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

3

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

23

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

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27 **Review registration:** PROSPERO: CRD42015029584.

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30 **Word count: 1076**

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36 **CAPSULE SUMMARY**

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

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64 **To the Editor**

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66 Acid suppressive medications, such as H2-receptor antagonists (H2RA) and proton pump
67 inhibitors (PPI), are the main treatment options for dyspepsia and gastroesophageal reflux
68 disease. These are common problems in pregnancy.¹ Recently, concerns have been raised
69 that prenatal exposure to these medications may increase the risk of allergic disease in the
70 offspring.¹ Dehlink and colleagues were the first to report these associations, proposing that
71 use of acid-suppressive medications in pregnancy may increase the risk of allergic disease in
72 the offspring through interference with maternal digestion of labile antigens, thereby
73 increasing the amount of allergen to which the fetus is exposed. PPI use has also been
74 linked to changes in the intestinal microbiota composition,² which may also increase the risk
75 of Th2-mediated conditions, such as asthma and allergy. Dehlink and colleagues therefore
76 proposed that acid-suppressive medications could operate through one or both of these
77 mechanisms, inducing a Th2 cytokine pattern in mothers, which could then cross the fetal
78 membrane and induce sensitization of fetal immune cells to food and airborne allergens prior
79 to birth.¹

80

81 An increasing number of studies have now investigated the impact of prenatal exposure to
82 acid-suppressive medications on the risk of allergic disease in the offspring, but with
83 inconsistent results.^{1,3-9} In order to obtain a clearer appreciation of the evidence base, we
84 undertook a systematic review and meta-analysis of these studies. We were also interested
85 in clarifying whether use of the sub-types of acid-suppressive medications, namely H2RA
86 and PPIs, was associated with asthma/allergy; and whether any associations uncovered
87 varied by time (trimester), dose, and frequency of exposure.

88

89 We included analytical epidemiological studies (i.e. cohort, case-control, and cross-sectional
90 studies). We excluded reviews, case studies and case series, and animal studies. All women
91 during preconception and pregnancy and their offspring who were ≤ 17 years were eligible for

92 inclusion. Our primary outcomes were objectively defined asthma, atopic dermatitis/eczema,
93 allergic rhinitis or hay fever, food allergy, urticarial and anaphylaxis; and atopic sensitization
94 as defined either by skin prick test or raised antigen specific IgE (see description of
95 secondary outcomes in the Online Repository).

96

97 To identify relevant studies, we searched 11 electronic databases and searched databases
98 of ongoing studies and conference abstracts (see details in the Online Repository). We also
99 contacted experts in the field to identify additional studies and any ongoing study. We
100 developed a detailed search strategy in MEDLINE, which was then adapted for searching
101 other databases (Table E1 in the Online Repository). All databases were searched from
102 inception to the end of 2015, with no language restrictions. Two reviewers (RD and BN)
103 independently screened all titles and/or abstracts; screened full texts of potentially eligible
104 studies; extracted study data onto a customized data extraction form; and quality appraised
105 all studies using the Effective Public Health Practice Project tool. Any discrepancies in the
106 process were resolved by discussion or a third reviewer (NM) arbitrated. We graded key
107 components from which we derived an overall grading for each study as strong, moderate, or
108 weak (see Tables E2 and E3 in the Online Repository).

109

110 We employed random-effects meta-analysis to quantify the pooled effect estimates for
111 reasonably homogeneous studies. Meta-analysis was possible with studies on risk of
112 asthma, but not for other outcomes due to insufficient number of studies. Dosage, trimester,
113 and frequency of exposure to acid-suppressive medications were differentially reported
114 across studies, hence we were unable to pool studies on these exposures. We quantified the
115 level of heterogeneity between studies using the I^2 statistic (values near zero indicate good
116 homogeneity across studies). Meta-analyses were undertaken using Stata 14, College
117 Station, TX: StataCorp LP. See the Online Repository for a fuller description of our approach
118 to data synthesis and application of the GRADE approach.

119

120 Of the 3282 records identified from our searches, eight studies^{1,3-9} met our inclusion criteria
121 (see Figure E1 in the Online Repository). Key characteristics of the studies are presented in
122 Table E2 in the Online Repository. Six studies were graded as strong and two as moderate.
123 In pooled analysis, use of any acid-suppressive medications (RR 1.36, 95%CI 1.16-1.61,
124 $I^2=87.6\%$), H2RA (HR 1.46, 95%CI 1.29-1.65, $I^2=15.3\%$), and PPI (HR 1.30, 95%CI 1.07-
125 1.56, $I^2=45.2\%$) were associated with an increased risk of asthma (Figures 1 and 2). Results
126 of sensitivity analyses are given in the Online Repository. Two studies that considered other
127 allergic disorders both reported an increased risk amongst offspring of mothers using any
128 acid-suppressive medications, H2RA, and PPIs compared to the offspring of non-using
129 mothers^{1,7} (see Table E2 in the Online Repository). By applying the GRADE approach, we
130 graded the evidence regarding the risk of asthma as moderate, but evidence regarding other
131 allergic outcomes as very low (see Table E4 in the Online Repository). The Egger's test (to
132 evaluate publication bias and small-study effect) for the association between use of any acid-
133 suppressive medications and risk of asthma showed $P=0.415$.

