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ORIGINAL ARTICLE

Prenatal paracetamol use and asthma in childhood: A systematic review and meta-analysis

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Abstract
Objectives: Some studies have suggested that prenatal paracetamol exposure might associate with the risk of child asthma. However, other studies have not confirmed this result. Therefore, we conducted a meta-analysis to investigate their relationship.
Methods: Two authors searched Pubmed and Embase databases up to June 2016. The strength of the association was calculated with the OR and respective 95% CIs. The random-effects model was chosen to calculate the pooled OR.
Results: A total of 13 articles of more than 1,043,109 individuals were included in the meta-analysis. A statistically significant association between prenatal paracetamol exposure and child asthma risk was found. The data showed that prenatal paracetamol exposure could increase the risk of child asthma (OR = 1.19; 95% CI, 1.12–1.27; $P < 0.00001$) in a random-effect model. Six studies reported paracetamol exposure during the first trimester of pregnancy. We found that paracetamol exposure during the first trimester of pregnancy was associated with increased risk of child asthma (OR = 1.21; 95% CI, 1.14–1.28; $P < 0.00001$). Furthermore, we observed that paracetamol exposure during the 2–3 trimesters of pregnancy was also associated with child asthma risk (OR = 1.13; 95% CI, 1.04–1.23; $P = 0.005$).
Conclusions: This study suggested that prenatal paracetamol exposure was significantly associated with the increased risk of child asthma.

Introduction

Asthma is a common chronic inflammatory disorder of the airways which is associated with airway hyperresponsiveness, smooth muscle spasm, and airflow obstruction. Over recent years, the global rates of asthma have increased significantly. Asthma affects about 9% of children in the world. Its frequency fluctuates from 1 to 30% among countries, being higher in Western countries.[1]

Paracetamol is the most commonly used analgesic and antipyretic worldwide and is widely available over the counter (OTC).[2] In the United States approximately

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50 million adults consume products containing paracetamol every week. Paracetamol is used by distinct populations spanning across life stages, who have varying information-seeking priorities. These include young children, pregnant women, and the elderly. Some studies suggested that prenatal paracetamol exposure might associate with the risk of child asthma. However, other studies did not confirm this result.[3–15] Therefore, we conducted a meta-analysis to investigate their relationship.

Methods

Publication search

Two authors searched Pubmed and Embase databases up to June 2016. The search criteria ''paracetamol'' and ''asthma'' were used in text word searches. The reference lists of the selected articles were also manually examined to find relevant studies that were not discovered during the database searches. There was no language restriction.

Inclusion and exclusion criteria

Studies were selected for meta-analysis if they met the inclusion criteria as follows: (1) cohort or case–control study design; (2) studies that investigated the association between prenatal paracetamol exposure and the risk of child asthma. The following exclusion criteria were defined as follows: (A) incomplete raw data, (B) repetitive reports, and (C) material and methods used were not well described or reliable.

Data extraction

Two investigators extracted all variables and outcomes of interest independently. Disagreements were resolved through discussion and consensus. Data on first author and year of publication, study design, race, follow-up duration, sample size, and confounders were extracted.

Quality assessment

The included studies were assessed using the Newcastle-Ottawa Scale (NOS). The NOS employs a star rating system to assess quality from three broad perspectives of the study: (1) selection of the study groups; (2) comparability of the groups; and (3) identification of the exposure (for case–control studies) or outcome of interest (for cohort studies). Scores ranged from 0 to 9 stars. We considered a study awarded 0–3, 4–6, or 7–9 as a low-, moderate-, or high-quality study, respectively.

Statistical analysis

The strength of the association between prenatal paracetamol exposure and child asthma risk was calculated with the OR and respective 95% CIs. The significance of the pooled OR was determined by the *Z* test, and *P*-values of less than 0.05 were considered significant. Statistical heterogeneity among studies was assessed with the I^2 statistics. The random-effects model was chosen to calculate the pooled OR. The presence of publication bias was assessed by a visual inspection of a funnel plot. All statistical tests were carried out using the Revman 5.1 software (Nordic Cochrane Center, Copenhagen, Denmark) and STATA 11.0 software (Stata Corporation, College Station, TX, USA).

Results

Literature search

The initial literature search retrieved 196 relevant articles. After carefully screening the titles, texts, and abstracts, a total of 13 articles of more than 1,043,109 individuals were included in the meta-analysis (Fig. 1). The characteristics of the included studies are summarised in Table 1. All studies included were in accordance with NOS scale and all studies defined as high-quality study.

