

Meta-analysis of antenatal infection and risk of asthma and eczema

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Abstract

Background: The influence of maternal infection during pregnancy on allergic disorders in offspring is not well understood. We performed a systematic review and meta-analysis to evaluate current evidence on the association between maternal infection during pregnancy and asthma or eczema in offspring.

Methods: We searched databases (PubMed, EMBASE, Medline, and Web of Science) for all relevant studies published before March 2016. Any cohort studies, case-control studies, or cross-sectional studies published in English and focused on the association between maternal infection during pregnancy and the risk of asthma or eczema in offspring were included. Random-effects models were used for combined analyses.

Results: A total of 10 studies with 299,830 participants were included. Maternal infection was associated with an increased risk for asthma (odds ratio [OR]: 1.55; 95% confidence interval [CI]: 1.24–1.92; $P < 0.01$) and eczema (OR: 1.36; 95% CI: 1.13–1.64; $P < 0.01$). Further analyses showed associations between asthma and several specific maternal infections: fever episode (OR: 1.73; 95% CI: 1.35–2.23), chorioamnionitis (OR: 1.42; 95% CI: 0.96–2.11), respiratory infection (OR: 1.49; 95% CI: 0.94–2.36), and urogenital infection (OR: 1.39; 95% CI: 1.18–1.64).

Conclusion: The results from this meta-analysis and systematic review provide evidence that maternal infection during pregnancy might be related to subsequent asthma and eczema in offspring. However, there was variation of included studies with regard to type of maternal infection, age of children, and methods of exposure ascertainment. Additional studies are needed to further confirm these associations.

Abbreviations: CI = confidence interval, NOS = Newcastle–Ottawa Scale, OR = odds ratio.

Keywords: asthma, eczema, infection, meta-analysis

Editor: Jian Liu.

Funding: This work was supported by the National Science Foundation of China (no. 81330016 and 31171020 to DM; no. 81172174 and 81270724 to YQ), the Major State Basic Research Development Program (2013CB967404), the Grants from Ministry of Education of China (IRT 0935, 313037, 20110181130002), the Grant from State Commission of Science Technology of China (2012BAI04B04), the Grants from Science and Technology Bureau of Sichuan province (2014SZ0149), and the Grant of clinical discipline program (neonatology) from the Ministry of Health of China (1311200003303).

Author contributions: TTZ and LZ contributed equally to this work. TTZ and LZ conceived and designed the study. ZDM and YQ conducted literature searches and data collection. TTZ and LZ performed the statistical analysis and wrote manuscript. ZDM revised the manuscript.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

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Medicine (2016) 95:35(e4671)

Received: 27 March 2016 / Received in final form: 6 July 2016 / Accepted: 21 July 2016

<http://dx.doi.org/10.1097/MD.0000000000004671>

1. Introduction

Asthma is characterized by an increased responsiveness of the airway and airway obstruction under various stimuli that is partially or completely reversible.^[1] Eczema is characterized by epidermal dryness and itchiness that causes typical relapsing lesions and plaques.^[2] Both are common chronic diseases that pose a global public health problem with significant impacts on direct, indirect, intangible, and opportunity costs. Worldwide prevalence rates of these disorders have remained high despite significant advances in disease prevention and therapy.^[3,4]

The underlying mechanisms for asthma and eczema are unknown. Increasing evidence from animal and human studies suggest that fetal programming is a very critical stage for subsequent development of the immune and neuroendocrine systems; prenatal exposures to adverse events may induce epigenetic and immunologic modifications that may contribute to a higher risk for allergic disorders.^[5,6] Maternal infections are one of the most common complications that occur during pregnancy. Maternal infection during pregnancy is associated with maternal morbidity, such as cesarean sections, and fetal and neonatal morbidity, such as premature rupture of membranes, low birth weight, bronchopulmonary dysplasia, and cerebral palsy.^[7–9]

There is inconsistent evidence from studies that have investigated the association between maternal infection during pregnancy and asthma or eczema. The objective of this systematic review and meta-analysis was to determine if maternal infections during pregnancy are associated with an increased risk of asthma or eczema in offspring.

