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Review article

Trimester-specific association between antibiotics exposure during pregnancy and childhood asthma or wheeze: the role of confounding

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ABSTRACT

Purpose: We conducted the meta-analysis to respectively evaluate the risk of prenatal antibiotics use during specific trimesters (first, second, and third trimester) on childhood asthma or wheeze and to explore whether the association was biased by potential confounding.
Methods: The quality of included articles was assessed according to Newcastle–Ottawa Quality Assessment Scale and the Strengthening the Reporting of Observational Studies in Epidemiology. A random effects model was used to calculate pooled risk ratios and corresponding 95% confidence interval (CI), and publication bias was tested by Egger statistical test.
Results: Eight studies were included finally. We found a crude positive association of prenatal antibiotics use during each pregnancy trimester and risk of childhood asthma or wheeze with RRs of 1.28 (95% CI, 1.09–1.51) for the first trimester of pregnancy, 1.25 (95% CI, 1.02–1.52) for the second trimester, and 1.25 (95% CI, 1.05–1.49) for the third trimester. However, when considering potential factors of maternal infections and presence of siblings, the relationship for each trimester was insignificant.
Conclusions: This systemic review and meta-analysis proposed a crude positive association between prenatal antibiotic use in every specific trimester and risk of childhood asthma or wheeze. However, adjustment for confounders decreased the relative risk estimates, supporting the concept that these associations are, at least in part, because of confounding by indication.

Introduction

Asthma, a syndrome of reversible respiratory obstruction that predominantly occurs among the children [1], poses a great disease burden in many countries in recent years [2]. In 2016, it was reported that asthma accounted for 2.87% in the global total Disability-Adjusted Life Year among children aged 5–14 years. A body of evidence from animal and epidemiologic studies suggest that embryonic and fetal development is a critical stage for subsequent development of the immune and neuroendocrine systems, and prenatal exposures to antibiotics potentially increase the risk of developing asthma and wheezing in children [3], which motivates many researchers to investigate the role of maternal antibiotics exposure during pregnancy in later occurrence of childhood asthma and wheeze [4–15].

Increasing epidemiologic studies suggest a significant association between prenatal exposure to antibiotics and increased risk of asthma or wheeze in offspring. A previous meta-analysis also pointed out that antibiotic exposure during pregnancy could increase the risk of wheeze or asthma in childhood, which mainly focused on the maternal antibiotics use throughout the pregnancy [16]. But the subgroup analysis on specific trimester was only based on two original studies, which may result in an unstable effect size largely influenced by only one study. So, in the following years, growing number of studies have been focused on trimester-specific risk; nevertheless, findings from different studies were inconsistent [6–12,15]. For instance, a study observed no statistical association between infant wheezing and prenatal antibiotics exposure during the second and third trimesters [8]. Another study showed that

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antibiotics exposure during the two trimesters were both significantly associated with the risk of asthma in children [11]. Therefore, there needed a meta-analysis and systematic review to evaluate the pooled trimester-specific effect of maternal antibiotics use. Induction of asthma by prenatal antibiotics is biologically plausible, which is considerably through the modification of the bacterial ecology of the mother and fetus.

An alternative explanation for the association is that it is because of confounding by indication. That is, this association is confounded by a third factor that is an indication for antibiotic prescription during pregnancy while at the same time being a risk factor for childhood asthma or wheeze. Family confounding may play an important role in the association, such as maternal age, maternal asthma history, and so on. Remarkably, infection during pregnancy leads to increased chance of antibiotics use, and it is reported that antenatal infections are associated with childhood asthma [11,17]. Besides, presence of siblings has been linked with asthma or wheeze [18,19]. But there is a dispute over the statements. Randomized controlled trials for this uncertain relationship may never be conducted, given the ethical concern. Therefore, the purposes of this meta-analysis were to (1) to specially evaluate the association between prenatal antibiotics exposure during specific trimester and the risk of asthma or wheeze in offspring and (2) clarify whether the association is independent of potential confounding.

Methods

Search strategy and study selection

PubMed, Web of Science, and Cochrane Central Register of Controlled Trials were searched for records up to March 7, 2018. Search strategy was shown in Table S1. No publication language restriction was applied. Eligible studies included case–control studies or cohort studies that assessed the relationship between prenatal antibiotics use during pregnancy and the risk of childhood asthma or wheeze.

Studies were included if they met the following criteria: (1) studies were published before March 7, 2018; (2) offspring's asthma or wheeze were diagnosed by physicians or met international guidelines or were reported as outcomes by parents; (3) cohort or case–control study design was used; (4) the targeted population included children aged 0–14 years; (5) studies reported risk estimates (odds ratio [OR], risk ratios [RR], hazard ratios [HR]) or allowed us to calculate one of these risk estimates; and (6) investigated the specific effect of maternal antibiotics exposure during at least one trimester of pregnancy.

Data extraction and study quality assessment

Two investigators (B.L. and C.Q.) independently evaluated the quality of each primary study based on the criteria derived from the Newcastle–Ottawa Scale (NOS) and the Strengthening the Reporting of Observational Studies in Epidemiology for quality assessment [20,21]. Any controversy was adjudicated by a third reviewer (Z.Y.). The NOS score consists of three groups: selection (including four items), comparability (including three items), and exposure or outcome (including one item). We considered studies being of high quality if they were scored above the median value ($\geq$5 points) [22].

Data were independently extracted by two reviewers (B. L. and C. Q.) using a standardized agreed data collection form, which consisted of first author's name, publication year, study area, study design, measurements of exposure and outcome, sample size, effect size and corresponding 95% confidence interval (CI) for each trimester, and adjusted or matched varieties such as maternal infections, maternal age, and so on. Any discrepancy was resolved by discussion with a third researcher (Z.Y.).