Meta-analysis

As shown in Fig. 2, a statistically significant association between prenatal paracetamol exposure and child asthma risk was found. The data showed that prenatal paracetamol exposure could increase the risk of child asthma (OR = 1.19; 95% CI, 1.12–1.27; $P < 0.00001$) in a random-effect model. Six studies reported paracetamol exposure during the first trimester of pregnancy. We found that paracetamol exposure during the first trimester of pregnancy was associated with increased risk of child asthma (OR = 1.21; 95% CI, 1.14–1.28; $P < 0.00001$; Fig. 3).

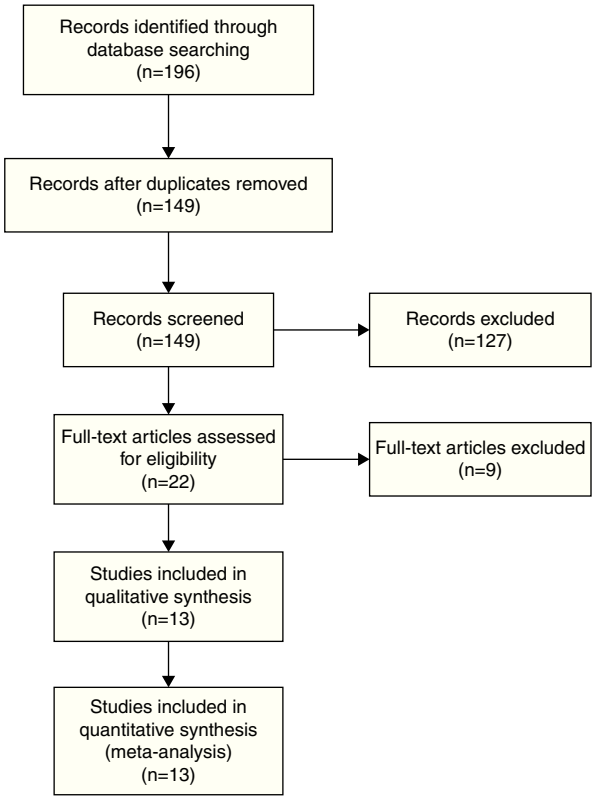

Figure 1 Flow of study identification, inclusion, and exclusion.

Table 1 Characteristics of the included studies.

First author	Year	Study design	Race	Follow-up duration (years)	Sample size	Quality score	Adjusted for
Shaheen	2005	Prospective cohort	Caucasian	7	8511	9	Gender, maternal asthma, maternal age, multiple pregnancy, maternal smoking, parity, mother's education level, mother's ethnicity, and other factors.
Persky	2008	Prospective cohort	Mixed	1	345	9	Maternal age, child's sex, home environment intervention group, maternal Mexican ethnicity, child breastfed for four or more weeks, active smoking in middle to late pregnancy, exposure to passive smoke during pregnancy, low birth weight, antibiotic use in late pregnancy, age at which formula introduced, and family history of asthma.
Rebordosa	2008	Prospective cohort	Caucasian	7	12,733	9	Gender, antibiotic use during pregnancy, exposure to tobacco smoke, social class.
Garcia-Marcos	2009	Retrospective cohort	Caucasian	3–5	1741	8	Smoking or non-smoking mother, duration of breast-feeding, older and younger siblings, cat ownership during the 1st year of the child's life and premature birth.
Perzanowski	2010	Prospective cohort	Mixed	5	301	7	Sex, ethnicity, birth order, maternal asthma, maternal hardship, exposure to environmental tobacco smoke and postnatal acetaminophen use.
Shaheen	2010	Prospective cohort	Caucasian	7	11,438	8	Partner's paracetamol use, postnatal paracetamol use.
Goksör	2011	Prospective cohort	Caucasian	4.5	4116	7	Prenatal paracetamol exposure, having a mother or father with asthma, eczema or rhinoconjunctivitis, male gender, maternal antibiotic use during pregnancy, maternal smoking during pregnancy, gestational age <37 weeks, caesarean section, asphyxia (Apgar at 5 min <7), treatment with broad-spectrum antibiotics during the first week of life, breast-feeding for four months or more, early fish introduction (before nine months of age), own eczema or doctor-diagnosed food allergy during the first year of life and parental level of education.
Andersen	2012	Prospective cohort	Caucasian	2–13	197,060	8	Gender, birth order, maternal smoking, maternal asthma, maternal age at delivery, maternal use of antibiotics, BMI, delivery mode, year of birth, county of residence, gestational age.
Kallen	2013	Retrospective cohort	Caucasian	2–10	685,015	9	Year of birth, parity, BMI, maternal age and smoking.
Migliore	2015	Prospective cohort	Caucasian	7	3538	7	Maternal educational level, maternal age at delivery, maternal smoking during pregnancy, siblings, maternal asthma/asthmatic bronchitis, maternal allergic rhinitis, maternal infections in the first/third trimester of pregnancy, and antibiotic use during pregnancy.

