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ORIGINAL ARTICLE

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

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**KEYWORDS**
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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).

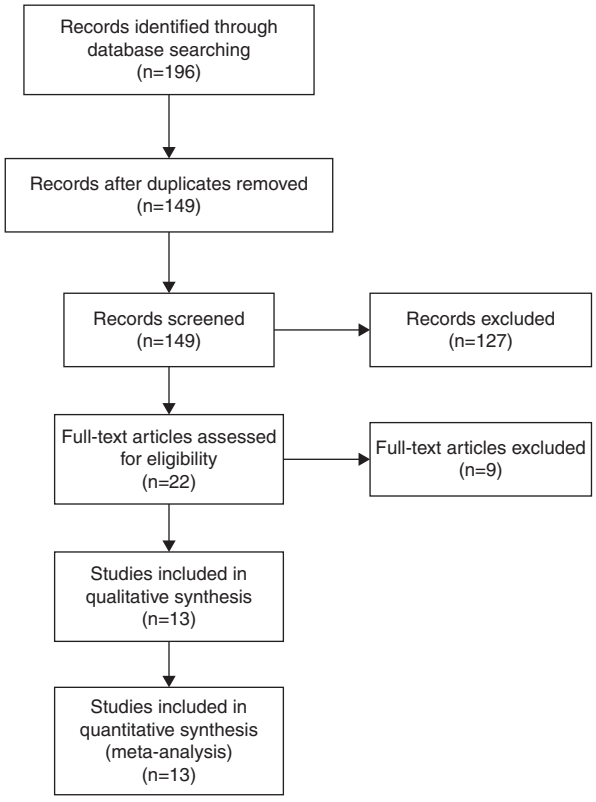


**Figure 1** Flow of study identification, inclusion, and exclusion.

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