Review Article

Risk and Protective Factors for Childhood Asthma: What Is the Evidence?

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To summarize the principal findings on risk and protective factors for childhood asthma, we retrieved systematic reviews on these topics in children (aged 1 to 18 years), up to January 2016, through MEDLINE, EMBASE, CINAHL, SCOPUS, and CDSR. A total of 227 studies were searched from databases. Among those, 41 systematic reviews (SRs) were included: 9 focused on prenatal factors, 5 on perinatal factors, and 27 on postnatal factors. Of these 41 SRs, 83% had good methodological quality, as determined by the Assess Systematic Reviews tool. After reviewing all evidence, parental asthma, prenatal environmental tobacco smoke, and prematurity (particularly very preterm birth) are well-established risk factors for childhood asthma. Current findings do suggest mild-to-moderate causal effects of certain modifiable behaviors or exposures during pregnancy (maternal weight gain or obesity, maternal use of antibiotics or paracetamol, and maternal stress), the perinatal period (birth by Caesarean delivery), or postnatal life (severe respiratory syncytial virus infection, overweight or obesity, indoor exposure to mold or fungi, and outdoor air pollution) on childhood asthma, but this suggestive evidence must be confirmed in interventional studies or (if interventions are not feasible) well-designed prospective studies. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;■:■-■)

Key words: *Asthma; Wheeze; Children; Meta-analysis; Protective factors; Risk factors*

Over the last 3 decades, childhood asthma has become a major public health problem worldwide, particularly in industrialized nations. This rapid rise in asthma burden can only be explained by changes in environment or lifestyle.[1]

A justifiable interest in understanding the etiology of the "asthma epidemic" has led to publication of hundreds of articles on environmental risk factors for childhood asthma in recent years. Attempts to synthesize the results of these studies have in turn led to systematic reviews, which can be defined as scientific investigations with preplanned methods and a collection of primary studies as their "subjects," using strategies to identify bias and random error.[2] However, reading around 50 published systematic reviews of risk factors for childhood asthma would be both challenging and time consuming. Thus, a summary and interpretation of these systematic reviews could be helpful to researchers, clinicians, and public health practitioners interested in asthma in children.

The objective of this article is to synthesize and critically examine the main findings of systematic reviews of risk or protective factors for childhood asthma, organized according to their presence or predominance in the prenatal, perinatal, and postnatal periods of life.

We identified studies published in the MEDLINE, EMBASE, CINAHL, and SCOPUS databases up to January 2016, using the terms: "((risk factors OR protective factors) AND (asthma or wheeze*) AND (child*) AND (meta-analysis))." No language restriction was employed; if a study was published in more than 1 language, the latest version was chosen. To be included in this review, all studies also had to: (1) be systematic reviews with a meta-analysis of observational or interventional studies of risk or protective factors for childhood asthma, and (2) focus on children (aged 1 to 18 years) or (if children and adults were included) report a separate analysis in children. Studies were excluded if they: (1) were published solely in abstract form, (2) focused on risk factors specific to a country, geographic region, or particular study group (eg, ISAAC, ENRIECO, GA2LEN), or (3) focused on genetics or pharmacologic treatments for asthma.

Data extraction and assessment of risk of bias

Titles, abstracts, and citations for studies meeting the inclusion criteria outlined above were independently analyzed by

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Abbreviations used
AMSTAR- Assess Systematic Reviews
BCG- Bacillus Calmette-Guérin
BMI- Body mass index
CO- Carbon monoxide
CI- Confidence intervals
ETS- Environmental tobacco smoke
GER- Gastroesophageal reflux
OR- Odds ratio
PMs- Particulate matters
PUFA- Polyunsaturated fatty acids
PVC- Polyvinyl chloride
NO_2- Nitrogen dioxide
N_2O- Nitrous oxide
SO_2- Sulfur dioxide
RCT- Randomized clinical trials
RR- Relative risk
RSV- Respiratory syncytial virus

3 authors (J.A.C-R, C.E.R-M, and E.F.). Full texts of all studies were then evaluated for eligibility, and the methodological quality of the eligible systematic reviews was assessed using the AMSTAR (Assess Systematic Reviews) tool.[3] The AMSTAR tool has a maximum of 11 points; a systematic review assigned 8 or more points is deemed of good quality. Disagreements between the 3 reviewers were discussed and resolved by consensus.

Of the 227 studies retrieved from the databases (Figure 1), 41 were included in this review. Of these 41 studies, 9 examined familial or prenatal factors, 5 examined perinatal factors, and 27 examined postnatal factors. The quality of their methodology (assessed using the AMSTAR tool) is shown in Table I (83% were of good quality, receiving $\geq$8/11 points).

Table II summarizes the main findings of systematic reviews of risk or protective factors for asthma or wheeze. For each meta-analysis, Table II shows the pooled odds ratio (OR) and its 95% confidence interval (CI), and the I^2 statistic or Cochran χ^2 heterogeneity test Q for heterogeneity across studies. A 2-sided $P < .01$ for the Cochran χ^2 indicates significant heterogeneity; for the I^2 statistic, cutoff values of 0%, 25%, 50%, and 75% were used for no, low, moderate, and high heterogeneity, respectively. Figure 2 shows the OR and relative risk (RR) for childhood asthma or wheeze from systematic review of familial or prenatal, perinatal, and postnatal factors.

FAMILIAL OR PRENATAL FACTORS

Parental asthma

A meta-analysis of 33 studies showed that children with maternal asthma (defined as self-reported physician-diagnosed asthma or as self-reported ever asthma) had approximately 3-fold greater odds of asthma than those without maternal asthma, with no significant heterogeneity.[4] Moreover, children with paternal asthma had 2.4 times higher odds of asthma than those without paternal asthma, with no significant heterogeneity. Compared with paternal asthma, maternal asthma was associated with significantly greater odds of childhood asthma ($P = .04$). However, there was no significant difference in the magnitude of the effect estimates between maternal (OR = 2.85) and paternal (OR = 2.48) asthma in an analysis restricted to 18 studies in which parental asthma was diagnosed by a physician ($P = .37$). Similarly, there was no significant difference in effect estimates between maternal asthma (OR = 3.15) and paternal asthma (OR = 2.60) in an analysis restricted to children 5 years and older ($P = .14$).