Statistical analysis

Meta-analysis was conducted to generate the overall RR and 95% CI for the association between prenatal antibiotics use and asthma or wheeze in offspring using STATA Version 12.0 (Stata, version 12; StataCorp, College Station, TX). HRs were directly considered as RRs, and RRs were transformed into ORs with this formula [23]: $RR = OR/[(1 - P_0) + (P_0 \times OR)]$, where P_0 is the incidence of the outcome of interest in the nonexposed group. The standard error of the resulting converted OR was subsequently determined using the formula: $SElog(RR) = SElog(OR) \times log(RR)/log(OR)$. We assessed heterogeneity by Cochrane Q test ($P < .05$ indicates statistically significant) and Higgins I^2 statistics (An I^2 value of 0%–25%, 26%–50%, 51%–75%, or >75% represents very low, low, moderate, or high heterogeneity, respectively). Because of the detected heterogeneity, a random effects model was conducted for all analyses in this study. Publication bias was evaluated by Egger statistical test ($P < .05$ was considered significant). Considering the different adjusted models among the included studies, which might play an important role in the association, we obtained pooled effect estimates of maternal antibiotics during each trimester by following steps: first, we respectively extracted crude effect estimates without controlling for confounding; second, we respectively extracted effect values that at least adjusted for some common confounders (maternal age, mode of delivery, etc.). Third, we extracted effect estimates that additionally adjusted for maternal infections during pregnancy and effect size that additionally adjusted for siblings besides common confounders described previously; fourth, a comparison was performed among risk estimates above to identify whether the association was independent of possible confounding. We also performed sensitivity analysis by successively removing one single study from all the included studies each time to evaluate the reliability and stability of the results. Stratified analysis was conducted based on assessment method of antibiotics exposure and outcome diagnosis (clinician diagnosis vs. parental report) and age of children (<4 vs. $\geq$4 years). According to the method introduced by Payton et al [24], we examined significant differences between effect estimates from stratified analyses of potential effect modifier.

Results

Literature search

We identified 3272 articles initially. Four hundred eighty-two records were excluded for duplicates, and 2757 records were excluded after screening the titles and abstracts. Full texts of 22 studies were assessed for their eligibility. Fourteen studies did not provide effect size for any specific trimester. Eight original studies met the inclusion criteria for the final meta-analysis (Fig. 1).

Characteristics of included studies

The characteristics of each included study were summarized in Table 1. The age of study population ranged from 0 to 14 years. Childhood asthma or wheeze was defined as at least one episode of wheezing or asthma in the first 14 years of life including infant wheezing. The first trimester was within 3 months after the last menstrual period (LMP), the second trimester was from the fourth month to the 27th week after LMP, and the third trimester was from 28th week after LMP to delivery. Maternal infection during pregnancy was defined as one or more infections during pregnancy.

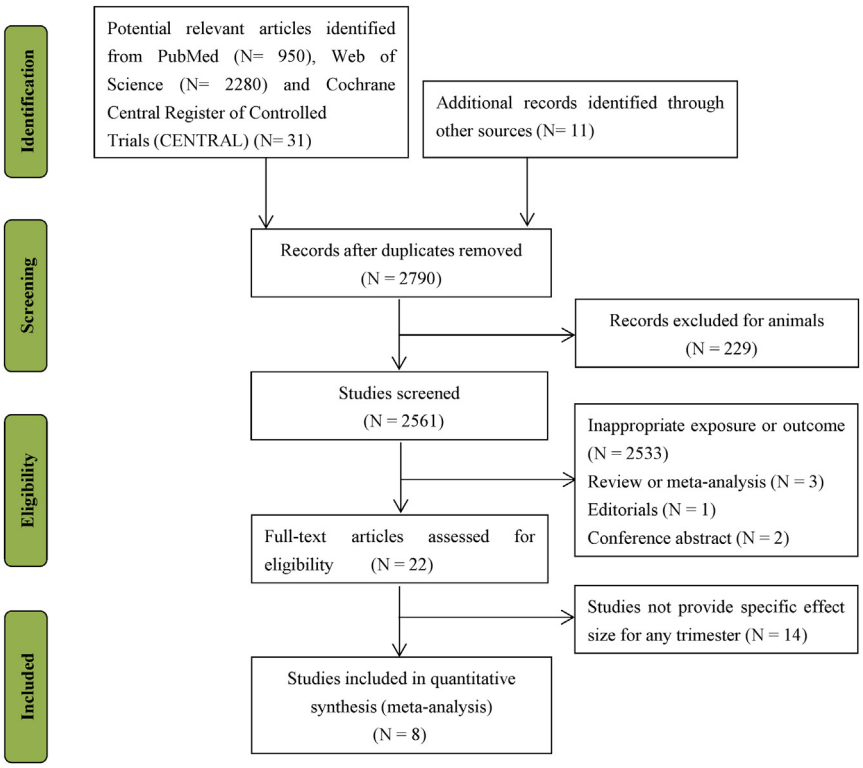

Fig. 1. Flow diagram of selecting studies.

Sibling was defined as the presence of siblings during childhood. Among included studies in this meta-analysis, seven were cohort studies, and one was case–control study. Four studies [6,8,11,15] used questionnaires or self-report to obtain information about antibiotics exposure, and the remaining [7,9,10,12] used database records. Questionnaires were used to obtain information of childhood asthma or wheeze in three studies [6,8,15], and medical records or diagnoses by physician [6,9–12] were used in the remaining to define asthma or wheeze. The childhood age at the end of follow-up in five studies was 4 years or more [7,9–12], and in other three studies was less than 4 years [6,8,15]. All included studies offered effect estimates adjusting for some common confounding factors such as maternal age, smoking during pregnancy, asthma history, and so on. Three studies reported risk estimates additionally adjusted for infection during pregnancy [7,8,15], and four studies supplied effect size additionally adjusted for sibling [7,9,12,15]. The scores of included studies according to NOS and Strengthening the Reporting of Observational Studies in Epidemiology were given in Tables S2 and S3.

