	Moderate	Strong	Strong	Moderate	Moderate	Weak
Mulder et al 2014; The Netherlands	Strong	Strong	Strong	Moderate	Strong	Strong
Soriano et al 2015; United Kingdom	Strong	Strong	Moderate	Strong	Strong	Moderate
Yitshak-Sade et al 2015; Israel	Strong	Strong	Strong	Moderate	Moderate	Strong

The overall risk assessment was based on the component risk assessments (i.e., 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).

Table E4: GRADE evidence profile for systematic review and meta-analysis of observational analytic epidemiologic studies on the association between maternal use of acid-suppressive medications during pregnancy and risk of asthma and allergy in the offspring

Outcome	No. of studies (No. of participants)	Quality assessment							Summary of findings		
		Study design	Study limitations	Consistency	Directness	Precision	Publication bias (P-value for Egger's test)	Other potential factors	Relative effect (95% CI)	Quality of the evidence (GRADE)	Importance of outcome
Asthma	8 (1620043)	Observational cohort and case-control studies	No serious limitations[1]	No important inconsistency[2]	Direct	Estimates precise	Unlikely[6] (p=0.415)	Very likely[7]	**Any ASM** (RR 1.36, 95% CI 1.16 to 1.61); **H2RA** (HR 1.46, 95% CI 1.29 to 1.65); **PPI** (HR 1.30, 1.07 to 1.56)	Moderate	Critical
Atopic dermatitis	1 (33536)	Observational cohort study	No serious limitations[1]	Only one study[3]	Direct	Only one study[3]	Unlikely[6]	Very likely[7]	Not estimated[3]	Very low	Important
Allergic rhinitis	1 (33536)	Observational cohort study	No serious limitations[1]	Only one study[3]	Direct	Only one study[3]	Unlikely[6]	Very likely[7]	Not estimated[3]	Very low	Important
Other or any allergic disorders	2 (619252)	Observational cohort studies	No serious limitations[1]	Some inconsistencies[4]	Direct	Estimates precise[5]	Unlikely[6]	Very likely[7]	Not estimated[4]	Very low	Important

Abbreviations: ASM = Acid-suppressive medications; HR = Hazard ratio; H2RA = H2- receptor antagonists; PPI = Proton pump inhibitors; RR = Risk ratio; 95% CI = 95% confidence interval

[1]All studies were registry-based studies derived from population-based healthcare registers or general practitioner database

[2]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

[3]Only one study evaluated this outcome, hence consistency across studies and precision of the pooled overall estimated could not be evaluated

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

[5]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

6It is unlikely that we had missed any eligible study for inclusion: with high 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's test for small-study effect for the pooled estimate was statistically non-significant

[7]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

Table E5: Conversion of odds ratios to risk ratios to aid calculation of pooled estimates[1]

Reference	Exposure[2]	Outcome	Baseline risk of outcome (proportion)	Source of baseline risk	Odds ratio (95% CI)	Formulae for conversion	Converted risk ratio (95% CI)
Dehlink et al 2009	Any ASM	Asthma	0.037	Reported in the same paper (Dehlink et al 2009)	1.51 (1.35 to -1.69)	Risk ratio = odds ratio/(1-p0+(p0xodds ratio)); *Where p0 is the baseline risk*	1.48 (1.33 to 1.65)
Hak et al 2013	Any ASM	Asthma	0.042	Based on Simpson CR & Sheikh A 2010[4]	1.23 (1.01 to 1.51)		1.22 (1.01 to 1.48)
Källén et al 2013	Any ASM	Asthma	0.063	Reported in the same paper (Källén et al 2013)	1.60 (1.40 to 1.76)		1.54 (1.37 to 1.68)
Mulder et al 2013a[3]	Any ASM	Asthma	0.11	Based on Mulder et al 2014[5]	1.85 (1.07 to 3.19)		1.69 (1.06 to 2.57)
Mulder et al 2013b[3]	Any ASM	Asthma	0.11	Based on Mulder et al 2014[5]	1.52 (1.11 to 2.10)		1.44 (1.10 to 1.87)

[1]Reference 9. The same formulae was used for converting the lower and upper 95% confidence intervals as suggested by Robert Grant in an electronic correspondence
[2]Abbreviations: ASM – Acid-suppressive medications; H2RA – H2- receptor antagonists; PPI – Proton pump inhibitors
[3]Mulder et al 2013 undertook two sets of analysis using the same asthma cases but different controls the same study and compared estimates from analyses: Mulder et al 2013a use siblings of the cases as the controls while Mulder et al 2013b used non-sibling as controls. Hence each analysis was regarded as independent on its own right given the different control populations
[4]Reference 11
[5]Reference 10