Maternal weight gain and obesity during pregnancy

Forno et al[5] conducted a meta-analysis of 14 studies of gestational obesity (n = 12) or weight gain (n = 5) during pregnancy and childhood asthma, with an aggregate sample size of 108,321 mothers whose children were followed up to an age ranging from 14 months to 16 years. In this meta-analysis, maternal overweight or obesity during pregnancy was significantly associated with 1.21 times increased odds of current asthma or wheeze in participating children, with moderate heterogeneity across studies. Moreover, each 1 kg/m^2 increment in maternal body mass index (BMI) was significantly associated with 2%-3% increased odds of childhood asthma. In that study, the association between maternal obesity and childhood asthma was stronger in studies with lower prevalence of maternal asthma; other factors including maternal age or the child's age at follow-up did not modify the effect size.

Maternal folate or vitamin D status during pregnancy

Crider et al[6] performed a systematic review of 5 studies (including 45,642 mother-child pairs) of prenatal folate or folic acid use and childhood asthma. In that meta-analysis, there was no significant association between maternal intake of folic acid supplements before the second trimester of pregnancy and asthma at school age (range: 5.5 to 7 years), with no heterogeneity across studies. Because of substantial heterogeneity in exposures and outcomes, no aggregate effect estimates could be generated for other indicators of folate status (eg, serum folate). However, most primary effect estimates showed no significant association between folate status and asthma.

Maternal diet and maternal dietary intake of nutrients or vitamins during pregnancy

Nurmatov et al[7] examined 62 studies of diet, vitamins, or nutrients and asthma, wheeze, or atopic disorders in children. Meta-analyses of 4 and 3 birth cohort studies showed that high maternal dietary intake of vitamin D and vitamin E during pregnancy was significantly associated with 44% and 32% reduced odds of wheezing outcomes, respectively, in early childhood (at ages 2 to 5 years). Maternal intake of vitamin D was not significantly associated with asthma at age 5 years. Results from other meta-analyses of a few birth cohorts were not supportive of prenatal effects of vitamin C, zinc, or selenium on childhood wheeze.

More recently, Beckhaus et al[8] examined 32 studies of maternal diet (including diverse nutrients, food groups, and dietary patterns) during pregnancy and childhood asthma. In that meta-analysis, higher maternal intake of vitamin D, vitamin E, and zinc during pregnancy were each associated with lower odds of wheeze—but not asthma—in childhood. No significant findings were reported for maternal intake of other vitamins (A, B, or C), copper, calcium, magnesium, manganese, selenium, or specific food groups such as vegetables, fruits, fish, meat, dairy, or fats.

Maternal stress

Van de Loo et al[9] examined 10 observational studies of prenatal maternal stress and respiratory morbidity in childhood. The prevalence of wheeze, asthma, and other respiratory symptoms was higher in children of mothers who were exposed to or experienced some form of psychological stress during pregnancy

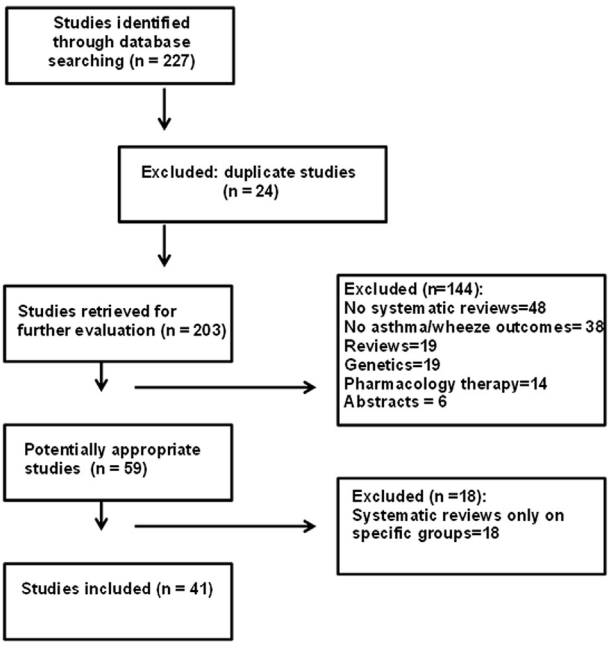

FIGURE 1. Study selection flowchart.

than in children of mothers who did not (OR = 1.56 [1.36-1.80], I^2 = 18). Subgroup analysis demonstrated that maternal stress during pregnancy was significantly associated with asthma (4 studies) or wheeze (8 studies).

Maternal use of antibiotics

In a meta-analysis of 10 studies (7 cohort studies and 3 case-control studies),[10] maternal use of antibiotics during pregnancy was associated with 1.2 times increased odds of childhood wheeze or asthma, but there was high heterogeneity across studies. After excluding case-control studies and prospective studies of inadequate quality, the association remained significant and of similar magnitude (pooled OR = 1.18, 95% CI = 1.11-1.26), but the heterogeneity across studies was markedly decreased (I^2 = 46.7%). In that analysis, the association between prenatal use of antibiotics and childhood wheeze or asthma was stronger for antibiotic use in the third trimester of pregnancy than that in the first or second trimester of pregnancy.

Maternal use of paracetamol

Several meta-analyses have been published on maternal paracetamol (acetaminophen) use during pregnancy and childhood asthma. In a meta-analysis of 6 studies (5 prospective cohorts and 1 cross-sectional study),[11] paracetamol use during pregnancy was significantly associated with 1.2 times increased odds of wheeze at ages 2.5 years to 7 years. However, there was high heterogeneity across studies.

A meta-analysis of 11 birth cohort studies[12] reported that maternal paracetamol use in the first, third, and second/third trimesters is significantly associated with 39%, 17%, and 49% increased odds of childhood asthma, respectively. However, there was considerable heterogeneity across studies. In contrast to the findings for prenatal use of paracetamol, there was no significant association between paracetamol use during infancy and childhood asthma after adjustment for lower respiratory tract infections.[12]

Environmental tobacco smoke (ETS)

Burke et al[13] performed a meta-analysis of 79 studies of ETS, wheeze, and asthma. The studies were grouped by type of ETS (prenatal maternal, postnatal maternal, postnatal paternal, or in the household) and the age at which the outcome was assessed ($\leq$2, 3-4, or 5-18 years). Prenatal maternal smoking was significantly associated with increased incidence of asthma or wheeze in all age groups, with ORs ranging from 1.28 in children aged 3 to 4 years to 1.52 in children aged 5 to 18 years. In that analysis, there was moderate to high heterogeneity across the 2 age groups below 5 years but not in the age groups 5 years and older. Postnatal maternal smoking was also significantly associated with wheeze in all age groups, but the magnitude of the association was higher in children younger than 5 years (ORs = 1.65-1.70) than in those 5 years and older (OR = 1.18). Household ETS exposure was significantly associated with wheeze, with similar findings across all age groups (ORs ranging between 1.06 and 1.32). Paternal smoking was significantly associated with 1.39 times increased odds of wheeze in 5-18 year olds; limited data precluded a meta-analysis in younger children. A meta-analysis of prenatal maternal, paternal, and household ETS exposure and asthma yielded findings that were similar to those for wheeze; although some results were not significant, they were in the same direction of association as in the analysis of wheeze.