134
135 Our literature search was comprehensive. We had no language restriction, reproducible
136 search strategies, and we applied rigorous review processes, which were enhanced by
137 publishing and registering a detailed protocol prior to undertaking the review.¹⁰ The degree of
138 heterogeneity between studies was low; the only case of high heterogeneity was due to
139 differences in the definition of the exposure. In the course of our literature search, we found a
140 recent systematic review from Google Scholar, published in Chinese in a local journal.¹¹ Five
141 studies were included in that review and were meta-analyzed. On translation to English, we
142 found that the systematic review process was deficient in many aspects, including: lack of
143 information about quality assessment, data extraction, or the number of reviewers involved;
144 unclear decisions regarding meta-analysis decisions (whether fixed-effect or random-effects
145 meta-analysis was used) or the approach employed to evaluate heterogeneity between
146 studies.

147

148 Animal models and studies undertaken in adults suggest that acid-suppressive medications
149 may interfere with peptide digestion, thereby inducing a Th2 cytokine dominance, which may
150 result in subsequent sensitization of the immune system.¹ Such interference may increase
151 the amount of allergen the fetus is exposed to via the placenta, thereby resulting in
152 sensitization and subsequent development of allergic disorders and asthma.¹ Our findings of
153 increased risk may reflect a true risk or may be explained by residual confounding and/or
154 confounding by indication. Of note is that none of the studies adjusted for the full panel of
155 known confounders in these associations. While we cannot recommend any changes to the
156 use of acid-suppressive medications by expectant mothers, further research is needed,
157 particularly through mounting pharmacovigilance studies, which may prove more ethically
158 acceptable and feasible than initiating randomized controlled clinical trials.

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166 Population Health Sciences and Informatics, The University of Edinburgh, Edinburgh, UK

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174 **CONFLICTS OF INTEREST**

175 The authors declare no competing interest related to this work.

176

177 **AUTHORS' CONTRIBUTIONS**

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

180

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187

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189

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194 Edda Fiebiger, Lucia Soriano, Rafael Gorodischer, and in particular to Maaya Yitshak-Sade
195 who provided additional data.

196

197 **FIGURE LEGENDS**

198 **Figure 1:**

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

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Figure 2:

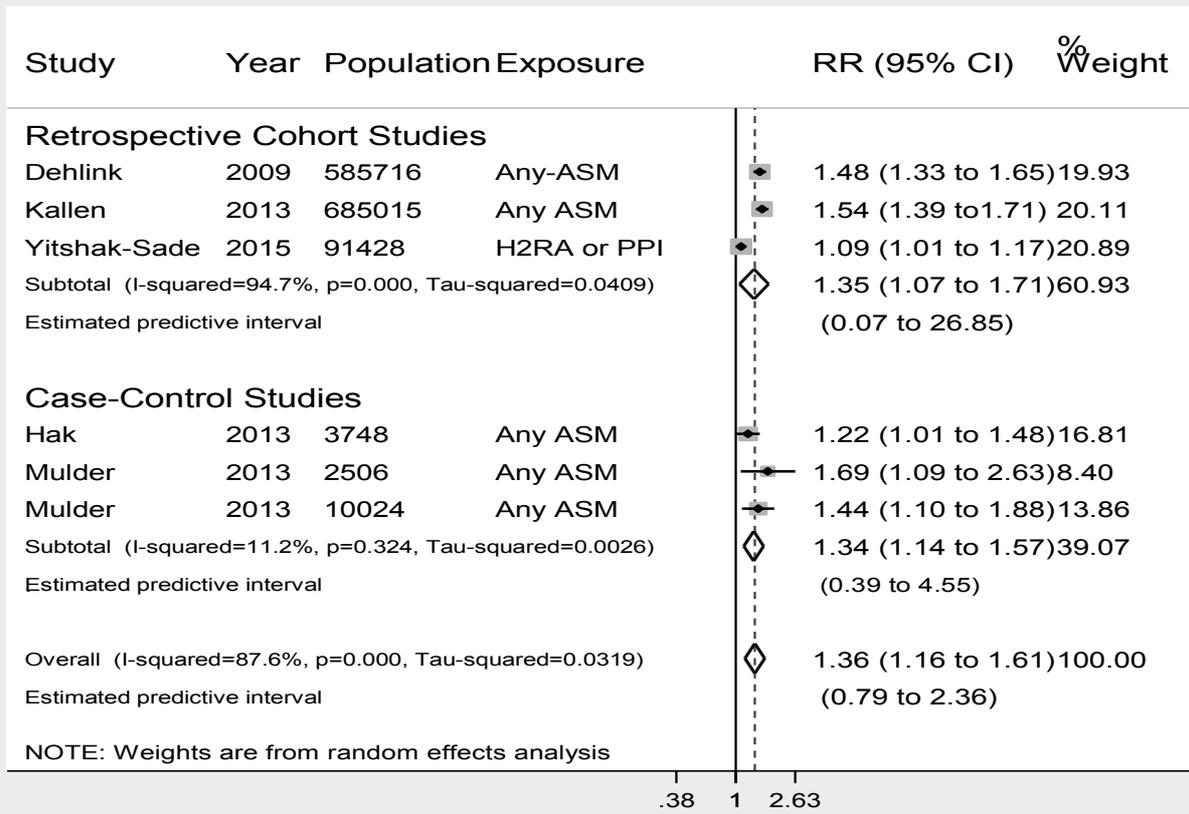
Meta-analysis of studies investigating the association between maternal use of H2- receptor antagonists (H2RA – **PANEL A**) and proton pump inhibitors (PPI – **PANEL B**) during pregnancy and the risk of asthma in the offspring. HR represents the hazard ratio of association. Population represents the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