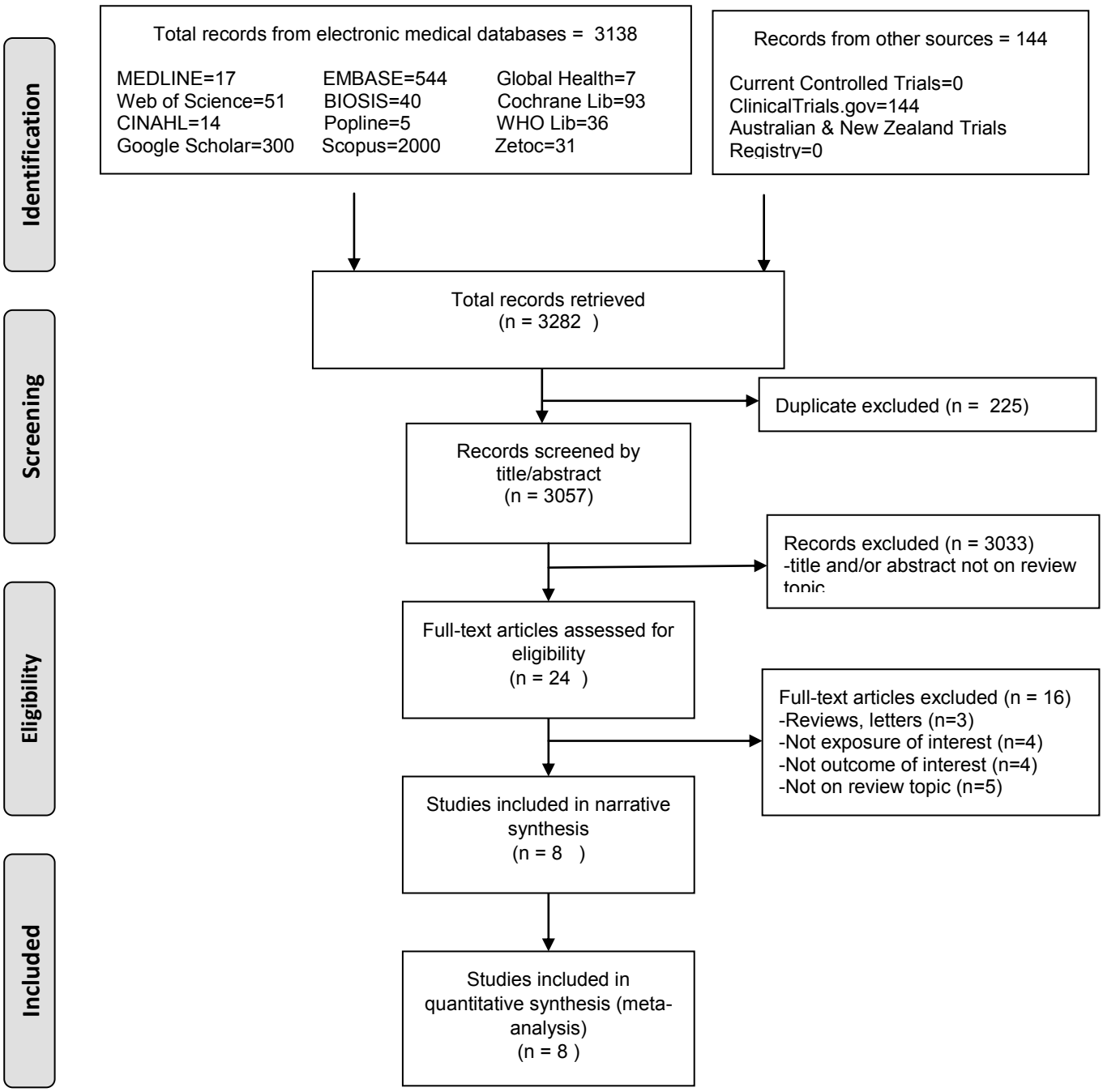

Figure E1 PRISMA flow diagram for database search of studies investigating the association between maternal use of acid-suppressive medications during pregnancy and risk of asthma and allergy in the offspring

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

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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 since the study is based on the published literature.

Protocol and registration

Prior to commencement of the review, we developed a detailed protocol, which was published[1] and registered with the International Prospective Register of Systematic Reviews (PROSPERO; http://www.crd.york.ac.uk/prospero/, reference CRD42015029584).

Eligibility criteria

We included analytical epidemiological studies, i.e. 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 (H2RA, 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; and 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 [PEF], forced expiratory volume in 1 second [FEV1], forced vital capacity [FVC], 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, two reviewers (RD and BN) independently screened all titles and/or abstracts. Full texts of potentially eligible studies were obtained and independently screened for inclusion by the two reviewers. Studies that did not fulfil the inclusion criteria were excluded. Any discrepancies in the screening process were resolved by discussion.

Data extraction and quality assessment

Two reviewers (RD and BN) 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 (NM). The PRISMA checklist guided reporting.[2]

Risk of bias in individual studies

Two reviewers (RD and BN) independently undertook the risk of bias analysis in the study using the Effective Public Health Practice Project tool, 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 (NM) arbitrated.