PERINATAL FACTORS

Birth by Caesarean section

In a meta-analysis of 23 studies,[14] birth by Caesarean section was significantly associated with 22% excess odds of asthma (aged 1 to 28 years), with moderate heterogeneity across studies. Restricting the analysis to childhood asthma (ascertained before age 18 years) yielded similar results (OR = 1.20), with reduced heterogeneity across studies.

Preterm delivery

In a meta-analysis of 19 studies including predominantly children, Jaakkola et al[15] reported that prematurity (a gestational age < 37 weeks) was associated with asthma at ages 1 to 31 years (fixed-effect OR = 1.074, random-effect OR = 1.37), with significant heterogeneity across studies. In a meta-regression adjusting for asthma definition, study design, population size, geographic location, language, and year of publication, the estimated effect of preterm birth on asthma decreased as the age of the subjects increased.

In a meta-analysis of 17 studies including 874,710 children,[16] preterm birth was associated with 1.46 times increased odds of asthma or wheezing disorders, but there was high heterogeneity across studies. The strength of the association between preterm birth and wheezing disorders was similar between children aged less than 5 years and older children. Of note, children born very preterm (<32 weeks' gestation) had a greater increase in the odds of asthma (OR = 2.81) than those born moderately preterm (32-36 weeks' gestation, OR = 1.37). Findings were most pronounced for studies with low risk of bias and were consistent across sensitivity analyses. The population-attributable risk of asthma for preterm birth was estimated as 3.1%, with 1.2%

TABLE I. Evaluation of the quality (using the AMSTAR tool[3]) of the 41 systematic reviews included

Ref./AMSTAR's Questions	1	2	3	4	5	6	7	8	9	10	11
Lim et al[4]	Y	Y	N	Y	N	Y	Y	Y	N	Y	Y
Forno et al[5]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Crider et al[6]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Nurmatov et al[7]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
Beckhaus et al[8]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Van de Loo et al[9]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Zhao et al[10]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Eyers et al[11]	Y	Y	Y	Y	N	Y	CA	CA	Y	Y	N
Cheelo et al[12]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
Burke et al[13]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	CA
Thavagnanam et al[14]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N
Jaakkola et al[15]	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y
Been et al[16]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Mu et al[17]	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y
Das and Naik[18]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
El-Zein et al[19]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Gdalevich et al[20]	Y	Y	N	Y	N	Y	Y	Y	Y	N	N
Brew et al[21]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Dogaru et al[22]	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y
Lodge et al[23]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Muley et al[24]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
Yang et al[25]	Y	Y	Y	CA	Y	Y	CA	CA	Y	Y	Y
Garcia-Marcos et al[26]	Y	Y	Y	Y	Y	Y	N	CA	Y	N	Y
Seyedrezazadeh et al[27]	Y	Y	Y	CA	Y	Y	Y	Y	CA	N	Y
Elazad et al[28]	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y
Zuccotti et al[29]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Thakkar et al[30]	Y	N	Y	Y	N	Y	Y	Y	N	N	Y
Marra et al[31]	Y	Y	Y	CA	Y	Y	Y	Y	Y	Y	N
Murk et al[32]	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y
Regnier et al[33]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Maas et al[34]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
Fisk et al[35]	Y	N	N	Y	N	N	Y	Y	N	Y	Y
Tischer et al[36]	Y	N	N	Y	N	Y	Y	Y	Y	Y	Y
Mendy et al[37]	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y
Genuneit[38]	Y	CA	Y	Y	Y	Y	Y	CA	Y	Y	N
Gasana et al[39]	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y
Jaakkola and Knight[40]	Y	CA	CA	CA	Y	Y	N	CA	Y	NA	Y
Vork et al[41]	Y	CA	Y	Y	N	Y	CA	CA	Y	N	CA
Lieberoth et al[42]	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y
Flaherman and Rutherford[43]	Y	N	N	Y	Y	Y	N	N	Y	Y	Y
Egan et al[44]	Y	N	Y	Y	Y	Y	Y	Y	Y	NA	Y
Chen et al[45]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y

AMSTAR, Asses Systematic Reviews; *CA*, cannot answer; *N*, no; *NA*, not applicable; *Ref*, reference; *Y*, yes.
AMSTAR's Questions: 1. Was an *a priori* design provided? 2. Was there duplicate study selection and data extraction? 3. Was a comprehensive literature search performed? 4. Was the status of publication (ie, gray literature) used as an inclusion criterion? 5. Was a list of studies (included and excluded) provided? 6. Were the characteristics of the included studies provided? 7. Was the scientific quality of the included studies assessed and documented? 8. Was the scientific quality of the included studies used appropriately in formulating conclusions? 9. Were the methods used to combine the findings of studies appropriate? 10. Was the likelihood of publication bias assessed? 11. Was the conflict of interest included?

attributable to very preterm birth and 1.9% attributable to moderately preterm birth.

Birth weight

A meta-analysis of 12 studies including 38,115 children[17] showed that low birth weight (<2500 g) was associated with 1.28 to 1.34 times higher odds of asthma than a birth weight > 2500 g or between 2500 g and 4000 g, with moderate heterogeneity across studies. In this analysis, a birth weight >4000 g was not significantly associated with asthma.

Neonatal hyperbilirubinemia

A meta-analysis of 7 studies (6 retrospective studies and 1 cohort study) including 101,499 children[18] showed that neonatal hyperbilirubinemia significantly increased the odds of childhood asthma (OR = 4.26), without heterogeneity across

TABLE II. Principal findings of 41 systematic reviews of risk and protective factors for childhood asthma