Overall effects

As shown in Figure S1, in the five studies providing crude effect size without adjustment, there was an increased risk of asthma or wheeze in children. In the eight studies offered effect estimate controlling for common confounding factors, a weaker but significant association was found. However, there was high between-study heterogeneity of these effects. We deleted one study every time to explore potential sources of high heterogeneity and discovered that the heterogeneity becomes very low or moderate (Fig. S1A vs. Fig. 2A; Fig. S1B vs. Fig. 2B) after deleting the study of Chu et al. [11]. Figure 2 displayed pooled results across different studies with their distinct adjusted models. Figure 2A showed a significant association for pooling effect estimates without adjustment (pooled OR: 1.35, 95% CI: 1.30–1.40 for the first trimester; 1.41, 95% CI: 1.33–1.50 for the second trimester; 1.35, 95% CI: 1.24–1.48 for the third trimester). Figure 2B presented a less strong association between antibiotics exposure during pregnancy and childhood asthma or wheeze based on results from studies controlling for some common confounders (pooled RR: 1.21, 95% CI: 1.14–1.28 for the first trimester; 1.27, 95% CI: 1.23–1.31 for the second trimester; 1.24, 95% CI: 1.19–1.29 for the third trimester). No publication bias was observed (Egger's test, $P > .05$ for any trimester). Figure 2C depicted the pooled RRs from studies additionally adjusted for maternal infections during pregnancy, showing an insignificant positive association for each trimester (first trimester: 1.07, 95% CI: 0.92–1.24, $P = .386$; second trimester: 1.14, 95% CI: 1.00–1.30, $P = .051$; third trimester: 1.17, 95% CI: 1.00–1.37, $P = .050$). Figure 2D presented the results by pooling RRs additionally controlled for sibling, revealing a weaker and insignificant relationship (first trimester: 1.07, 95% CI: 0.88–1.29; second trimester: 1.03, 95% CI: 0.89–1.18; third trimester: 1.09, 95% CI: 0.92–1.29). Table 2 summarily described the pooled ORs across different adjusted models, suggesting that the association become weakened and even insignificant with more confounding factors being controlled in studies.

Subgroup meta-analysis

In consideration of the significantly high heterogeneity, we first stratified the included studies by assessment methods of antibiotics exposure. As presented in Table 3, when antibiotics exposure was assessed by questionnaires or self-report, prenatal antibiotics use during the third trimester was statistically associated with childhood asthma or wheeze with the pooled RR of 1.19 (95% CI: 1.01–1.40), but no significant association was observed during both the first trimester (1.09, 95% CI: 0.94–1.26) and the second trimester (1.13, 95% CI: 0.99–1.29). According to the results of

Table 1
Characteristics of included studies in this meta-analysis

Study	Design	Cases/total (person-year)	Age (y)	Measurements of exposure and outcome	Effect estimates (95% CI)			
					Unadjusted	Adjusted 1*	Adjusted 2†	Adjusted 3‡
Popovic et al. [15] (Italy)	Cohort study	1627/7515	0–1.5	Exposure: assessed by questionnaires Asthma: at least one episode of wheezing in the first 6 mo or between 6 and 18 mo of life	First trimester: 1.25 (1.00–1.57) Third trimester: 1.34 (1.11–1.64)	—	First trimester: 1.14 (0.91–1.43) Third trimester: 1.25 (1.02–1.52)	First trimester: 1.02 (0.80–1.30) Third trimester: 1.12 (0.90–1.39)
Chu et al. [11] (USA)	Cohort study	2201/39,907	0–7	Exposure: take antibiotics by oral or injection at any month during pregnancy by asking regarding medication. Asthma: medical records by pediatricians.	First trimester: 1.08 (1.04–1.12) Second trimester: 1.03 (1.00–1.06) Third trimester: 1.02 (0.98–1.05)	First trimester: 1.08 (1.04–1.11) Second trimester: 1.02 (0.99–1.06) Third trimester: 1.01 (0.97–1.04)	—	—
Örtqvist et al. [9] (Sweden)	Cohort study	29,753/493,785	0–5.5	Exposure: prescriptions of systemic antibiotics (Anatomical Therapeutic Chemical [ATC] classifications system code J01A-J01X) Swedish from Prescribed Drug Register Asthma: registered in the National Patient Register and fulfilled one or both of two criteria for asthma drugs (ATC: R03) from the Swedish Prescribed Drug Register	First trimester: 1.35 (1.30–1.40) Second trimester: 1.39 (1.34–1.44) Third trimester: 1.33 (1.28–1.39)	First trimester: 1.29 (1.23–1.34) Second trimester: 1.30 (1.25–1.35) Third trimester: 1.26 (1.21–1.31)	First trimester: 1.09 (0.97–1.23) Second trimester: 0.97 (0.87–1.08) Third trimester: 0.95 (0.84–1.06)	—
Bisgaard et al. [10] (Denmark)	Cohort study	21,352/846,689	0–14	Exposure: prescription of antibiotics and inhaled corticosteroids from the National Prescription Registry Asthma: at least two inpatient hospital admissions separated by at least 1 mo or the child was followed in outpatient care for at least 1 y	—	First trimester: 1.19 (1.14–1.23) Second trimester: 1.26 (1.22–1.30) Third trimester: 1.20 (1.15–1.25)	—	—
Stensballe et al. [7] (Denmark)	Cohort study	162/18,606	0–5	Exposure: at least one prescription of antibiotics during pregnancy Asthma: recorded in the Danish National Patient Registry	First trimester: 1.55 (1.22–1.95) Second trimester: 1.11 (0.85–1.46) Third trimester: 1.11 (0.87–1.43)	—	First trimester: 1.33 (1.05–1.69) Second trimester: 0.95 (0.72–1.24) Third trimester: 0.99 (0.77–1.28)	First trimester: 1.20 (0.50–2.89) Second trimester: 1.36 (0.70–2.63) Third trimester: 0.82 (0.39–1.74)
Jedrychowski et al. [8] (Poland)	Cohort study	31/102	0–1	Exposure: prenatal interviewing of pregnant women Wheeze: trained interviewers conducted a standardized interview with mothers	—	—	—	First trimester: 1.09 (0.90–1.31) Second trimester: 1.13 (0.99–1.29) Third trimester: 1.28 (1.01–1.63) Second to third trimester: 1.18 (1.04–2.94)
Lapin B et al. [6] (Chicago)	Cohort study	44/298	3	Exposure: by questionnaire of pregnant women Asthma: ever having an asthma diagnosis by a physician by 3 y of age based on the self-reported answer	—	First trimester: 2.23 (0.90–5.49) Second to third trimester: 3.33 (1.52–7.27)	—	—