2. Methods

2.1. Search strategy and study selection

There is no registered protocol for this search. The PubMed, EMBASE, Medline, and Web of Science databases were searched for all relevant studies published before March 2016. Search terms included MeSH terms and free texts [e.g., (prenatal OR antenatal OR gestational OR maternal) AND (infection OR chorioamnionitis OR febrile) AND (asthma OR wheeze OR eczema)] (search strategy see in sTable 1, <http://links.lww.com/MD/B228> and sTable 2, <http://links.lww.com/MD/B228>). The search was restricted to human studies published in the English language. We also identified additional relevant studies through manual searches of the reference lists of included studies. Titles and abstracts of the articles were initially screened; subsequently, 2 reviewers (ZDM and YQ) independently reviewed full-text articles to determine qualification based on selection criteria. Any differences in opinion were resolved through discussions with the study team.

Studies were included if they met the following criteria: they were on the topic of association between maternal infection during pregnancy and the risk of asthma or eczema in offspring; the study design was cohort, case-control, or cross-sectional; and they reported risk estimates (e.g., OR [ratio odd], RR [relative risk], HR [hazard ratios]) or original data from which risk estimates could be calculated. Studies that were case reports, case series, or letters were excluded. If the same research had duplicate reports, only the most recent one was included in the meta-analysis.

2.2. Data extraction and study quality assessment

Two researchers (ZDM and YQ) independently extracted data from all included studies on first author's name, publication year, study location, study design, maternal infection, children's allergic disorder information, sample size, effect size and 95% confidence interval (CI), and adjusted or matched varieties. Disagreements about study information were resolved through discussing with a third author (TTZ).

All included studies were appraised independently by 2 authors using the Newcastle-Ottawa Scale (NOS).^[10] This scale consists of 3 parts for cohort and case-control studies: selection (4 items), comparability (1 item), and outcome/exposure (3 items). The maximum score is 9 stars. The scores of 0 to 4, 5 to 7, and 8 to 9 stars correspond to studies that are considered as low, moderate, and high quality, respectively. Any disagreements between authors were resolved by discussion with a third author.

2.3. Data synthesis and statistical analysis

We conducted a meta-analysis to generate pooled ORs and 95% CI for the association between maternal infection during pregnancy and asthma or eczema in offspring using RevMan 5.3.5 and STATA Version 12.0.

Statistical heterogeneity across eligible studies was assessed by both the Cochran Q statistic test and the I^2 heterogeneity test. The P -value for significance of the Cochran Q test was set to <0.10 . Heterogeneity was divided into three levels according to the value of the I^2 statistic: mild ($I^2=0-25\%$), moderate ($I^2=25-50\%$), and high ($I^2=50-100\%$). A random effects model was performed for all analyses in this study, as there was significant heterogeneity across studies in the pooled analysis and a small number of studies (<5 studies) in the subgroup meta-analyses for types of maternal infections.^[11] In regards to study design, an

outcome of asthma and adjustments for confounding factors were not consistent between studies; we conducted a sensitivity analysis to detect sources of heterogeneity and to examine the influence of various exclusion criteria on the overall risk estimate. We also conducted a sensitivity analysis by removing each study sequentially to examine the effect of elimination on the remaining pooled results. Publication bias was assessed by inspection of the funnel plots as well as Egger and Begg statistical test.

2.4. Ethical statement

As all analyses were based on previously published studies, ethical approval was not necessary.

3. Results

3.1. Literature search

A total of 426 potential, nonduplicate studies were identified from the online databases and screening reference lists of selected studies. After screening titles and abstracts of these articles, 373 records were excluded for being duplicate records, irrelevant topics, reviews, animal studies, in another language, or having no outcome data. Full texts of the remaining 32 studies were assessed for eligibility. Finally, we included 10 studies in this systematic review and meta-analysis. A flow diagram of study selection is presented in the supplemental data (PRISMA 2009 Flow Diagram, <http://links.lww.com/MD/B228>).