Authors	No. of studies	Study design	Total no. of subjects	OR or RR [95% CI] for meta-analysis	Heterogeneity
Familial or prenatal factors					
Lim et al[4]	33	25 PBC, 8 CC	254,820	OR = 3.04 [2.59-3.56] for maternal asthma and asthma in children; OR = 2.44 [2.14-2.79] for paternal asthma and asthma in children	Q stat $P = .13$; $P = .06$
Forno et al[5]	14	14 O	108,321	OR = 1.21 [1.07-1.37], $P = .003$ for maternal overweight/obesity in pregnancy and current asthma/wheeze in children	$I^2 = 69.1\%$
Crider et al[6]	5	3 C, 2 NCC	45,642	RR = 1.01 [0.78-1.30], $P = .95$ for prenatal folate exposure and childhood asthma	$I^2 = 0\%$
Nurmatov et al[7]	62	21 C, 15 CC, 26 CS	NR	OR = 0.25 [0.10-0.40], $P = .002$ for high vitamin A level and childhood asthma; OR = 0.68 [0.52-0.88], $P = .004$ for high maternal vitamin E intake during pregnancy and childhood asthma; OR = 0.56 [0.42-0.73], $P < .001$ for high maternal vitamin D intake during pregnancy and childhood asthma; OR = 0.75 [0.60-0.94], $P = .01$ for high fruit intake and childhood asthma	$I^2 = 0\%$; $I^2 = 0\%$; $I^2 = 15.8\%$; $I^2 = 66\%$
Beckhaus et al[8]	32	29 PC, 3 RC	123,032	OR = 0.58 [0.38-0.88], $P \leq .01$ for higher maternal vitamin D and childhood wheeze; OR = 0.54 [0.41-0.71], $P \leq .0001$ for higher maternal vitamin E and childhood wheeze; OR = 0.57 [0.41-0.81], $P = .002$ for higher maternal zinc intake and childhood wheeze	$I^2 = 59\%$; $I^2 = 0\%$; $I^2 = 0\%$
Van de Loo et al[9]	10	8 C, 1 CC, 1 CS	3,210,204	OR = 1.45 [1.25-1.68] for maternal stress and childhood asthma; OR = 1.87 [1.42-2.45] for maternal stress and childhood wheeze	$I^2 = 13\%$; $I^2 = 76\%$
Zhao et al[10]	10	7 C, 3 CC	16,610	OR = 1.20 [1.13-1.27] for maternal antibiotics exposure and childhood asthma/wheeze	$I^2 = 83\%$
Eyers et al[11]	6	5 PC, 1 CS	28,038	OR = 1.21 [1.02-1.44] for exposure to paracetamol during pregnancy and wheezing	$I^2 = 76\%$
Cheelo et al[12]	11	9 PC, 1 RC	921,529	OR = 1.39 [1.01-1.91]; OR = 1.17 [1.04-1.31]; and 1.49 [1.37-1.63] for exposure to paracetamol during 1st, 3rd, and 2nd-3rd trimester, respectively; and childhood asthma	$I^2 = 64\%$; $I^2 = 0\%$; $I^2 = 0\%$
Burke et al[13]	79	79 PC	NR	OR = 1.41 [1.20-1.67]; OR = 1.28 [1.14-1.44]; and OR = 1.52 [1.23-1.87] for prenatal maternal smoking and wheeze in children aged ≤2 y; 3-4 y; and 5-18 y old, respectively	$I^2 = 85.2\%$; $I^2 = 65.6\%$; $I^2 = 21.1\%$
				OR = 1.70 [1.24-2.35]; OR = 1.65 [1.20-2.28]; and OR = 1.18 [0.99-1.40] for postnatal maternal smoking and wheeze in children aged ≤ 2 y; 3-4 y; and 5-18 y, respectively	$I^2 = 0\%$; $I^2 = 48.5\%$; $I^2 = 19.4\%$
				OR = 1.35 [1.10-1.66]; OR = 1.06 [0.88-1.27]; and OR = 1.32 [1.12-1.55] for household ETS exposure and wheeze in children aged ≤ 2 y; 3-4 y; and 5-18 y, respectively	$I^2 = 64.5\%$; $I^2 = 54.4\%$; $I^2 = 0\%$
Perinatal factors					
Thavagnanam et al[14]	23	22 C, 1 CC	1,206,679	OR = 1.22 [1.14-1.29], $P < .001$ for birth by Caesarean section and childhood asthma	$I^2 = 46\%$
Jaakkola et al[15]	19	13 C, 5 CS, 1 CC	456,651	OR = 1.074 [1.07-1.08], $P < .001$ for preterm delivery and childhood asthma	Q stat ($P = .001$)

(continued)

TABLE II. *(Continued)*

Authors	No. of studies	Study design	Total no. of subjects	OR or RR [95% CI] for meta-analysis	Heterogeneity
Been et al[16]	17	7 RC, 5 PC, 5 CS	874,710	aOR = 1.46 [1.29-1.65], $P < .001$ for preterm (<37 wk) delivery and childhood wheeze; aOR = 2.81 [2.55-3.12], $P < .001$ for very preterm (<32 wk) delivery and childhood wheeze	$I^2 = 80\%$; and $I^2 = 0\%$
Mu et al[17]	17	15 C, 2 CS	38,115	OR = 1.28 [1.09-1.50], $P < .003$ for low birth weight as compared with birth weight >2500 g and childhood asthma; OR = 1.34 [1.13-1.60], $P < .001$ for low birth weight as compared with birth weight 2500-4000 g and childhood asthma	$I^2 = 51\%$; $I^2 = 62\%$
Das and Naik[18]	7	6 R, 1 C	101,499	OR = 4.26 [4.04-4.5], $P < .0001$ for neonatal hyperbilirubinemia and childhood asthma; OR = 3.81 [3.53-4.11], $P < .0001$ for neonatal phototherapy (bilirubin > 15 mg/dL) and childhood asthma	$I^2 = 0\%$; $I^2 = 26\%$
Postnatal factors					
El-Zein et al[19]	16	7 RC, 5 CS, 3 CC, 1 PC	67,179	OR = 0.86 [0.79-0.93] for BCG vaccination and childhood asthma	$I^2 = 0\%$
Gdalevich et al[20]	12	12 PC	8,183	OR = 0.70 [0.60-0.81] for exclusive breastfeeding during first 3 mo and childhood asthma	$I^2 = 11.3\%$
Brew et al[21]	31	15 LBC, 10 CS, 6 CC	417,880	OR = 0.92 [0.86-0.98], $P = .008$ for any breastfeeding and current wheeze in children; OR = 1.10 [1.00-1.22], $P = .05$ for any breastfeeding and childhood asthma	$I^2 = 40\%$; $I^2 = 4\%$
Dogaru et al[22]	113	57 C, 47 CS, 13 CC	832,013	OR = 0.76 [0.67-0.86] for breastfeeding (more vs less) and current asthma in children; OR = 0.81 [0.76-0.87] for breastfeeding (more vs less) and current wheezing in children	I^2= 91.6%; $I^2 = 86.6\%$
Lodge et al[23]	42	23 C, 17 CS, 2 CC	391,238	OR = 0.90 [0.84-0.97] for breastfeeding (more vs less) and childhood asthma	$I^2 = 63\%$
Muley et al[24]	5	5 RCT	1,932	OR = 0.97 [0.65-1.47], $P = .9$ for dietary omega-3-fatty acid supplementation on childhood asthma incidence	$I^2 = 52.2\%$
Yang et al[25]	4	4 C	12,481	OR = 0.76 [0.61-0.94] for fish intake in infancy and childhood asthma incidence; OR = 0.71 [0.42-0.96] for children whose mothers had high levels of n3 PUFA in breast milk and childhood asthma incidence	$I^2 = 11.5\%$; $I^2 = 0\%$
Garcia-Marcos et al[26]	8	8 CS	39,804	OR = 0.85 [0.75-0.98], $P = .02$ for Mediterranean diet adherence in children and current wheezing; OR = 0.86 [0.78-0.95], $P = .004$ for Mediterranean diet adherence in children and asthma ever	Q stat $P = .24$; $P = .98$
Seyedrezazadeh et al[27]	14	13 CS, 1 C	346,615	RR = 0.81 [0.74-0.88] for high intake of fruits and childhood wheeze; RR = 0.88 [0.79-0.97] for high intake of vegetables and childhood wheeze	$I^2 = 83.1\%$; $I^2 = 83.7\%$
Elazab et al[28]	5	5 RCT	3,257	RR = 0.99 [0.81-1.21], $P = .92$ for probiotics supplementation during pregnancy and childhood asthma	$I^2 = 0\%$
Zuccotti et al[29]	8	8 RCT	1,890	RR = 0.99 [0.77-1.27], $P = .95$ for probiotics infants supplementation and childhood asthma; RR = 0.91 [0.67-1.23], $P = .76$ for probiotics infants supplementation and wheezing	NR
Thakkar et al[30]	5	4 PC, 1 PB	2,824	OR = 5.6 [4.3-6.9] for gastroesophageal reflux prevalence and childhood asthma	NR