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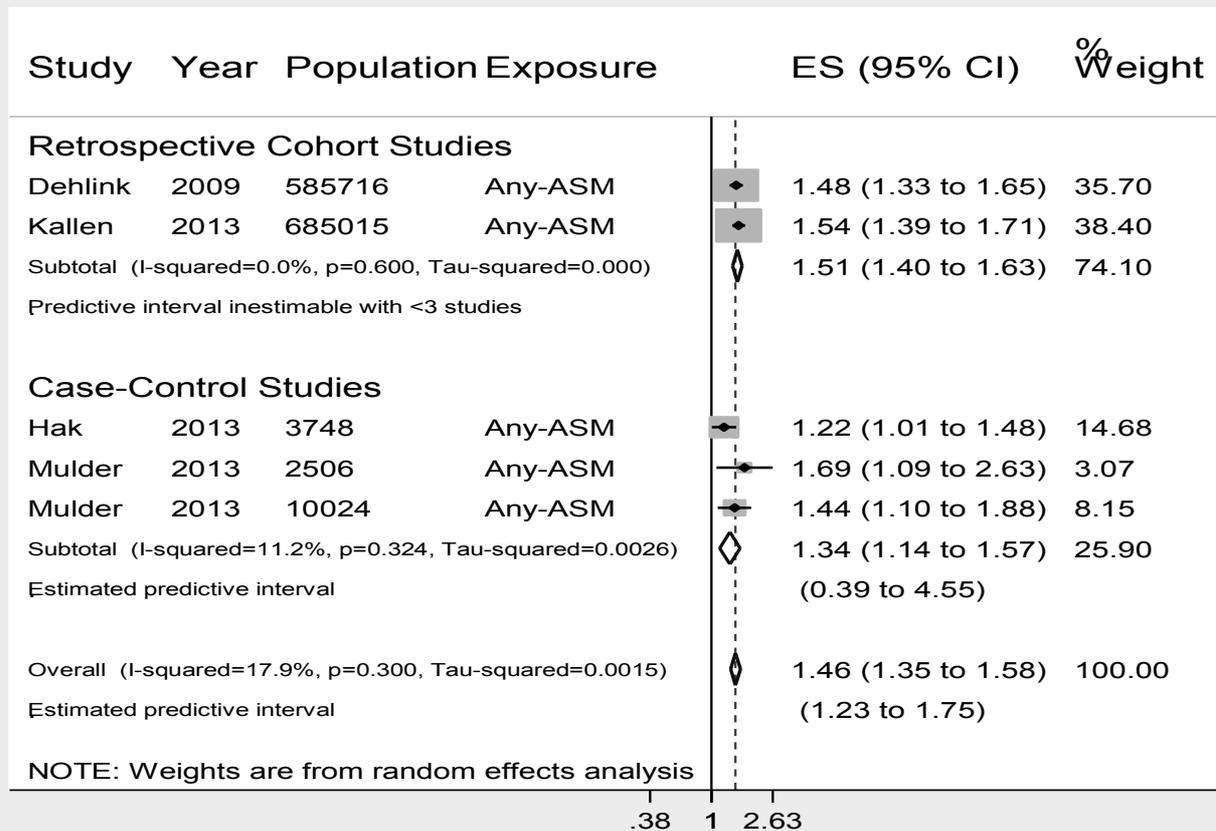