3.2. Characteristics of included studies

Primary characteristics of included studies are summarized in Table 1. Seven cohort studies,^[1,12-16,19] 2 case-control studies,^[17,18] and 1 cross-sectional study^[2] were included in the analysis. Publishing year ranged from 1999 to 2015. There was a pooled total of 299,830 participants from the 10 included studies. Half of the studies ($n=5$) reported a positive association between maternal infection during pregnancy and asthma in offspring,^[1,14,17-19] while the remaining 5 studies did not show a significant association. Five studies^[2,15,17-19] were from Europe, 4^[1,12,13,16] from America, and 1^[14] from Australia. Nine studies^[1,2,12-15,17-19] adjusted for or matched cases with potential confounding factors such as maternal age at delivery, maternal history of allergic disorders, maternal smoking during pregnancy, birth weight, gestational age, child's age, child's sex.

Included studies diagnosed maternal infection in a variety of ways: 7 studies were based on medical record or questionnaires,^[2,12,14,16-19] 1 diagnosed cases according to the International Classification of Diseases (ICD-9),^[11] 1 according to stool samples to measure geohelminth infection,^[11] and 1 cultured microbes from amniotic fluid samples.^[15] In all studies, maternal infection occurred before delivery.

Outcome assessment varied between studies. Five studies^[2,12,13,15,17] used questionnaires (of which 3 studies^[13,15,17] specified "report of physician-diagnosed asthma or eczema"), and 5^[1,14,16,18,19] studies diagnosed by physician or medical record review. Participant age range varied between studies, including 2 to 5 years,^[14] 15 to 17 years,^[15] 3 to 14 years,^[2] and 5 to 16 years.^[18] Others were at a single time ranging from 1 to 8 years.

3.3. Quality assessment

The NOS scores for included studies ranged from 6 to 9 (median NOS score=7), suggesting overall methodological quality of

Table 1
Characteristics of included studies.

Refs.	Location	Study design	Case/sample size	Maternal infection during pregnancy	Infection case ascertainment	Child allergic disorder	Child's age	ASD case ascertainment	Adjustment or matched variants
Cooper ^{1,2]}	Brazil	Cohort	478 (wheeze), 664 (eczema)/2404	Geohelminth infections	Stool samples to measure geohelminth infections	Eczema	3 y	Questionnaires and examinations	Ethnicity, maternal education, area of residence, sex, SES, birth order, maternal allergy, house overcrowding, pets, child's pneumonia, child's geohelminth
Pesce et al ^[2]	Italy	Cross-sectional	842/3907	Febrile infections, gynecological infections	Questionnaire	Eczema	3–14 y	Questionnaire	Sex, age, familiar history of allergy, maternal age at delivery, presence of mold or damp in the bedroom during the first year of life, maternal stress, maternal use of drugs, breastfeeding, child's use of antibiotics
Collier et al ^[1,3]	USA	Cohort	214/1428	Any infection during pregnancy	Medical record	Asthma	6 y	Questionnaire (doctor-diagnosed asthma)	Income, gestational diabetes, birth weight, cockroaches in the home, maternal smoking during pregnancy
Algert et al ^[1,4] Getahun ^[1]	Australia USA	Cohort Cohort	7245/240,511 56,474/397,852	Urinary tract infection Chorioamnionitis	Medical record ICD-9-CM	Asthma physician-diagnosed asthma	2–5 y 8 y	ICD-10 ICD-9-CM	Maternal age, ethnicity, education, smoking during pregnancy, prenatal care, maternal asthma, antibiotic use during pregnancy, and child's sex
Keski-Nisula et al ^[1,5]	Finland	Cohort	55/460	Positive microbial culture of amniotic fluid	Positive microbial culture of amniotic fluid	Asthma	15–17 y	Questionnaire (doctor-diagnosed asthma)	Sex, current BMI, maternal age and parity at delivery, maternal smoking during pregnancy, paternal occupation, gestational age, birth weight, season of birth, maternal allergy, maternal and neonatal antibiotic administration, and electricity of the operation
Kumar ^[1,6]	USA	Cohort	168 (asthma), 341 (eczema)/1077	Chorioamnionitis	Medical record	Asthma eczema	2.2±2 y	Medical record	Child's age, sex, breastfeeding, postnatal passive smoking, maternal ethnicity, maternal atopic diseases, maternal smoking during pregnancy, antibiotics, maternal education