Marra et al[31]	8	5 RC, 3 PC	12,082	OR = 2.05 [1.41-2.99] for antibiotic exposure during first year of life in all studies and incident of childhood asthma; OR = 1.12 [0.88-1.42] for antibiotic exposure during first year of life in prospective studies and incident of childhood asthma	Q stat $P < .01$
Murk et al[32]	22	8 RC, 8 DB, 6 PC	685,820	OR = 1.52 [1.30-1.77], $P < .001$ for antibiotic exposure during pregnancy or in the first year of life and childhood asthma	$I^2 = 95\%$
Régnier and Huels[33]	15	6 L	82,008	OR = 3.84 [3.23-4.58], $P = .03$ for RSV hospitalization in early life and incidence of asthma/wheeze	$I^2 = 45\%$
Mass et al[34]	9	9 LBC	3,271	OR = 0.72 [0.54-0.96], $P = .02$ for multifaceted intervention reducing inhalant and food allergens before 5 y of age and childhood asthma; OR = 0.52 [0.32-0.85], $P = .009$ for multifaceted intervention reducing inhalant and food allergens after 5 y of age and childhood asthma	$I^2 = 0\%$; $I^2 = 0\%$
Fisk et al[35]	17	NR	NR	OR = 1.53 [1.39-1.68] for the presence of dampness and mold in home and wheezing; OR = 1.56 [1.30-1.86] for the presence of dampness and mold in home and current asthma	NR
Tischer et al[36]	61	29 CS, 16 CC, 16 C	203,798	OR = 1.49 [1.28-1.72] for visible mold exposure and childhood asthma; OR = 1.68 [1.48-1.90] for visible mold exposure and wheeze	NR
Mendy et al[37]	19	10 C, 8 CS, 1 CC	13,793	OR = 1.48 [1.10-1.98] for early endotoxin exposure and wheeze at infants/toddlers; OR = 0.82 [0.69-0.97] for early endotoxin exposure and asthma at school age	$I^2 = 46.2\%$; $I^2 = 0\%$
Genuneit[38]	29	29 LBC	130,428	OR = 0.77 [0.60-0.99] for living in a farm residence and childhood asthma	$I^2 = 68\%$
Gasana et al[39]	19	10 CS, 9 C	163,597	OR = 1.05 [1.0-1.11]; 1.02 [1.0-1.04]; and 1.06 [1.01-1.12] for NO_2, N_2O, and CO exposure and childhood asthma prevalence, respectively. OR = 1.04 [1.01-1.07] for SO_2 exposure and prevalence of wheezing in children, and OR = 1.05 (1.04-1.07) for PMs exposure in incidence of wheezing in children	$I^2 = 0\%$; $I^2 = 0\%$; $I^2 = 37.7\%$. $I^2 = 16.5\%$; $I^2 = 0\%$
Jaakola and Knight[40]	5	3 CS, 2 CC	20,899	OR = 1.55 [1.18-2.05] for PVC surface materials at home and childhood asthma	Q stat $P = .64$
Vork et al[41]	8	8 C	25,167	aRR = 1.33 [1.41-1.36] for exposure to secondhand tobacco and childhood asthma incidence	NR
Lieberoth et al[42]	7	4 RC, 3 PC	22,859	OR = 1.37 [1.15-1.64], $P = .0005$ for early menarche (<12 y) and childhood asthma	$I^2 = 55\%$
Flaherman and Rutherford[43]	12	8 PC, 4 RC	121,386	RR = 1.50 [1.2-1.8] for BMI $\geq$ 85 percentile and childhood asthma	NR
Egan et al[44]	6	6 PC	25,374	RR = 1.35 [1.15-1.58], $P = .0002$ for overweight (BMI $\geq$ 85 percentile) and childhood asthma; RR = 1.50 [1.22-1.83], $P < .001$ for obese (BMI >95 percentile) and childhood asthma	$I^2 = 2\%$; $I^2 = 44\%$
Chen et al[45]	6	6 PC	18,760	RR = 1.19 [1.03-1.37], $P = .02$ for overweight and childhood asthma incidence; and RR = 2.02 [1.16-3.50], $P = .01$ for obesity and childhood asthma incidence	NR

aOR, Adjusted odds ratio; *BCG*, Bacillus Calmette-Guérin; *BMI*, body mass index; *C*, cohort; *CC*, case control; *CI*, confidence intervals; *CO*, carbon monoxide; *CS*, cross-sectional; *DB*, database; *ETS*, environmental tobacco smoke; *L*, longitudinal; *LBC*, longitudinal birth-cohort; *NCC*, nested case-control; NO_2, nitrogen dioxide; N_2O, nitrous oxide; *NR*, not reported; *O*, observational; *OR*, odds ratio; *PB*, population based; *PBC*, population-based cohort; *PC*, prospective cohort; *PMs*, particulate matters; *PUFA*, polyunsaturated fatty acids; *PVC*, polyvinyl chloride; *RC*, retrospective cohort; *RCT*, randomized clinical trial; *RR*, relative risk; *RSV*, respiratory syncytial virus; SO_2, sulfur dioxide.