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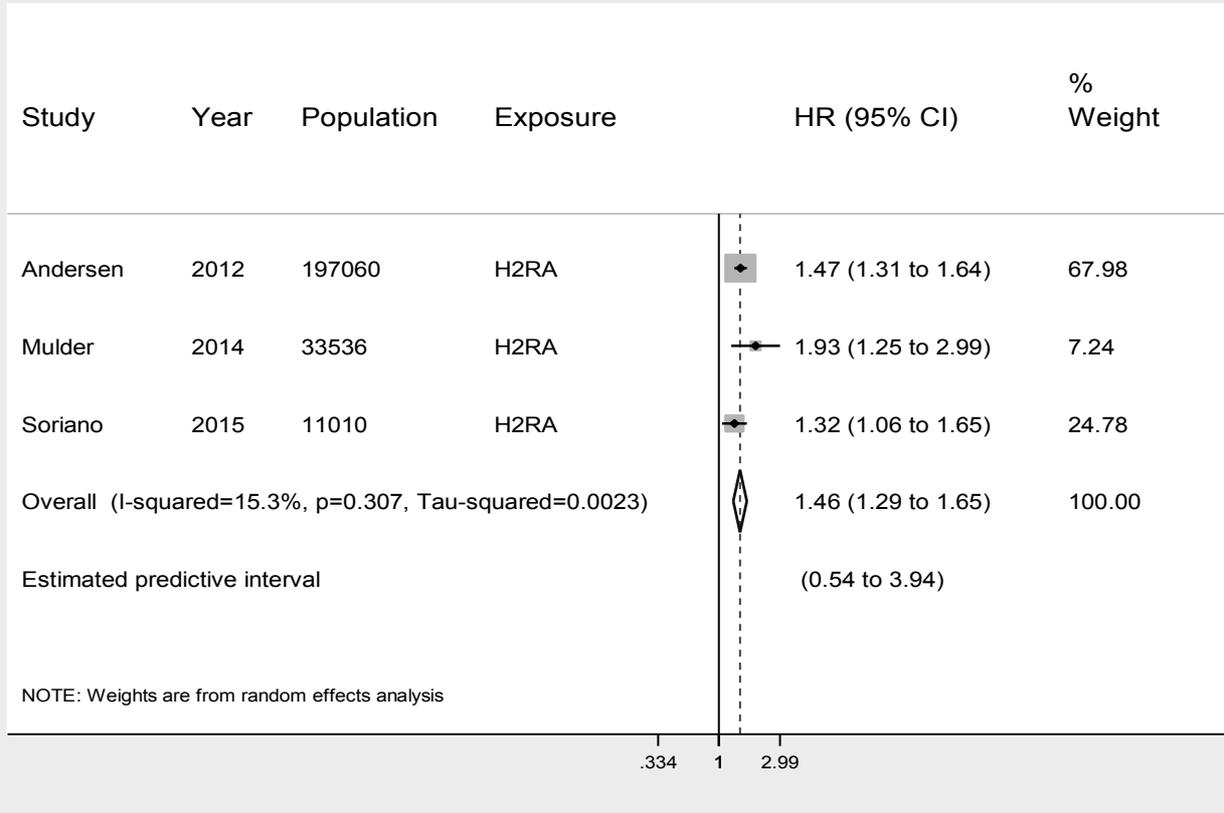
PANEL A