Refs.	Location	Study design	Case/sample size	Maternal infection during pregnancy	Infection case ascertainment	Child allergic disorder	Child's age	ASD case ascertainment	Adjustment or matched variants
Calvani ^[17]	Italy	Case-control	338/805	Fever episode and flu	Questionnaire	Asthma	~7	Questionnaire (physician-diagnosed)	Age, sex, maternal asthma, maternal smoking during pregnancy, skin prick test positivity, and atopic dermatitis
Hughes et al ^[18]	UK	Case-control	200/400	Respiratory tract infections	Medical record	Asthma	5-16 y	Medical record	Sex, maternal allergy, maternal smoking, Townsend score
Xu et al ^[19]	Finland	Cohort	263/8088	Vaginitis and febrile infection	Questionnaire	Asthma	7 y	Questionnaire	Maternal age, maternal BMI, maternal allergy, social classes, season of birth, birth order, birth weight, GA

SES = socioeconomic status; ICD = International Classification of Diseases; USA = United States of America, UK = United Kingdom.

eligible studies was moderate to high (sTable 3, <http://links.lww.com/MD/B228>). The cross-sectional^[2] and case-control studies^[17,18] were considered high quality, while the cohort studies^[1,12-16,19] were considered moderate or high quality.

3.4. Maternal infection and the risk of asthma and eczema in offspring

Pooled results identified a positive association between maternal infection and the risk of asthma in offspring (pooled OR: 1.55; 95% CI: 1.24-1.92) (Fig. 1). However, significantly high heterogeneity across studies was noted in the overall analyses ($I^2=88\%$; $P<0.01$). A funnel plot (Fig. 2) was visually asymmetrical, but the Egger test and Begg test (all $P>0.05$) confirmed that there was no publication bias in this meta-analysis.

In the sensitivity analyses, exclusion of 2 case-control studies^[17,18] yielded decreased results (OR: 1.47; 95% CI: 1.16-1.87; $P<0.01$), with evidence of significant heterogeneity ($I^2=90\%$; $P<0.01$). Exclusion of 2 correlated estimates from Getahun et al^[1] showed similar results (OR: 1.57; 95% CI: 1.38-1.79; $P<0.01$), but heterogeneity decreased to a nonsignificant level ($I^2=9\%$; $P=0.36$). Additional exclusion of any single study did not significantly alter the overall pooled OR.

We further analyzed the association between several specific kinds of maternal infection and asthma. Strong associations of asthma were found with fever episode (OR: 1.73; 95% CI: 1.35-2.23), chorioamnionitis (OR: 1.42; 95% CI: 0.96-2.11), respiratory infection (OR: 1.49; 95% CI: 0.94-2.36), and urogenital infection (OR: 1.39; 95% CI: 1.18-1.64) (Fig. 3). There were a small number of included studies provided the data of eczema, so that we could not analyze the specific kinds of maternal infection and eczema.

There was a statistically significant association of maternal infection with eczema (OR: 1.36; 95% CI: 1.13-1.64; $P<0.01$) (Fig. 4). No significant heterogeneity was detected in the combined analysis ($I^2=0\%$; $P=0.87$). The funnel plot indicated no publication bias and the Egger test was not significant ($P=0.482$). In sensitivity analyses, exclusion of any single study did not significantly alter the overall combined OR.