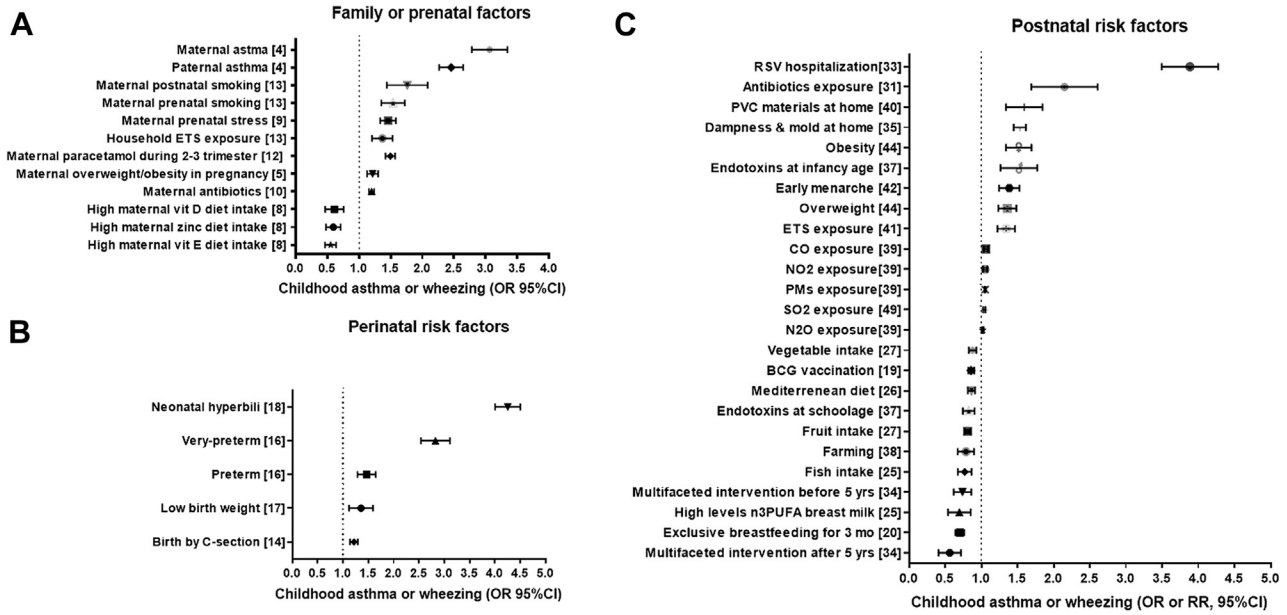

FIGURE 2. Odds ratio (OR) or relative risk (RR) (and 95% confidence intervals) for childhood asthma or wheeze from systematic reviews of familial or prenatal factors (**A**), perinatal factors (**B**), and postnatal factors (**C**). The OR or RR was chosen for asthma if available, or for current wheezing otherwise. When 2 ORs or RRs existed for the same outcome, we selected the highest estimate for risk factors and the lowest estimate for protective factors. *BCG*, Bacillus Calmette-Guérin; *CO*, carbon monoxide; *NO_2*, nitrogen dioxide; *N_2O*, nitrous oxide; *PM*, particulate matters; *ETS*, environmental tobacco smoke; *PUFA*, polyunsaturated fatty acids; *PVC*, polyvinyl chloride; *RSV*, respiratory syncytial virus; *SO_2*, sulfur dioxide.

studies. Neonatal phototherapy also increased the odds of asthma (OR = 3.81) with low heterogeneity. As observational studies were included, the GRADE evidence generated was of low quality.

POSTNATAL FACTORS

Bacillus Calmette-Guérin (BCG) vaccination

El-Zein et al[19] performed a meta-analysis of 16 studies of BCG vaccination and asthma with a total of 67,179 participants. In this analysis, BCG vaccination was significantly associated with a 14% reduction in the odds of asthma, with no heterogeneity across studies. However, only 1 prospective study was included in this meta-analysis.

Breastfeeding

In a meta-analysis of 12 studies including 8183 subjects,[20] exclusive breastfeeding during the first 3 months of life was associated with 30% reduced odds of childhood asthma (mean age 4.1 years), with minimal heterogeneity across studies. The estimated protective effect of breastfeeding on asthma was greater in studies of children with a family history of atopy (OR = 0.52 [0.35-0.79]) than in studies of the general population (OR = 0.73 [0.62-0.86]). After the analysis was restricted to studies that only included children without a family history of atopy, there was no significant association between breastfeeding and childhood asthma (OR = 0.99 [0.48-2.03]).

In another meta-analysis, including 31 studies and 417,880 subjects,[21] there was no significant association between any or exclusive breastfeeding (for 3 or 4 months) and asthma or current wheeze in children aged more than 5 years, though there was moderate heterogeneity across studies. However, a subgroup analysis revealed that any breastfeeding is associated with a mild reduction (8%) in the odds of current wheeze (with moderate heterogeneity across studies), but also nonsignificantly associated with a 10% increment in the odds of asthma ($P = .05$, with minimal heterogeneity across studies).

A meta-analysis of 113 studies[22] showed that breastfeeding for at least 6 months was associated with 24% reduced odds of "recent asthma," as well as with 19% reduced odds of "recent wheeze," with high heterogeneity across studies. After stratification by age, there was a strong inverse association between breastfeeding and asthma or wheeze up to age 2 years (without heterogeneity), but this association weakened as age increased.

In a recent meta-analysis of 42 studies,[23] ever (vs never) breastfeeding was associated with 12% reduced risk of asthma in children aged 5-18 years, with moderate heterogeneity across studies. There was a reduced risk of asthma for ever-breastfed children in high-income countries (OR = 0.90 [0.83, 0.97], I^2 = 18%), as well as in medium/low-income countries (OR = 0.78 [0.70, 0.88], I^2 = 0%). This association was attenuated and became nonsignificant when the analysis was restricted to cohort studies.

Diet and nutrients

In meta-analyses of observational studies of children, Nurmatov et al[7] showed that serum vitamin A level and high dietary intake of fruits are significantly associated with 75% reduced odds of asthma and 25% reduced odds of wheeze, respectively.

Muley et al[24] conducted a meta-analysis of 5 randomized clinical trials (RCTs) of omega-3 fatty acids (for up to 12 months) to prevent asthma, including 1932 children who were randomized, had available outcomes, and were followed for an average of 3.5 years (range 0.5-8 years). In that analysis, there was no significant association between dietary omega-3 fatty acid supplementation and asthma. A meta-analysis of 4 cohort studies including 12,481 children[25] reported a 24% reduced risk of asthma for fish intake and a 29% reduction in the risk of asthma among children whose mothers had high levels of long-chain n-3 polyunsaturated fatty acids (PUFA) in breast milk, with minimal heterogeneity across studies.