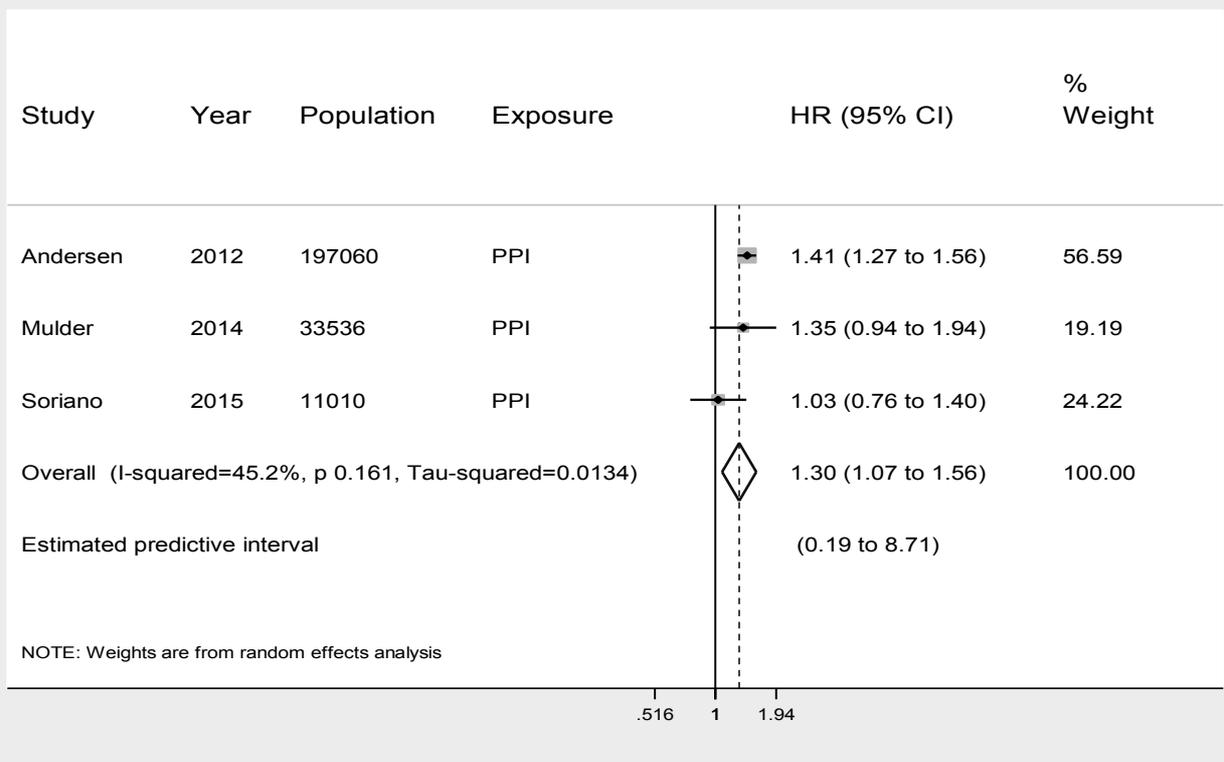
PANEL B



PANEL A



PANEL B



**Acid-suppressive medications during pregnancy and risk of asthma and allergy in children:
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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); and trimester (1 st , 2 nd & 3 rd combined) of exposure. Also considered pre-conception and post-pregnancy exposures	Asthma: having a record of a hospitalization, outpatient 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): 1 st trimester (1.46, 1.27 to 1.67); 2 nd /3 rd trimester (1.34, 1.15 to 1.56)	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 (1 st 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); 1 st 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 (1 st /2 nd trimester; 3 rd trimester)	Asthma: received a diagnosis of asthma and was prescribed any asthma medications at least 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 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); 1 st /2 nd trimester (1.01, 0.79 to 2.08); 3 rd 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 2 nd or 3 rd 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 (1 st /2 nd trimester, 3 rd 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 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) 1 st /2 nd trimester: (1.64, 1.12 to 2.41) 3 rd 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); 1 st trimester (1.15, 0.77 to 1.72); 2 nd trimester (1.75, 1.25 to 2.47); 3 rd trimester (1.20, 0.93 to 1.54); all three trimesters (1.26,	Strong

				considered trimester of exposure (1 st , 2 nd , 3 rd , all three trimesters).			antihistamines during pregnancy, sex of child	0.51 to 3.08) PPI: Anytime (1.03, 0.76 to 1.40); 1 st trimester (1.07, 0.76 to 1.51); 2 nd trimester (1.11, 0.60 to 2.05); 3 rd 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)); <i>reference is non-use.</i> 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) 1 st trimester: (1.08, 0.97 to 1.21) 2 nd trimester: (1.11, 0.93 to 1.32) 3 rd 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 ⁵ (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 ⁵	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 ⁵	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 ⁵	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

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

²Overall, 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

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

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

⁵Although 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

⁷It 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 estimates¹

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-p ₀ +(p ₀ ×odds ratio)); <i>Where p₀ is the baseline risk</i>	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)

¹Reference 9. The same formulae was used for converting the lower and upper 95% confidence intervals as suggested by Robert Grant in an electronic correspondence

²Abbreviations: ASM – Acid-suppressive medications; H2RA – H2- receptor antagonists; PPI – Proton pump inhibitors