3.5. Timing of antenatal maternal infection and risk of asthma and eczema

Most studies lacked data on the “sensitive period,” that is, the time period during pregnancy where maternal infection may be

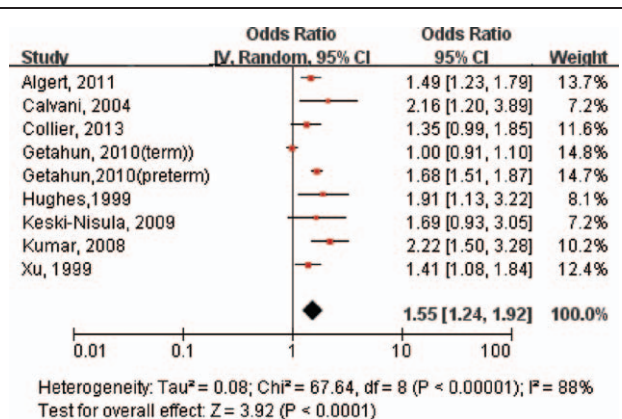


Figure 1. Forest plot shows association between maternal infection during pregnancy and risk of asthma. CI = confidence interval, OR = odds ratio.

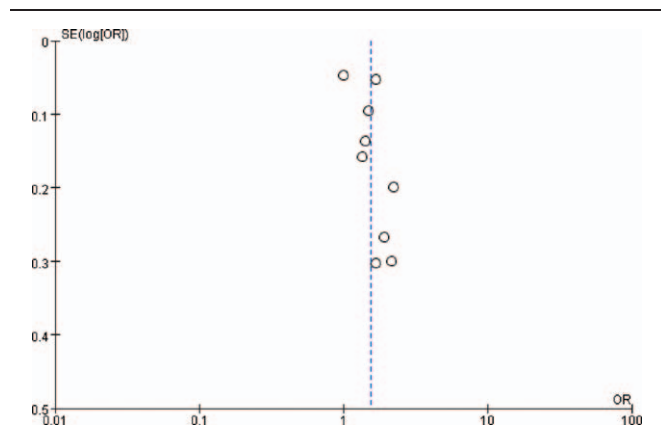


Figure 2. Funnel plot of overall asthma risk in offspring with maternal infection during pregnancy exposure. SE=standard error.

most harmful to the fetus. However, Hughes et al^[18] found a stronger association of childhood asthma with respiratory infection during the first trimester compared with the second and third trimesters. A recent study conducted by Algert et al^[14] observed that gestational age at time of first antenatal urinary tract infection had no effect on the risk of childhood asthma. Pesce et al^[2] reported that the risk of eczema was significantly

higher in children born to mothers who reported febrile infections during the first trimester or gynecological infections during the third trimester of pregnancy.

4. Discussion

In the present study, we performed a meta-analysis and systematic review of publications that evaluated the strength of association between maternal infection and asthma or eczema in their offspring. We showed that maternal infection was associated with an increased risk of asthma and eczema in offspring compared with control groups. The magnitude of pooled risk remained almost unchanged in the sensitive analysis. We observed that the substantial heterogeneity changed to be a rather lower level after excluding the study with 2 effect estimates, indicating that the overall heterogeneity could likely be explained by the nonindependent estimates in study. Heterogeneity was also reduced in the further separate analysis according to type of maternal infection. However, the conclusion of the adverse effect of maternal infection on asthma and eczema should be treated with caution for that maternal chorioamnionitis and respiratory infection during pregnancy showed a trend toward increased ORs but did not reach significant difference statistically.