In a meta-analysis of 8 cross-sectional studies,[26] a Mediterranean diet (generally low in saturated fatty acids and rich in fiber, antioxidants, and n-3 PUFA derived from olive or fish oil) was significantly associated with 15% lower odds of current wheeze and 14% lower odds of ever asthma. Of note, however, some results were driven mainly by studies performed in Mediterranean populations. Consistent with findings for a Mediterranean diet, Seyedrezazadeh et al[27] reported lower risk of wheeze among children with high intake of fruits and vegetables, with very similar results for asthma.

Probiotics

A meta-analysis of RCTs[28] showed that probiotic supplementation during pregnancy or infancy was not significantly associated with physician-diagnosed asthma or incident wheeze. In a more recent meta-analysis of RCTs, Zuccotti et al[29] also reported no significant association between probiotic supplementation and asthma or wheeze.

Gastroesophageal reflux (GER)

Thakkar et al[30] examined 5 studies of GER that included children with and without asthma. In those studies, estimates of the prevalence of GER were 22% and 4.8% in children with and without asthma, respectively. Moreover, GER was significantly associated with 5.6 times increased odds of asthma (pooled OR = 5.6 [4.3-6.9]). Because of methodologic limitations, paucity of population-based studies, and a lack of longitudinal studies, several aspects of this association are unclear.

Antibiotics

In a meta-analysis of 8 studies by Marra et al,[31] including 12,082 subjects (of whom 1,817 had asthma), antibiotic use in the first year of life was significantly associated with 2-fold increased odds of childhood asthma, with significant heterogeneity across studies. However, this association was markedly weakened and became nonstatistically significant when the analysis was restricted to prospective studies (OR = 1.12, 95% CI = 0.88-1.42), which are less susceptible to "reverse causation" or recall bias.

Murk et al[32] recently showed that antibiotic exposure during pregnancy or in the first year of life (22 studies, n = 685,820 subjects) was significantly associated with 1.52 times increased odds of childhood asthma; however, there was high heterogeneity across studies. Similar to the findings of Marra et al,[31] there was no significant association between antibiotic use in the first year of life and asthma when the analysis was restricted to prospective studies (OR = 1.07, 95% CI = 0.89-1.28), with no heterogeneity across studies. In contrast, prenatal use of antibiotics was significantly associated with childhood asthma, even when the analysis was restricted to 3 prospective studies (OR = 1.70, 95% CI = 1.11-2.60).

Viral infections

A meta-analysis of 15 studies including 82,008 children[33] showed that hospitalization for respiratory syncytial virus (RSV) infection in early life was associated with 3.84 times increased odds of incident asthma or wheeze later in childhood, with low-to-moderate heterogeneity across studies. To date, there has been no meta-analysis of studies of rhinovirus infection and asthma.

Allergens

A meta-analysis[34] of 9 studies including 3271 children showed that multifaceted interventions to reduce both inhalant and food allergens were associated with 28% to 48% significantly reduced odds of asthma before and after age 5 years, with no heterogeneity across studies. In contrast, there was no significant association between monofaceted interventions to reduce inhalant (but no food) allergens and asthma. Indirect comparisons between these treatments did not demonstrate a significant difference between multiple interventions and monointerventions in reducing the odds of asthma in children under 5 years (OR = 0.64 [0.40-1.04], $P = .07$) or in those 5 years and older (OR = 0.63 [0.35-1.13], $P = .12$).

Mold and fungi

A meta-analysis of 17 studies found that household dampness and mold is associated with 53% increased odds of childhood wheeze, perhaps independently of allergy.[35] Moreover, a combined analysis of 33 studies of children and adults found that household dampness and mold is significantly associated with 56% increased odds of current asthma.

In another meta-analysis[36] of 61 studies including more than 200,000 subjects, signs of mold in the home were significantly associated with 49% and 68% increased odds of asthma and wheeze, respectively.

Endotoxin

A meta-analysis of 19 studies[37] showed that endotoxin exposure in early life was significantly associated with 48% increased odds of wheeze in infants and toddlers, with moderate heterogeneity across studies. In contrast, endotoxin exposure in early life was significantly associated with 18% reduced odds of asthma at school age, with no heterogeneity across studies. All 4 studies in younger children and 3 of 5 studies in school-aged children were prospective.

Farm environment

In a meta-analysis of birth cohort studies,[38] living in a farm residence was significantly associated with 23% reduced odds of asthma, with moderate heterogeneity across studies. This association was even stronger in children who lived in a farm and had parents who worked in a farm environment (OR = 0.69 [0.64-0.76], $I^2 = 35\%$). The heterogeneity across studies was reduced when the analysis was restricted to geographic locations in the Alps.

Air pollution

A meta-analysis by Gasana et al[39] included 19 studies assessing different exposures: nitrogen oxides (nitric oxide [NO], nitrogen dioxide [NO_2], nitrous oxide [N_2O]), particulate matters (PMs), carbon monoxide (CO), sulfur dioxide (SO_2), and ozone. In that

meta-analysis, N_2O and NO_2 were significantly associated with 2% and 5% increased odds of prevalent asthma, with no heterogeneity across studies, and CO was associated with 6% increased odds of prevalent asthma, with low heterogeneity across studies. Moreover, NO_2 and SO_2 were associated with increased incident asthma, with minimal heterogeneity across studies, and SO_2 and PMs were each associated with increased odds of wheeze. Of note, no separate analysis was conducted for the 9 longitudinal studies.

Toxins

Jaakkola and Knight[40] conducted a meta-analysis of 5 (non-longitudinal) studies in children, which showed an association between polyvinyl chloride (PVC) surface materials in the home and 45% increased odds of asthma, without significant heterogeneity across studies.

ETS

In a meta-analysis of 38 studies,[41] ETS was significantly associated with 1.33 times increased risk of incident asthma among children aged 6-18 years, adjusting for atopy. There was no reported assessment of heterogeneity across studies.

Menarche

A meta-analysis of 7 studies including 22,859 children[42] showed that girls with early menarche (<12 years) had 1.37 times significantly increased odds of asthma, with moderate heterogeneity across studies. A sensitivity analysis showed that the risk estimate was not markedly changed when excluding any of the analyzed studies.

Overweight or obesity

In a meta-analysis of 12 studies including more than 120,000 subjects,[43] a subgroup analysis of 4 studies showed that increased body weight during middle childhood was significantly associated with 50% increased risk of subsequent asthma, and a subgroup analysis of 9 studies showed that high birth weight is associated with 20% increased risk of childhood asthma.