Table 1 (*continued*)

Study	Design	Cases/total (person-year)	Age (y)	Measurements of exposure and outcome	Effect estimates (95% CI)			
					Unadjusted	Adjusted 1*	Adjusted 2†	Adjusted 3‡
Lapin B et al. [6] (Chicago)	Cohort study	65/298	3	Exposure: by questionnaire Wheeze: a positive response within the year before their third-year visit based on the designed questions	—	First trimester: 1.32 (0.58–3.02) Second to third trimester: 1.77 (0.92–3.59)	—	—
Mulder B et al. [12] (Netherlands)	Case-sibling and case–control	1228/2456 and 3754/26,278	0–5	Exposure: at least a 1 d supply of systemic antibiotics (ATC group J01) during pregnancy Asthma: received at least three prescriptions for asthma medication (ATC group R03)	First trimester: 1.49 (0.31–1.68) Second trimester: 1.57 (1.40–1.77) Third trimester: 1.61 (1.44–1.79)	First trimester: 1.23 (1.08–1.41) Second trimester: 1.30 (1.15–1.47) Third trimester: 1.40 (1.25–1.57)	First trimester: 0.70 (0.50–0.98) Second trimester: 1.25 (0.92–1.69) Third trimester: 1.37 (1.02–1.83)	—

CI = confidence interval.

* Adjusted for maternal age at delivery, marital status at pregnancy, race, educational level, parity, smoking during pregnancy, maternal asthma history, and maternal history of drug allergy.

† Additionally adjusted for siblings.

‡ Additionally adjusted for maternal infection during pregnancy.

statistical differences test, significantly higher RRs were found for any trimester when antibiotics exposure was measured by database records (first trimester: 1.23, 95% CI: 1.16–1.30; second trimester: 1.27, 95% CI: 1.24–1.31; third trimester: 1.25, 95% CI: 1.18–1.31; Fig. S2A–C). Second, the analysis was stratified by methods of outcome diagnosis; similarly, stronger association was discovered when asthma or wheeze was measured by database records than by questionnaires (Fig. S2D–F). Third, analysis was also stratified by the age of children (<4 vs. ≥4 years). Significantly higher pooled RR was appeared in children aged older than 4 years than that in children less than 4 years for each pregnancy trimester (Fig. S2G–I). In addition, we respectively analyzed the data by separating the studies according to outcome classification (either wheeze or asthma). When only analyzing studies focused on asthma, similar effect estimate was observed (Fig. S3 vs. Fig. 2). Because only two [6,8] of included studies explored association of prenatal antibiotics use and childhood wheeze, and only one study [8] provided effect size during the second and third trimesters, meta-analysis specified on childhood wheeze could not be performed. Finally, according to study design, we conducted meta-analysis separately for cohort study and case–control study. Because only one study was case–control study, we extracted all cohort studies to conduct the meta-analysis. As shown in Figure S4, little change was observed compared with results in previous step (Fig. 2).

To confirm the finding in the present meta-analysis, we also performed the same analysis across all studies that provided effect estimates for the whole pregnancy, not only confined to trimester-specific association. As presented in Figure S5, the attenuation of the association was likewise observed.

Discussion

Summary of main results

If pregnant mother's exposure to antibiotics can elevate the risk of childhood asthma or wheeze, identifying the critical time-window will be important for both early detection and intervention of such disease in practice. To our knowledge, it was the first meta-analysis to specially evaluate pooled effects of prenatal antibiotics use in each trimester and to explore potential confounding factors in the observed association. Our results revealed positive crude association between maternal use of antibiotics during each trimester and increased risk of asthma or wheeze in children. However, when only pooled effect size across studies adjusted for identified confounders, as well as those additionally adjusted for sibling or maternal infection, we found a weaker and even insignificant effect (Table 2). The present results from random effects models support the hypothesis that the reported association between maternal antibiotics use during pregnancy and childhood asthma or wheeze can be mainly, if not completely explained by confounding, such as maternal infection and sibling. But we were unable to affirmatively conclude the confounding