Table 1 (*Continued*)

First author	Year	Study design	Race	Follow-up duration (years)	Sample size	Quality score	Adjusted for
Sordillo	2015	Prospective cohort	Mixed	7–10	1490	7	Acetaminophen in infancy, ibuprofen in infancy, prenatal acetaminophen, prenatal ibuprofen, and covariates for child's sex and multivitamin intake, mother's age at enrolment, race/ethnicity, pre-pregnancy BMI, household income, number of children under 12 years of age in the home, breastfeeding duration, passive smoking exposure, smoking during pregnancy, childcare attendance, maternal and paternal history of asthma.
Liu	2016	Prospective cohort	Caucasian	11.5	63,652	8	Maternal age at delivery, maternal parity, maternal pre-pregnancy body mass index, socioeconomic status, maternal smoking during pregnancy, maternal history of asthma, maternal fever during pregnancy, maternal inflammation or infection during pregnancy, maternal antibiotic use for respiratory tract infections, maternal muscle or joint disease during pregnancy, maternal nausea during pregnancy, and sex of the child.
Magnus	2016	Prospective cohort	Caucasian	7	53,169	9	Maternal age, parity, education, pre-pregnancy body mass index, smoking during pregnancy, asthma, respiratory tract infections/influenza during pregnancy, fever during pregnancy, pain during pregnancy and antibiotic use during pregnancy, in addition to the child's gender, birth weight, breastfeeding the first six months of life, respiratory tract infections by six months, body mass index at six months and use of antibiotics by six months.

BMI, body mass index.

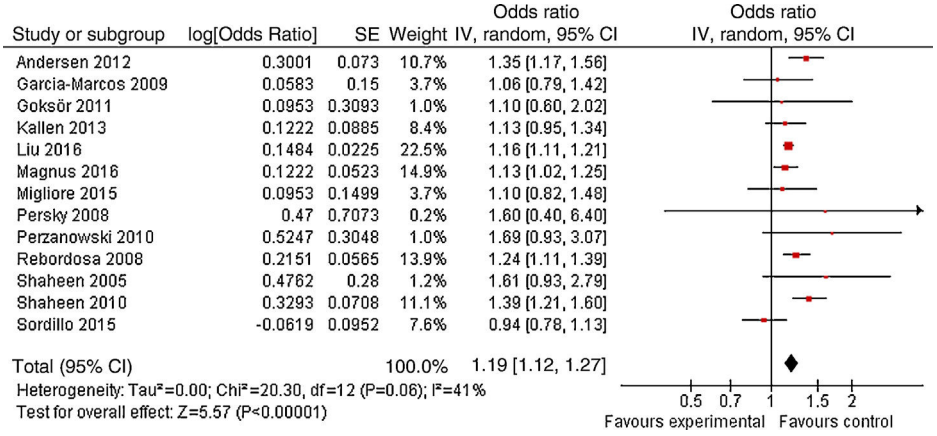

Figure 2 Effect of prenatal paracetamol exposure on child asthma risk.