A meta-analysis of 6 studies including 25,734 children[44] showed that obesity (defined as BMI $\geq$ 95th percentile) was significantly associated with 50% increased risk of incident asthma in both boys and girls, with no heterogeneity across studies. The magnitude of this association was greater in girls (RR = 1.53 [1.09-2.14], $P = .01$) than in boys (RR = 1.40 [1.01-1.93], $P = .04$). However, there was much more heterogeneity in studies of boys ($I^2 = 81\%$) than in studies of girls ($I^2 = 34\%$).

In another meta-analysis of 6 studies including 18,760 children,[45] overweight (defined as a BMI $\geq$ 85th percentile) and obesity (BMI $\geq$ 95th percentile) were significantly associated with 1.19 times and 2.02 times increased risk of incident asthma, respectively. Moreover, there was a significant dose-response relationship between BMI and incident asthma. In this analysis, the estimated effect of obesity on asthma was greater in obese boys (RR = 2.47 [1.57-3.87], $P < .001$) than in obese girls (RR = 1.25 [0.51-3.03], $P = .04$).

DISCUSSION

A systematic review or meta-analysis is ultimately dependent on the underlying quality of the primary studies included in the analysis. Limitations include the design of the original studies (eg, observational or cross-sectional), the covariates included in the original analyses (eg, different studies may have adjusted for different confounders), and unknown sources of bias that may have been inadvertently included in the primary studies. The degree of heterogeneity between studies is also important and has been highlighted within each section. Moreover, results from such analysis have to be interpreted in the context of other supporting evidence.

Familial or prenatal factors

Current evidence supports strong causal effects (OR or RR $\geq$ 2) of parental (paternal or maternal) asthma (a non-modifiable risk factor) on childhood asthma. Systematic reviews of observational studies, together with findings from interventional studies and data on the impact of public health policy measures, strongly support mild-to-moderate causal effects (OR or RR $\geq$ 1.2 but <2) of prenatal ETS on childhood asthma.

Current evidence suggests that maternal weight gain or obesity during pregnancy, maternal use of paracetamol, and maternal stress during pregnancy each have mild-to-moderate effects on increasing asthma risk in childhood, but interventional studies are needed to firmly establish causality. Similarly, maternal use of antibiotics during pregnancy may have mild-to-moderate causal effects on asthma, but this needs further assessment in longitudinal studies.

Maternal vitamin D insufficiency (a serum 25(OH)D < 30 ng/mL) is not likely to have moderate or strong causal effects on asthma, but there is inconclusive evidence for modest (yet potentially clinically significant) effects from 2 RCTs.[46,47] In an RCT of high-dose prenatal vitamin D (4400 IU/day) versus low-dose prenatal vitamin D (400 IU/day) to prevent asthma or wheeze at age 3 years in 806 children in the United States,[46] 218 children developed asthma or recurrent wheeze: 98 of 405 (24.3%; 95% CI, 18.7%-28.5%) in the intervention arm versus 120 of 401 (30.4%, 95% CI, 25.7%-73.1%) in the control group (hazard ratio, 0.8 [0.6-1.0]; $P = .05$). Future RCTs should have larger simple size and consider postnatal vitamin D supplementation.

Existing evidence does not support a causal role for maternal folic acid status on childhood asthma, and there is insufficient or conflicting evidence for a causal role of maternal diet or maternal nutrient intake during pregnancy on childhood asthma.

Perinatal factors

Moderate-to-high-quality evidence suggests that 3 correlated perinatal factors have mild-to-moderate effects on increasing the risk of childhood asthma (birth by Caesarean section, prematurity, and low birth weight), and that very preterm birth is a strong risk factor for childhood asthma. Compared with vaginal delivery, Caesarean delivery before rupture of the membranes was recently shown to be more strongly associated with childhood asthma (incidence RR = 1.20 [1.16-1.23] than Caesarean delivery after rupture of the membranes incidence RR = 1.12 [1.09-1.16]).[48] An RCT of vaginal versus nonemergent Caesarean delivery may be difficult to implement but could help to firmly establish causality. Whether neonatal hyperbilirubinemia predisposes to childhood asthma or wheeze cannot be determined from existing evidence, but warrants proper assessment in longitudinal studies.

Postnatal exposures

Severe RSV infection in early life (leading to hospitalization) is likely to be a strong risk factor for childhood asthma.

Confirmation of a causal role of severe RSV infection (eg, by vaccination) is pending, awaiting trials of RSV vaccination or treatment to prevent childhood asthma.

High-quality evidence supports mild-to-moderate effects of both overweight/obesity and indoor mold/fungi on increasing the risk of childhood asthma. However, interventional studies are needed to both confirm causality and assess the relative contribution of these factors to disease pathogenesis. Studies of moderate quality also support mild-to-moderate effects of outdoor air pollution (particularly NO_2 and SO_2) on asthma risk, and warrant follow-up in well-designed longitudinal studies.

High-quality evidence suggests that living in a farm residence or exposure to indoor endotoxin has mild-to-moderate protective effects against asthma, particularly at or after school age. Longitudinal studies are needed to identify specific exposures (eg, microbial) underlying the putative protective effects of a farming environment against asthma. Although there is some evidence of potential beneficial effects of multifaceted interventions to reduce indoor allergen exposure, such interventions are generally cumbersome and likely to be prohibitively expensive.

There is limited, conflicting, or insufficient evidence of a causal role of BCG vaccination, breastfeeding, diet or dietary patterns, early menarche, and exposure to PVC in childhood asthma. Ongoing longitudinal studies of breastfeeding, accounting for introduction and parallel consumption of foodstuff, should help clarify its role, if any, on asthma. Similarly, longitudinal studies are needed to assess whether certain diets (eg, Mediterranean) reduce asthma risk, as well as to better characterize the relation between PVC exposure and asthma. Current evidence does not support a causal role of postnatal use of antibiotics or probiotics in childhood asthma.

Summary

After reviewing all evidence, parental asthma, prenatal environmental tobacco smoke, and prematurity (particularly very preterm birth) are well-established risk factors for childhood asthma. Current findings do suggest mild-to-moderate causal effects of certain modifiable behaviors or exposures during pregnancy (maternal weight gain or obesity, maternal use of antibiotics or paracetamol, and maternal stress), the perinatal period (birth by Caesarean delivery), or postnatal life (severe RSV infection, overweight or obesity, indoor exposure to mold or fungi, and outdoor air pollution) on childhood asthma, but this suggestive evidence must be confirmed in interventional studies or (if interventions are not feasible) well-designed prospective studies.

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