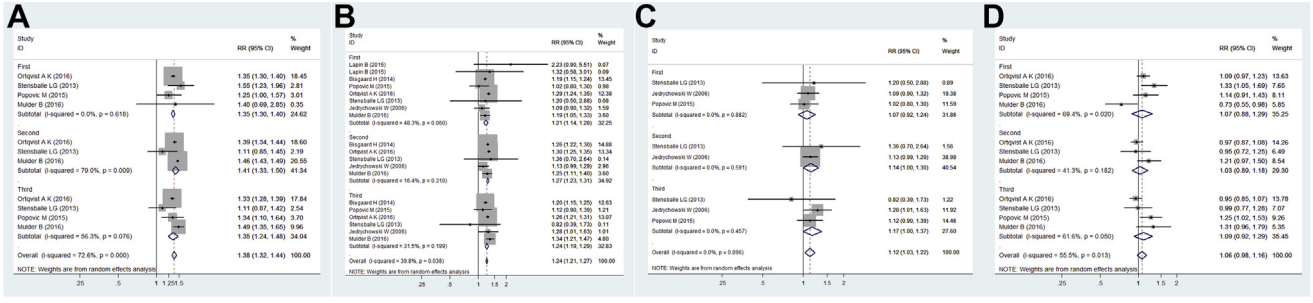

Fig. 2. (After deleting one study [11]) Meta-analysis with the random effects model for the association between maternal antibiotics exposure during different trimesters and the risk of childhood asthma or wheeze. Squares represent study-specific estimates without adjustment (A), adjusting for common confounding factors (B); additionally adjusting for maternal infection during pregnancy, besides some common confounding (C); additionally adjusting for presence of siblings, besides some common confounding (D), and horizontal lines indicate 95% CIs. Pooled estimates with 95% CIs are represented by filled black diamonds. CI = confidence interval.

Table 2
Pooled ORs and corresponding 95% CI of studies adjusted for different confounders

Trimester	Unadjusted [7,9,12,15]	Adjusted 1*[6–12,15]	Adjusted 2†[7,8,15]	Adjusted 3‡[7,9,12,15]
First trimester	1.35 (1.30–1.40)§	1.21 (1.14–1.28)§	1.07 (0.92–1.24)	1.07 (0.88–1.29)
Second trimester	1.41 (1.33–1.50)§	1.27 (1.23–1.31)§	1.14 (1.00–1.30)	1.03 (0.89–1.18)
Third trimester	1.35 (1.24–1.48)§	1.24 (1.19–1.29)§	1.17 (1.00–1.37)	1.10 (0.92–1.29)

CI = confidence interval; OR = odds ratio.
* Adjusted for maternal age at delivery, marital status at pregnancy, race, educational level, parity, smoking during pregnancy, maternal asthma history, and maternal history of drug allergy.
† Additionally adjusted for maternal infection during pregnancy.
‡ Additionally adjusted for sibling.
§ $P < .05$.

effect of siblings in this association owing to lack of available data (only four studies provided RRs adjusted for sibling). Similarly, given the small number of included studies that supplied effect estimates adjusted for infection in pregnancy, a type I error (inadequate sample size) may be appeared although no heterogeneity was observed. However, when we performed the same meta-analysis for the whole pregnancy, similar phenomenon was appeared (Figure S5), which strengthened our conclusion that association between prenatal antibiotics exposure during each trimester and risk of childhood asthma or wheeze at least partly because of confounding.

The presented positive effect of mother's use of antibiotics during pregnancy on risk of asthma in the child may be mediated through the human microbiome. Antibiotics use during pregnancy can affect maternal microbiome to a much greater extent [25]. Disturbance in microbial ecology induced by antibiotics could last for long. Infants acquire their commensal bacteria from other humans, and most importantly, from the mother [26]. That is, a disturbed maternal microflora may be offered as a possible explanation for a disturbed infant intestinal flora [27]. The gut microbiota has a wide range of key functions in the modulation of maturation and maintenance of the immune system [28]. Antibiotics exposure may profoundly affect the symbiotic relationship between gut flora and the immune system, ultimately modifying the nature and intensity of immune response [4], which could lead to increased risk of asthma or wheeze in children.

Previous studies have reported a higher risk of asthma in children whose mother experienced infections in different trimesters [29–32]. Also, Örtqvist et al. and Stokholm et al. suggested that the association between prenatal antibiotics use and childhood asthma or wheeze could be greatly explained by confounding factors, particularly maternal infection in pregnancy [15,33]. Unlike this, a recent study did not observe significant association between infections during pregnancy and childhood asthma but found significant risk effect of antibiotics use during pregnancy [14]. However, the study was a retrospective case–control study and only selected cases with complete data sheets, which might lead to information bias and poor representation. The mechanism through which infection during pregnancy increases the risk of asthma or wheeze in children is still not clear. But maternal infection is associated with a strong proinflammatory response that increases inflammatory cytokines [27]. Exposing fetus to high levels of proinflammatory cytokines after maternal infections may have dramatic effects on the early programming of the developing immune system [34], and fetal exposure to inflammatory cytokines, including tumor necrosis factor α, interleukin 6, and interleukin 8, has been linked to a consequence of lung damage, which may increase the risk of asthma or wheeze in offspring [35,36]. Based on

Table 3
Stratified analyses for childhood asthma or wheeze and maternal antibiotics exposure during different trimesters