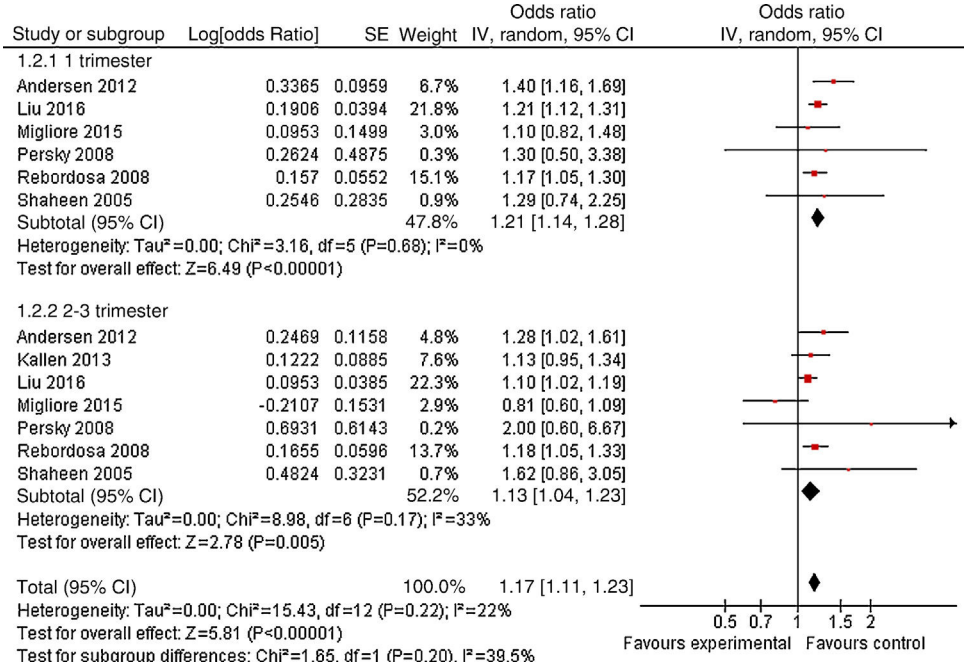

Figure 3 Subgroup analysis of the effect of prenatal paracetamol exposure on child asthma risk.

Furthermore, we observed that paracetamol exposure during the 2–3 trimesters of pregnancy was also associated with child asthma risk (OR = 1.13; 95% CI, 1.04–1.23; $P = 0.005$; Fig. 3). The funnel plot is symmetrical (Fig. 4), suggesting no publication bias. Egger test further verified that no publication bias existed ($P = 0.51$).

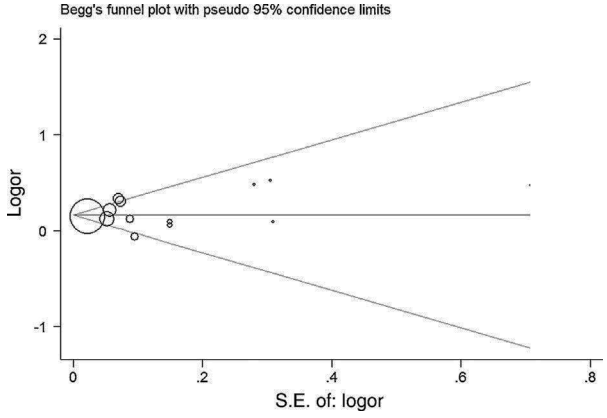

Figure 4 Funnel plot to assess publication bias.

Discussion

This meta-analysis suggested prenatal paracetamol exposure might increase the risk of child asthma. Paracetamol exposure during the first trimester and 2–3 trimesters could also increase child asthma risk.

Thiele et al. provided strong evidence that prenatal paracetamol interfered with maternal immune and endocrine adaptation to pregnancy, affected placental function, and impairs foetal maturation and immune development.[16] Dimova et al. found that acetaminophen decreased intra-

cellular GSH in human pulmonary macrophages and type II pneumocytes and the secretion of TNF-alpha and possibly IL-6 by human pulmonary macrophages.[17] Kozer et al. suggested that paracetamol was associated with reduced antioxidant status and erythrocyte glutathione concentrations.[18]

Several limitations should be identified. First, as a meta-analysis of observational studies, it was prone to bias (e.g., recall and selection bias) inherent in the original studies. However, the adjusted ORs were used in this meta-analysis, suggesting that our results were robust. Second, lacking the original data of the eligible studies limited the evaluation of the subgroup analyses by gender, age, and other factors. Third, almost all the studies were performed in Caucasian populations. Thus, our results may be applicable only to this population.

In conclusion, this study suggested that prenatal paracetamol exposure was significantly associated with the increased risk of child asthma.

Ethical disclosures

Confidentiality of data. The authors declare that no patient data appears in this article.

Right to privacy and informed consent. The authors declare that no patient data appears in this article.

Protection of human subjects and animals in research. The authors declare that no experiments were performed on humans or animals for this investigation.

Conflict of interest

None.

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