Summary measures

Eligible studies reported one of the following effect measures: hazard ratio (HR), risk ratio (RR), or odds ratio (OR). Although Andersen et al[3] 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[10] and Soriano et al[12] also reported HR. Yitshak-Sade et al[4] reported RR; estimates of studies reporting OR[5,6-8] were converted to RR using the formulae by Grant[9] and then pooled with the Yitshak-Sade et al[4] study. The formulae for conversion is given as follows: RR = OR/(1-p0+(p0 x OR)); where p0 is the baseline risk. The baseline risks for Dehlink et al[5] and Källén et al[6] were taken from the respective papers. The baseline risk for Mulder et al 2013[7] was taken from Mulder et al 2014,[10] which was based on the same study population. For Hak et al,[8] we used the prevalence estimate (4.2%) reported elsewhere but based on a similar primary care database.[11] The RR derived from these calculations are presented in Table E5.

Data synthesis

Of the eight studies, six were retrospective cohort studies,[3-6,10,12] while two were case-control studies.[7,813,14] 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[7] analyzed two sets of control populations that were compared to 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 acid-suppressive medications, H2RA only, and PPIs only; there were no data on use of antacids. Dosage of acid-suppressive medications 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 acid-suppressive medications on the risk of asthma in new studies would lie.[13] Given that the number of studies for each meta-analysis was small, thus lacking the required power (i.e less than the recommended minimum of 10 studies),[14] 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.[15] Meta-analyses were undertaken using Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.

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 acid-suppressive medications, we excluded that study to assess its impact on the heterogeneity across studies.

Grading the quality of the overall body of evidence

Using the 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.[16]

RESULTS

Study selection

We identified 3282 records, of which 3057 were included for screening by title and/or abstract after de-duplication. 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 eight papers that met our inclusion criteria (Figure E1).[3-8,10,12]

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[7,10] Sweden[5,6] and United Kingdom,[8,12] whereas one study each was undertaken in Denmark[3] and Israel.[4] All studies considered asthma as an outcome while two in addition considered other allergic disorders, including atopic dermatitis/eczema and allergic rhinitis.[5,10] Whereas most studies considered use of any acid-suppressive medication or H2RA/PPIs,[5-8,10] the independent role of H2RA and PPIs were examined in three studies,[3,4,10] but no study examined the role of antacids alone. Seven of the studies also considered the trimester of exposure to acid-suppressive medications, while three 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, six studies were graded as strong and two as moderate. The overall quality grading was derived from the grading for the different components of the studies. Apart from Mulder et al[7], which was graded weak for confounding adjustment, all other studies were graded moderate or strong for all components (Table E3).

Use of acid-suppressive medications and risk of asthma

Across individual studies, offspring of mothers who used any acid-suppressive medications during pregnancy were at an increased risk of asthma compared to offspring of non-users (Table E2). The results were similar when H2RA and PPIs were examined separately, except for imprecise estimates from two studies.[10,12] Higher dosage of acid-suppressive medications appeared to show a greater risk compared to lower dosage (Table E2). Whereas use of acid-suppressive medications 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 acid-suppressive medications 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 acid-suppressive medications and other allergic disorders was investigated by two studies,[5,10] both reporting an increased risk amongst offspring of mothers using any acid-suppressive medications, H2RA, and PPIs, compared to those of non-using mothers (Table E2). Mulder et al[10] in addition reported an increased risk of atopic dermatitis/eczema and allergic rhinitis with use of acid-suppressive medications, 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[5] (OR) and Mulder et al[10] (HR), and considering that only Mulder et al 2014 examined atopic dermatitis/eczema and allergic rhinitis, we could not calculate pooled estimates of the association between acid-suppressive medications and risk of allergic disorders other than asthma.

Sensitivity analyses

By stratifying the association between use of any acid-suppressive medication or H2RA/PPIs by study design the results showed that the high heterogeneity was specific to the cohort studies (Figure 1). Further exclusion of the study by Yitshak-Sade et al[4] reduced the heterogeneity in all studies from the initial 87% to 18% and the heterogeneity in the cohort studies from 95% to 0% (Figure 1). Stratification of the results by study design and exclusion of the Yitshak-Sade et al

203 study[4] did not dramatically change the pooled relative effect estimates, but did result in a more
204 precise predictive interval (1·23-1·75) (Figure 1).
205
206 **Grading quality of the overall body of evidence**
207 By applying the GRADE system (Table E4), we graded the evidence regarding risk of asthma as
208 moderate. None of the studies assessed the possible influence of confounding by indication,
209 unmeasured confounding, and acid-suppressive medications data were based on either prescribed
210 or dispensed medication without information on actual use. It is therefore possible that the results
211 could be partly explained by these factors. Given very few studies, we graded the evidence
212 regarding atopic dermatitis/eczema, allergic rhinitis, and other allergic outcomes as very low.
213
214 **Assessment of publication bias**
215 We calculated the Egger's test for the association between use of any acid-suppressive
216 medications and risk of asthma and the result showed *P*=0.415 (Table E5), indicating that
217 publication bias or small study effect was unlikely to have influenced our results.
218

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