Subgroup types	Number of studies (n)	Trimester	Heterogeneity		Pooled OR (95% CI)
			I^2 (%)	P - value	
Exposure assessment*					
Self-report or questionnaires [6,8,11,15]	5	First	0.0	.407	1.09 (0.94–1.26)
		Second	—	—	1.13 (0.99–1.29)
		Third	0.0	.418	1.19 (1.01–1.40)
Database records [7,9,10,12]	4	First	62.7	.045	1.23 (1.16–1.30)
		Second	0.0	.638	1.27 (1.24–1.31)
		Third	53.2	.09	1.25 (1.18–1.31)
Outcome diagnosis†					
Questionnaires [6,8,15]	4	First	0.0	.407	1.09 (0.94–1.26)
		Second	—	—	1.13 (0.99–1.29)
		Third	0.0	.418	1.19 (1.01–1.40)
Database records or by physician [7,9–12]	5	First	60.7	.054	1.24 (1.17–1.31)
		Second	0.0	.653	1.28 (1.25–1.31)
		Third	70.1	.018	1.26 (1.18–1.35)
Age (y)‡					
≥4 [7,9,10,12]	4	First	62.7	.05	1.23 (1.16–1.30)
		Second	0.0	.638	1.27 (1.24–1.31)
		Third	53.2	.093	1.25 (1.18–1.31)
<4 [6,8,15]	4	First	0.0	.407	1.09 (0.94–1.26)
		Second	—	—	1.13 (0.99–1.29)
		Third	53.1	.42	1.19 (1.01–1.40)

CI = confident interval; RR = rate ratio.
* Stratified by method of measuring exposure of antibiotics.
† Stratified by method of measuring childhood asthma or wheeze.
‡ Stratified by age of children.

previous epidemiologic evidence, not only prenatal but also childhood infections might play an important role in persistent wheeze or later development of asthma [37]. Mediation role of pregnancy outcomes or complications, such as sepsis [38], and early infantile factors, such as respiratory viral infections [39], should also be considered. Because of existing limited research, future work needs take these factors into consideration.

Besides infections in pregnancy, this study suggested that the association between mother's antibiotics use and childhood asthma or wheeze was affected by factors shared by siblings. The mechanism of siblings acting on childhood asthma or wheeze is complicated. Sibling is a marker of an unknown exposure, which is often used by different characterizations, such as being firstborn, birth order, number of siblings, number of younger or older siblings, and so on. But epidemiologic studies have shown that the presence of siblings and first-born probably make children at increased risk of asthma or wheeze [18,19]. It is perceived that the presence of older siblings is likely a protective factor of childhood asthma or wheeze; instead, presence of younger siblings may be a risk factor. Based on various immunologic explanations, a lot of hypotheses emerged to explain the associations of asthma with siblings, such as “Hygiene hypothesis” [40]. But the clear mechanism remained in dispute [41,42].

In sensitivity analysis, no substantial change of the pooled RR was observed when we randomly removed one single study from all the included studies and separately focused our analysis on cohort studies or studies whose outcome was childhood asthma, which implied the robustness of our results. But when we drop one study, heterogeneity decreased dramatically. We also explored the reason why the study of Chu et al. [11] could lead to great heterogeneity. First, the study only included “definite asthma” confirmed by pediatricians and excluded suspected asthma, which might omit some cases and lead to an underestimate of risk effect. Second, the study calculated antibiotic-specific risk for each trimester, but the sample size for antibiotics was so different (ranged from 385 to 6208) that the effect would be influenced by a particular type of antibiotics if the type of antibiotics plays a part in the association.

We conducted subgroup analysis stratifying by methods of antibiotics exposure assessment and methods of childhood asthma/wheeze diagnosis. As shown in Table 3, studies assessing exposure by database records presented a higher pooled RR estimate than that of studies using questionnaires or self-report. This might be explained by several possible reasons. Mothers who took a small amount of antibiotics or occasionally use it might make a negative answer in self-report and questionnaire, which could cause an underreporting and further underestimate the effect of antenatal antibiotics exposure. Conversely, the information required from database record was more accurate. In addition, because of different knowledge level of drugs, some mothers may do not know the medicine she took belongs to antibiotics, which would lead to an underestimated exposure rate. Similarly, judging childhood asthma or wheeze by questionnaires from mother may lead to an underestimated rate of childhood asthma or wheeze. Therefore, pooled effect across studies measuring childhood asthma or wheeze by database records also showed a stronger association than those by questionnaires. But the studies for stratifications were so limited that we may not draw such conclusions. Children aged 4 years or older showed a significantly higher RRs than those aged less than 4 years, which may be attributed to follow-up period. The longer duration of follow-up (means older age of children) could found more children with wheeze or asthma. Therefore, it would contribute to the increased risk of childhood wheeze or asthma in children aged 4 years or older. In addition, an accurate diagnosis of asthma in children aged younger 4 years is often difficult, so studies whose outcome was asthma in children aged younger than 4 years may lead to miss diagnosis of asthma and thus underestimated the risk effect.

The present study was focused on trimester-specific association between maternal antibiotics during pregnancy and childhood asthma or wheeze and exploring whether the association was biased by potential confounders, particularly pregnancy infection and sibling. Some common confounding factors were not discussed separately because those factors were often controlled together in included studies. And, a smaller effect was observed when adjusted for these acknowledged factors, compared with that unadjusted (Table 2). These confounding factors can be divided into three parts: prenatal (e.g., maternal asthma history, and smoking), intrapartum (e.g., mode of delivery), and postpartum exposure (e.g., birth weight), which have been discussed previously [14,43]. However, there are moderate differences among common confounding factors adjusted in included studies. For example, only two studies controlled for breastfeeding [6,7], which was considered a protective factor of childhood asthma/wheeze [44]. Breastfeeding not only modulates neonatal bacterial colonization and immune maturation but also is a direct source of maternal bacteria. After birth, skin-to-skin contact and nursing ensure direct transfer of maternal bacteria to the infant to enhance healthy immune and metabolic maturation [26]. Moreover, antibiotics exposure during pregnancy can alter maternal bacterial phyla and reduce bacterial species diversity [45]. The immune factors and bacteria of breast milk may be varied between mothers using antibiotics and those not using. Therefore, breastfeeding should be regarded as a confounder, and it should be controlled in the analysis of the link between antibiotics exposure during pregnancy and childhood asthma or wheeze. Besides, mode of delivery, maternal age at pregnancy, birth weight, and the other factors has also been linked with elevated risk of childhood asthma [46,47]. We did not discuss here anymore.