³Mulder 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

⁴Reference 11

⁵Reference 10

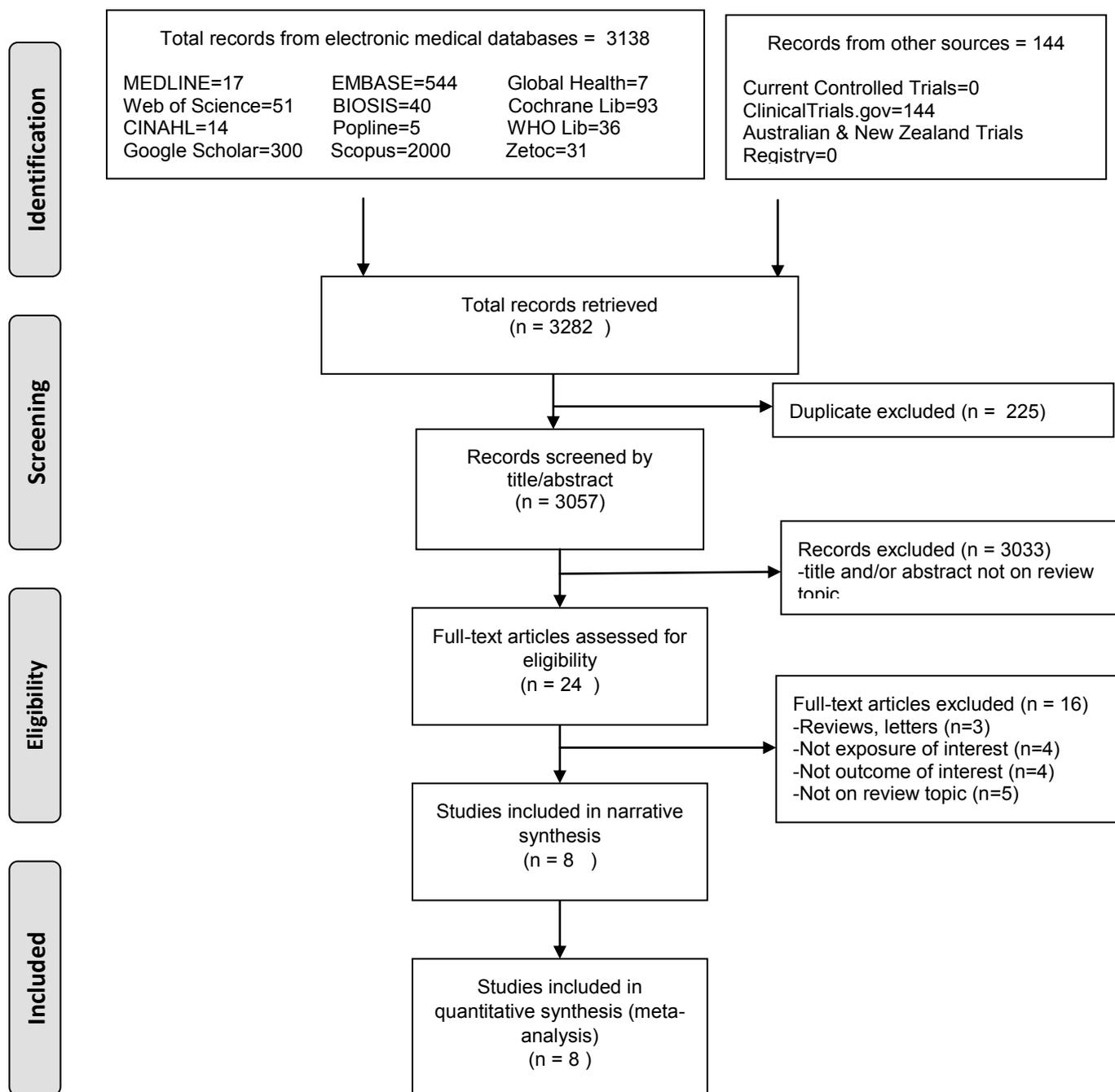


Figure E1 PRISMA flow diagram for database search of studies investigating the association between maternal use of acid-suppressive medications during pregnancy and risk of asthma and allergy in the offspring

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

3

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31 **METHODS**

32 **Ethics approval**

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

36

37 **Protocol and registration**

38 Prior to commencement of the review, we developed a detailed protocol, which was published¹ and
39 registered with the International Prospective Register of Systematic Reviews (PROSPERO;
40 <http://www.crd.york.ac.uk/prospero/>, reference CRD42015029584).

41

42 **Eligibility criteria**

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

46

47 **Types of exposure**

48 We considered all studies that investigated the association between maternal use of any type of
49 acid-suppressive medications (H2RA, PPIs, and antacids) during pregnancy and the risk of asthma
50 and allergy in the offspring. We also considered the dose, frequency, and timing (trimester) of use
51 of these medications.