Maternal infections during pregnancy not only have an adverse impact on the mothers, but also are likely to be an independent

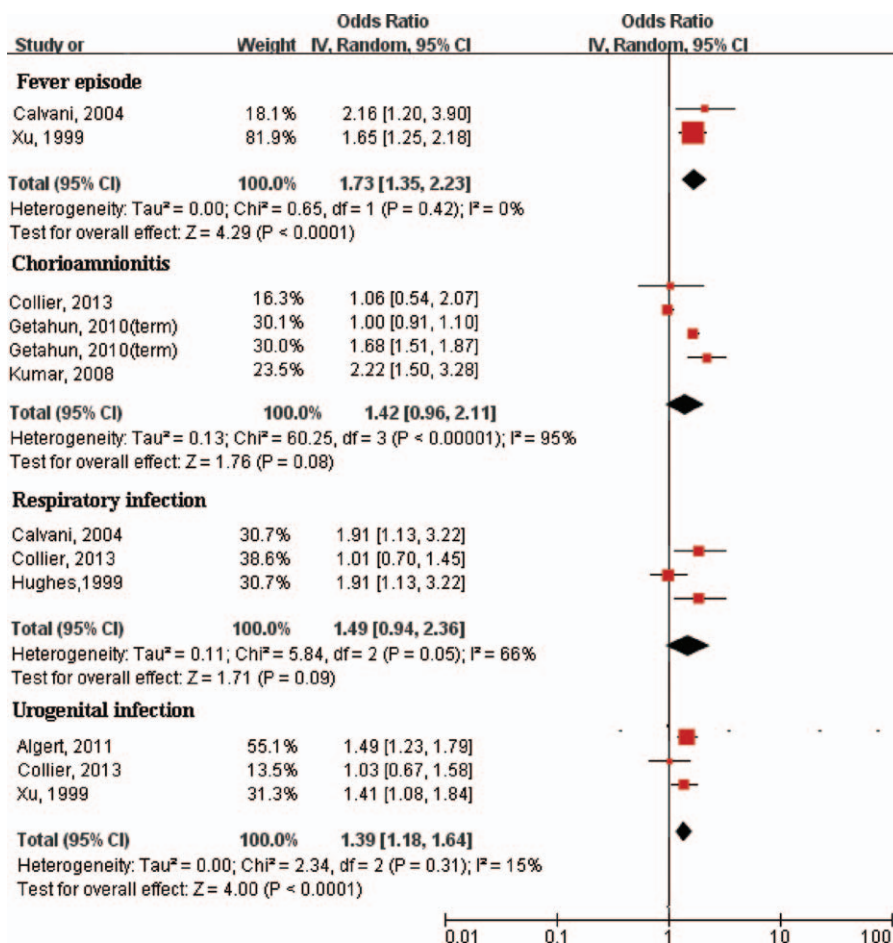


Figure 3. Forest plot of different kinds of maternal infection during pregnancy and risk of asthma. Fever episode and urogenital infection during pregnancy was significantly associated with asthma. CI=confidence interval, OR=odds ratio.

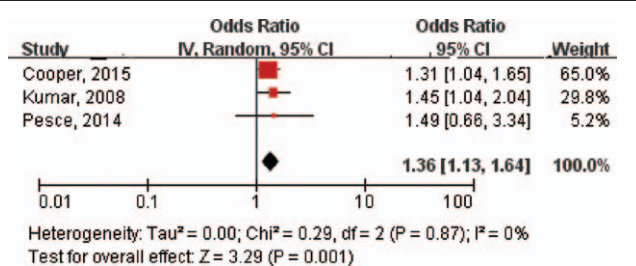


Figure 4. Forest plot shows association between maternal infection during pregnancy and risk of eczema. CI=confidence interval, OR=odds ratio.