Strengths and limitations

The systematic review and meta-analysis will shed light on the detailed risk estimation for each trimester. Furthermore, we took potential confounders into consideration including pregnancy infection, presence of siblings, which help to clarify true association between maternal antibiotics use and childhood asthma or wheeze. Because exposure and disease are not acting on the same individual and maternal antibiotics exposure during any trimester precedes asthma or wheeze in offspring, bias induced by reverse causation will not be our concern, which is similar to Zhao et al. [16]. It should be acknowledged that although we have considered some confounding factors in this relation, because of limited studies, we are not able to explore some other confounding such as breastfeeding, birth weight, and so on and not able to stratify by different types of maternal infections. Furthermore, the adjusted models, which might play an important role in the risk estimate of childhood asthma or wheeze, differed among the included studies. Finally, because of inadequate studies at present, the subgroup analysis was only stratified by the method of antibiotics assessment and childhood asthma or wheeze measurement and age of children.

Overall, this systemic review and meta-analysis proposed a crude positive association between prenatal antibiotic use in every specific trimester and risk of childhood asthma or wheeze. However, adjustment for confounders, such as infections during pregnancy and sibling, decreased the relative risk estimates, supporting the concept that these associations are, at least in part, because of confounding by indication.

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Supplementary data

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References

[1] World Health Organization. Chronic respiratory diseases. Asthma Pamplona Consulted. 2016. http://www.who.int/respiratory/asthma/es/. [Accessed 26 November 2017].
[2] Global Initiative For Asthma. Global Strategy for Asthma Management and Prevention. 2016. http://www.ginasthma.org. [Accessed 26 November 2017].
[3] Murk W, Risnes KR, Bracken MB. Prenatal or early-life exposure to antibiotics and risk of childhood asthma: a systematic review. Pediatrics 2011;127:1125–38.
[4] Metsälä J, Lundqvist A, Virta LJ, Kaila M, Gissler M, Virtanen SM. Prenatal and post-natal exposure to antibiotics and risk of asthma in childhood. Clin Exp Allergy 2015;45:137–45.
[5] Wu P, Feldman AS, Rosas-Salazar C, James K, Escobar G, Gebretsadik T, et al. Relative importance and additive effects of maternal and infant risk factors on childhood asthma. PLoS One 2016;11(3):e0151705.
[6] Lapin B, Piorkowski J, Ownby D, Freels S, Chavez N, Hernandez E, et al. Relationship between prenatal antibiotic use and asthma in at-risk children. Ann Allergy Asthma Immunol 2014;114:203–7.
[7] Stensballe LG, Simonsen J, Jensen SM, Bønnelykke K, Bisgaard H. Use of antibiotics during pregnancy increases the risk of asthma in early childhood. J Pediatr 2013;162:832–8.
[8] Jedrychowski W, Gałaś A, Whyatt R, Perera F. The prenatal use of antibiotics and the development of allergic disease in one year old infants. A preliminary study. Int J Occup Med Environ Health 2006;19:70–6.
[9] Örtqvist AK, Lundholm C, Kieler H, Ludvigsson JF, Fall T, Ye W. Antibiotics in fetal and early life and subsequent childhood asthma: nationwide population based study with sibling analysis. BMJ 2014;349:g6979.
[10] Bisgaard H, Stokholm J, Sevelsted A, Bønnelykke K. Maternal antibiotic use and risk of asthma in offspring—Authors' reply. Lancet Respir Med 2014;2(10):e17.
[11] Chu S, Yu H, Chen Y, Chen Q, Wang B, Zhang J. Periconceptional and gestational exposure to antibiotics and childhood asthma. PLoS One 2015;10:e0140443.
[12] Mulder B, Pouwels KB, Schuiling-Veninga CC, Bos HJ, de Vries TW, Jick SS, et al. Antibiotic use during pregnancy and asthma in preschool children: the influence of confounding. Clin Exp Allergy 2016;46(9):1214–26.
[13] Dom S, Droste JH, Sariachvili MA, Hagendorens MM, Oostveen E, Bridts CH, et al. Pre- and post-natal exposure to antibiotics and the development of eczema, recurrent wheezing and atopic sensitization in children up to the age of 4 years. Clin Exp Allergy 2010;40:1378–87.
[14] Kashanian M, Mohtashami SS, Bemanian MH, Moosavi SAJ, Moradi Lakeh M. Evaluation of the associations between childhood asthma and prenatal and perinatal factors. Int J Gynaecol Obstet 2017;137(3):290–4.
[15] Popovic M, Rusconi F, Zugna D, Galassi C, Merletti F, Migliore E, et al. Prenatal exposure to antibiotics and wheezing in infancy: a birth cohort study. Eur Respir J 2015;47:810–7.
[16] Zhao D, Su H, Cheng J, Wang X, Xie M, Li K, et al. Prenatal antibiotic use and risk of childhood wheeze/asthma: A meta-analysis. Pediatr Allergy Immunol 2015;26:756–64.
[17] Mckeever TM, Lewis SA, Smith C, Hubbard R. The importance of prenatal exposures on the development of allergic disease[J]. Am J Respir Crit Care Med 2002;166(6):827–32.