52

53 **Study outcomes**

54 Our primary outcomes were objectively defined asthma, atopic dermatitis/eczema, allergic rhinitis
55 or hay fever, anaphylaxis, food allergy, urticaria and anaphylaxis by physician or hospital record or
56 self-reported; and atopic sensitization as defined either by skin prick test or raised antigen specific
57 IgE. Secondary outcomes included objective and subjective measures of disease severity and
58 impact on quality of life, including asthma exacerbations, use of asthma medications,
59 hospitalization for asthma, wheeze as defined by self-report or objective diagnosis; indicators of

60 airway function including (peak expiratory flow [PEF], forced expiratory volume in 1 second [FEV1],
61 forced vital capacity [FVC], forced expiratory flow rate or alternative age appropriate pulmonary
62 function tests [oscillometry or exhaled nitric oxide analysis]); and measures of health related quality
63 of life.

64

65 **Information sources, search strategy and study selection**

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

80

81 **Data extraction and quality assessment**

82 Two reviewers (RD and BN) independently extracted study data onto a customized data extraction
83 form. The data extraction form was piloted and revised prior to use in collecting data from all
84 studies. Discrepancies in data extraction were resolved by discussion and arbitration by a third
85 reviewer (NM). The PRISMA checklist guided reporting.²

86

87 **Risk of bias in individual studies**

88 Two reviewers (RD and BN) independently undertook the risk of bias analysis in the study using
89 the Effective Public Health Practice Project tool, which was adapted for use in this review. We
90 graded key components of each study as strong, moderate, or weak: suitability of the study design
91 for the research question; validity of exposure and outcome assessments; potential for selection
92 bias; and appropriate adjustment for confounding factors. From these component-specific
93 assessments, we derived an overall grading for each study as strong, moderate, or weak. Any
94 discrepancies were resolved by discussion or a third reviewer (NM) arbitrated.

95

96 **Summary measures**

97 Eligible studies reported one of the following effect measures: hazard ratio (HR), risk ratio (RR), or
98 odds ratio (OR). Although Andersen et al³ stated that they estimated incidence rate ratios using
99 Cox proportional hazard regression, we took these estimates as HR in the pooled analysis
100 because the Cox model estimates the hazard function. Mulder et al¹⁰ and Soriano et al¹² also
101 reported HR. Yitshak-Sade et al⁴ reported RR; estimates of studies reporting OR^{5,6-8} were
102 converted to RR using the formulae by Grant⁹ and then pooled with the Yitshak-Sade et al⁴ study.
103 The formulae for conversion is given as follows: $RR = OR/(1-p_0+(p_0 \times OR))$; where p_0 is the
104 baseline risk. The baseline risks for Dehlink et al⁵ and Källén et al⁶ were taken from the respective
105 papers. The baseline risk for Mulder et al 2013⁷ was taken from Mulder et al 2014,¹⁰ which was
106 based on the same study population. For Hak et al,⁸ we used the prevalence estimate (4.2%)
107 reported elsewhere but based on a similar primary care database.¹¹ The RR derived from these
108 calculations are presented in Table E5.

109

110 **Data synthesis**

111 Of the eight studies, six were retrospective cohort studies,^{3-6,10,12} while two were case-control
112 studies.^{7,8,13,14} We summarized the overall evidence both narratively and quantitatively. For the
113 quantitative synthesis, we employed random-effects meta-analysis to quantify the pooled effect
114 estimates for sufficiently clinically, methodologically, and statistically homogeneous studies. Mulder
115 et al 2013⁷ analyzed two sets of control populations that were compared to the same asthma
116 cases: sibling-based controls and non-sibling-based controls. In the analysis, we treated these sets

117 of case-control populations independently. This was applicable for use of any acid-suppressive
118 medications, H2RA only, and PPIs only; there were no data on use of antacids. Dosage of acid-
119 suppressive medications and trimester of exposure were differentially reported across studies,
120 hence we were unable to pool studies on these exposures. Meta-analysis was possible only with
121 studies on asthma and not for other outcomes as an insufficient number of studies were available
122 for other allergic outcomes. In the meta-analysis, studies reporting HR and RR were separately
123 pooled. We quantified the level of heterogeneity between studies using the I^2 statistic. In addition to
124 the overall summary effect estimate, we also estimated the 95% prediction interval, which takes
125 into account the overall uncertainty surrounding the summary effect and heterogeneity across
126 studies to provide a range for which we are 95% confident that the effect of acid-suppressive
127 medications on the risk of asthma in new studies would lie.¹³ Given that the number of studies for
128 each meta-analysis was small, thus lacking the required power (i.e less than the recommended
129 minimum of 10 studies),¹⁴ we were unable to graph the funnel plots to evaluate possible publication
130 bias or small study effect; hence we performed the Begg and Egger tests for this purpose.¹⁵ Meta-
131 analyses were undertaken using Stata Statistical Software: Release 14. College Station, TX:
132 StataCorp LP.