risk factor for allergic disorders in their children. Fetal programming is a biological mechanism that may explain why maternal infection during pregnancy is associated with children's allergic disorders, and prenatal or postnatal factors may have dramatic consequences in the early programming of the developing immune system.^[20] Maternal infection is associated with a strong proinflammatory response that increases inflammatory cytokines. Studies based on animal models and human samples clearly showed that chorioamnionitis increased the expression of interleukin (IL)-6, tumor necrosis factor (TNF)- α , interferon (IFN)- β , monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-1 β , and IL-8 in uterus.^[21–23] Tracheal aspirate samples collected from ventilated preterm infants showed higher concentrations of IL-1 α , IL-1 β , and IL-8 in a group of infants with chorioamnionitis.^[24]

Among these inflammatory cytokines, serum TNF- α has been found to have a significant negative correlation with forced expiratory volume in 1 second (FEV1) in asthmatic children.^[25] IL-8 levels were increased in children who developed wheezing illnesses in response to rhinovirus^[26]; in another cohort, individuals who wheezed with rhinovirus were at additional risk of persistent wheezing at follow up at age 3 years.^[27] Fetal exposure to inflammatory cytokines, including IL-6, IL-8, and TNF- α , is increased with chorioamnionitis and has been linked to chronic lung disease.^[28] Since fetal lung and skin are in constant contact with amniotic fluid, exogenous toxins or mediators of inflammation released through or from the placenta may lead to fetal exposure. It is also possible that early neonatal infection caused by bacterial colonization during delivery could be more common in children who have a genetic predisposition to allergy and asthma through a defective innate immune response in the early phase of life.

Although atopy plays an important role in the pathogenesis of asthma, fewer than half of childhood asthma cases are attributable to atopy.^[29] Other potential risk factors associated with childhood asthma include preterm birth, low birth weight, and maternal antibiotic use during pregnancy.^[30–32] Previous studies found an increased risk of preterm birth and low birth weight due to maternal infection during pregnancy.^[7–9] A comprehensive meta-analysis by Zhao et al^[32] showed that antenatal antibiotics were significantly associated with asthma or wheezing in childhood. In the present study, only 3 included studies (1 for eczema and 2 for asthma) reported that maternal infection was significantly associated with asthma and eczema after adjustment for maternal antibiotic usage,^[1,2,15] suggesting that maternal infection might be an independent risk factor for asthma in children. However, we cannot completely rule out some residual confounding, as data were not available on specific types of antibiotics used or frequency of administration.

There were several strengths in this meta-analysis including the use of sensitivity analyses to further assess significant results and a large sample size. However, some potential limitations should be discussed. First, we only included studies published in English. A systemic bias might exist in this study due to the exclusion of languages other than English. Second, the results are lack of power, since the relatively small number of studies in the combined analysis. Third, eligible studies contained a variety of types of maternal infection during pregnancy, and analysis stratified by types of maternal infection showed insignificant results for chorioamnionitis and respiratory infection. Finally, although major confounding factors were adjusted in the included studies, we were unable to remove potential confounding factors, such as antibiotic exposure, birth weight, and breastfeeding.

On the basis of our findings, several questions arise. First, is there a strong link between maternal infection and allergic disorders in their offspring? Future studies need to consider many issues, including adequate control for confounding factors, use of a validated outcome measurement, and assessment of different types of allergic disorders. Second, is the association of maternal infection with asthma and eczema influenced by different pathogens or in different organ systems? Collier et al demonstrated that urinary tract infections are associated with a 60% increase in the odds of childhood asthma. Other types of antepartum infection, including gynecologic infections and respiratory infections, were not associated with an increased risk of childhood asthma.^[12] There is no clear explanation for how prenatal urinary tract infections are more likely to lead to persistent asthma in children over other infections. Third, whether or not there is a “sensitive period” for vulnerability is an issue that must be resolved to understand the underlying biological mechanisms of allergic disorders in children and to consider novel therapeutic interventions; this was challenging to interpret due to significant variation among studies in design, exposure, and outcome measurements.

In conclusion, this meta-analysis and systematic review provides evidence that maternal infection during pregnancy may increase the risk of asthma and eczema in offspring. Given the limitations existing in current article, more studies are needed to further this confirmed this association and explore the underlying questions.

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