[18] Bercedo-Sanz A, Lastra-Martínez L, Pellegrini-Belinchón J, Vicente-Galindo E, Lorente-Toledano F, García-Marcos L. Wheezing and risk factors in the first year of life in Cantabria, Spain. The EISL study. Allergol Immunopathol (Madr) 2015;43(6):543–52.
[19] Zekveld C, Bibakis I, Bibakiliakou V, Pedioti A, Dimitroulis I, Harris J, et al. The effects of farming and birth order on asthma and allergies. Eur Respir J 2006;28(1):82–8.
[20] Wells GA, Shea BJ, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analysis. Appl Eng Agric 2000;18:727–34.
[21] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies. Lancet 2007;370(9569):1453–7.
[22] Huang J, Zhu T, Qu Y, Mu D. Prenatal, perinatal and neonatal risk factors for intellectual disability: a systemic review and meta-analysis. PLoS One 2016;11:e0153655.
[23] Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA 1998;280:1690–1.
[24] Payton ME, Greenstone MH, Schenker N. Overlapping confidence intervals or standard error intervals: what do they mean in terms of statistical significance? J Insect Sci 2003;3(1):34.
[25] Stokholm J, Schjørring S, Eskildsen CE, Pedersen L, Bischoff AL, Følsgaard N, et al. Antibiotic use during pregnancy alters the commensal vaginal microbiota. Clin Microbiol Infect 2014;20:629–35.
[26] Rautava S, Luoto R, Salminen S, Isolauri E. Microbial contact during pregnancy, intestinal colonization and human disease. Nat Rev Gastroenterol Hepatol 2012;9(10):565–76.
[27] Lundequist B, Nord CE, Winberg J. The composition of the faecal microflora in breastfed and bottle fed infants from birth to eight weeks. Acta Paediatr Scand 1985;74:45–51.
[28] Severance EG, Prandovszky E, Castiglione J, Yolken RH. Gastroenterology issues in schizophrenia: why the gut matters. Curr Psychiatry Rep 2015;17:574.
[29] Algert CS, Bowen JR, Lain SL, Allen HD, Vivian-Taylor JM, Roberts CL. Pregnancy exposures and risk of childhood asthma admission in a population birth cohort. Pediatr Allergy Immunol 2011;22(8):836–42.
[30] Pesce G, Marcon A, Marchetti P, Girardi P, de Marco R. Febrile and gynecological infections during pregnancy are associated with a greater risk of childhood eczema. Pediatr Allergy Immunol 2014;25:159–65.
[31] Xu B, Pekkanen J, Järvelin MR, Olsen P, Hartikainen AL. Maternal infections in pregnancy and the development of asthma among offspring. Int J Epidemiol 1999;28(4):723–7.
[32] Zhu T, Zhang L, Qu Y, Mu D. Meta-analysis of antenatal infection and risk of asthma and eczema. Medicine 2016;95:e4671.
[33] Örtqvist AK, Lundholm C, Fang F, Fall T, Almqvist C. Parental antibiotics and childhood asthma-a population-based study. J Allergy Clin Immunol Pract 2017;5(5):1451–4.
[34] Jones CA, Kilburn SA, Warner JA, Warner JO. Intrauterine environment and fetal allergic sensitization. Clin Exp Allergy 1998;28(6):655–9.
[35] Lemanske Jr RF, Jackson DJ, Gangnon RE, Evans MD, Li Z, Shult PA, et al. Rhinovirus illnesses during infancy predict subsequent childhood wheezing. J Allergy Clin Immunol 2005;116(3):571–7.
[36] Prendergast M, May C, Broughton S, Pollina E, Milner AD, Rafferty GF. Chorioamnionitis, lung function and bronchopulmonary dysplasia in prematurely born infants. Arch Dis Child Fetal Neonatal Ed 2011;96(4):F270–4.
[37] Fuchs O, Von ME. Prenatal and childhood infections: implications for the development and treatment of childhood asthma[J]. Lancet Respir Med 2013;1(9):743–54.
[38] Nafstad P, Samuelsen S, Irgens L, Bjerkedal T. Pregnancy complications and the risk of asthma among Norwegians born between 1967 and 1993. Eur J Epidemiol 2003;18:755–61.
[39] Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. Am J Respir Crit Care Med 2000;161:1501–7.
[40] Strachan DP. Hay fever, hygiene, and household size. BMJ 1989;299:1259–60.
[41] Strachan DP, Aïtkhaled N, Foliaki S, Mallol J, Odhiambo J, Pearce N, et al. Siblings, asthma, rhinoconjunctivitis and eczema: a worldwide perspective from the International Study of Asthma and Allergies in Childhood. Clin Exp Allergy 2015;45(1):126–36.
[42] Karmaus W, Johnson C. Invited commentary: Sibship effects and a call for a comparative disease approach. Am J Epidemiol 2005;162(2):133–8.
[43] Rosas-Salazar C, Hartert TV. Prenatal exposures and the development of childhood wheezing illnesses. Curr Opin Allergy Clin Immunol 2017;17(2):110–5.
[44] Dogaru CM, Nyffenegger D, Pescatore AM, Spycher BD, Kuehni CE. Breastfeeding and childhood asthma: systematic review and meta-analysis. Am J Epidemiol 2014;179(10):1153–67.
[45] Gray LE, O'Hely M, Ranganathan S, Sly PD, Vuillermin P. The maternal diet, gut bacteria, and bacterial metabolites during pregnancy influence offspring asthma. Front Immunol 2017;8:365.
[46] Sonnenschein-van der Voort AM, Arends LR, de Jongste JC, Annesi-Maesano I, Arshad SH, Barros H, et al. Preterm birth, infant weight gain, and childhood asthma risk: a meta-analysis of 147,000 European children. J Allergy Clin Immunol 2014;133(5):1317–29.
[47] Cho CE, Norman M. Cesarean section and development of the immune system in the offspring. Am J Obstet Gynecol 2013;208(4):249–54.