133

134 **Sensitivity analyses**

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

141

142 **Grading the quality of the overall body of evidence**

143 Using the GRADE system, we first identified all potentially relevant outcomes and rated their
144 relative clinical importance: asthma was considered a critical outcome; atopic dermatitis/eczema,
145 allergic rhinitis, and other allergic disorders were considered as important outcomes. Second, we

146 appraised the quality of the overall evidence for each outcome and presented this information
147 using the GRADE evidence profiling table template.¹⁶

148

149 **RESULTS**

150 **Study selection**

151 We identified 3282 records, of which 3057 were included for screening by title and/or abstract after
152 de-duplication. Of these, 3033 were excluded for not meeting the inclusion criteria, leaving 24
153 papers for full text screening. A further 16 papers were excluded, leaving eight papers that met our
154 inclusion criteria (Figure E1).^{3-8,10,12}

155

156 **Study characteristics**

157 All studies were either based on a primary care database or population-based prescription or
158 dispensing database. Two studies each were undertaken in The Netherlands^{7,10} Sweden^{5,6} and
159 United Kingdom,^{8,12} whereas one study each was undertaken in Denmark³ and Israel.⁴ All studies
160 considered asthma as an outcome while two in addition considered other allergic disorders,
161 including atopic dermatitis/eczema and allergic rhinitis.^{5,10} Whereas most studies considered use of
162 any acid-suppressive medication or H2RA/PPIs,^{5-8,10} the independent role of H2RA and PPIs were
163 examined in three studies,^{3,4,10} but no study examined the role of antacids alone. Seven of the
164 studies also considered the trimester of exposure to acid-suppressive medications, while three
165 examined the dosage of use, commonly defined as defined daily doses; however, marginally
166 different definitions of trimester and dosage were used across studies.

167

168 **Risk of bias within studies**

169 Based on overall risk of bias assessment in the studies, six studies were graded as strong and two
170 as moderate. The overall quality grading was derived from the grading for the different components
171 of the studies. Apart from Mulder et al⁷, which was graded weak for confounding adjustment, all
172 other studies were graded moderate or strong for all components (Table E3).

173

174 **Use of acid-suppressive medications and risk of asthma**

175 Across individual studies, offspring of mothers who used any acid-suppressive medications during
176 pregnancy were at an increased risk of asthma compared to offspring of non-users (Table E2). The
177 results were similar when H2RA and PPIs were examined separately, except for imprecise
178 estimates from two studies.^{10,12} Higher dosage of acid-suppressive medications appeared to show
179 a greater risk compared to lower dosage (Table E2). Whereas use of acid-suppressive medications
180 during any trimester of pregnancy was associated with an increased risk of asthma, there was no
181 clear indication that any specific trimester was associated with greatest risk (Table E2). The high
182 heterogeneity in the analysis of the use of any acid-suppressive medications was reduced in
183 further exploration, as explained in the sensitivity analysis section.

184

185 **Use of ASMs and risk of other allergic disorders**

186 The association between use of acid-suppressive medications and other allergic disorders was
187 investigated by two studies,^{5,10} both reporting an increased risk amongst offspring of mothers using
188 any acid-suppressive medications, H2RA, and PPIs, compared to those of non-using mothers
189 (Table E2). Mulder et al¹⁰ in addition reported an increased risk of atopic dermatitis/eczema and
190 allergic rhinitis with use of acid-suppressive medications, although estimates were imprecise in
191 some cases for the independent roles of H2RA and PPIs (data not shown). Given the different
192 effect measures used by Dehlink et al⁵ (OR) and Mulder et al¹⁰ (HR), and considering that only
193 Mulder et al 2014 examined atopic dermatitis/eczema and allergic rhinitis, we could not calculate
194 pooled estimates of the association between acid-suppressive medications and risk of allergic
195 disorders other than asthma.

196

197 **Sensitivity analyses**

198 By stratifying the association between use of any acid-suppressive medication or H2RA/PPIs by
199 study design the results showed that the high heterogeneity was specific to the cohort studies
200 (Figure 1). Further exclusion of the study by Yitshak-Sade et al⁴ reduced the heterogeneity in all
201 studies from the initial 87% to 18% and the heterogeneity in the cohort studies from 95% to 0%
202 (Figure 1). Stratification of the results by study design and exclusion of the Yitshak-Sade et al

203 study⁴ 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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