

## Review Article

# Association between *Mycoplasma pneumoniae* infection and asthma: a meta-analysis and systematic reviews

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**Abstract:** *Mycoplasma pneumoniae* (MP) is caused by both upper and lower respiratory infections and could lead to serious complications. Recent publications have revealed that MP is associated with asthma; however, a single study may be affected by many factors and is controversial. In this study, a meta-analysis was performed to review the potential association between asthma occurrence and MP infection. According to the inclusion and exclusion criteria, an electronic search of the PubMed database identified 11 case-control studies involving a total of 1069 patients and 854 control cases. This meta-analysis showed that asthma patients had an MP antibody titer that was 2.69 times significantly higher than the control group ( $P = 0.0001$ ,  $OR = 2.69$ , 95%  $CI: 1.62-4.46$ ). These results indicate a strong relationship between MP infection and asthma.

**Keywords:** Asthma, *Mycoplasma pneumoniae*, meta-analysis

## Introduction

*Mycoplasma pneumoniae* (MP) was first isolated from cultures of sputum of a patient with primary atypical pneumonia [13]. What was referred to as "Eaton's agent" was shown to be a *Mycoplasma* species. MP is a very small bacterium in the class Mollicutes. It is a human pathogen that causes MP, a form of atypical bacterial pneumonia related to cold agglutinin disease. MP is characterized by the absence of a peptidoglycan cell wall and resulting resistance to many antibacterial agents. The persistence of MP infections even after treatment is associated with its ability to mimic the composition of the cell surfaces of hosts.

The incidence of disease does not appear be related to season or geography; however, infections tend to occur more frequently during the summer and fall months when other respiratory pathogens are less prevalent [21]. Approximately 40% of community-acquired pneumonias are due to MP infections, with children and elderly individuals being most susceptible.

However, no personal risk factors for acquiring MP-induced pneumonia have been determined [7, 21, 36]. Transmission of MP can only occur through close contact and the exchange of aerosols. Outbreaks of MP infections tend to occur within groups of people in close and prolonged proximity, including at schools, institutions, military bases, and households [21].

Symptomatic infections tend to develop over a period of several days, and manifestation of pneumonia can be confused with a number of other bacterial pathogens and conditions that cause pneumonia. However, several studies have shown that there is a cycle of MP epidemics every 3-5 years [36].

Asthma is a common long-term inflammatory disease of the airways [7, 21, 28, 36]. It is characterized by variable and recurring symptoms, reversible airflow obstruction, and bronchospasm [7, 15, 28, 36] and is thought to be caused by a combination of genetic and environmental factors [6, 15, 28, 36]. Environmental factors include exposure to air pollution and

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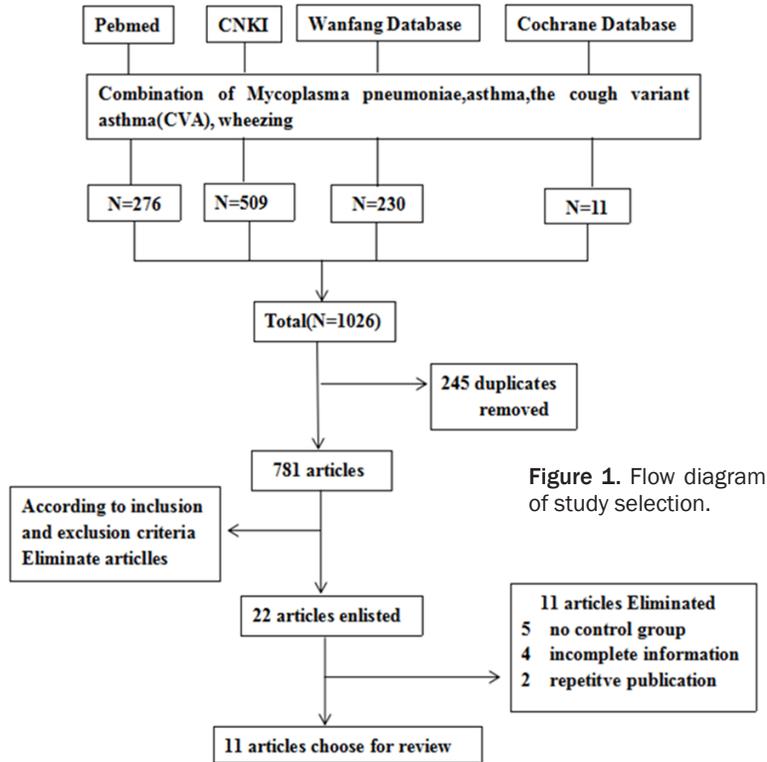


Figure 1. Flow diagram of study selection.

allergens. Other potential triggers include medications such as aspirin and beta blockers. Diagnosis is usually based on the pattern of symptoms, response to therapy over time, and spirometry [6, 15, 16]. Asthma is classified according to the frequency of symptoms, forced expiratory volume in 1 s (FEV<sub>1</sub>), and peak expiratory flow rate [6, 16]. It may also be classified as atopic or non-atopic, where atopy refers to a predisposition toward developing a type 1 hypersensitivity reaction [16, 19].

Asthma is the most common chronic disease in children. Because of its high economic burden, the World Health Organization considers it a disease of major public health importance. The link between respiratory tract infections and acute exacerbation has been recognized for a long time.

Use of antibiotics early in life has been linked to the development of asthma [6, 15, 16, 28]. Delivery via Caesarean section is also associated with an increased risk (estimated at 20-80%) of asthma; this is attributed to the lack of healthy bacterial colonization that the newborn would have acquired from passage through the birth canal.

The hygiene hypothesis attempts to explain the increased rates of asthma worldwide as a direct and unintended result of reduced exposure to non-pathogenic bacteria and viruses during childhood [9, 19, 42]. This may be due, in part, to increased cleanliness and decreased family size in modern societies [8]. Exposure to bacterial endotoxins in early childhood may prevent the development of asthma [4, 23].

There is increasing evidence of a relationship between MP infection and asthma in children. The role of MP infection in the pathogenesis of asthma has been a subject of continuing research [4, 8, 9, 19, 42] but these studies have had limitations, and no systematic reviews on this topic

have been conducted. Hence, we performed a systematic review and meta-analysis of prospective studies on the relationship between MP infection and asthma, which could provide a basis for its diagnosis and treatment in children.

### Materials and methods

#### Literature search

We performed a literature search on 'MP' and 'asthma' using the China National Knowledge Infrastructure (CNKI), Cochrane, PubMed, and Wanfang databases up to December 2015. No limitation was placed on language or year of publication. The index terms used were 'Mycoplasma', 'pneumoniae', and 'Eaton agent' together, which included the clinical symptoms asthma, atypical bacterial infection, cough variant asthma (CVA), and wheezing. We collected primary publications as well as additional publications in the reference lists. Databases were also searched using the term 'MP' together with the first author of each article, and the five forward most related links to all articles in PubMed were examined.

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**Table 1.** Characteristics of the 10 articles [1, 5, 25-27, 29, 30, 32, 35, 39] showing a correlation between mycoplasma pneumonia infection and asthma in children

Article	The first author	Year	Country	Population	Trial group (n/N)	Control group (n/N)	Mp detection method
[30]	Shuncui Gao	2015	China	≤ 14	38/78	22/71	LgM and IgE
[26]	Osama.M.S.	2015	Arabia	≤ 14	4/45	0/45	IgM
[39]	Wood.P.R.	2013	USA	5-17	51/79	36/64	IgM
[25]	Osama.M.S Abdul-Wahab	2013	Arabia	5-9	4/45	0/45	IgM
[1]	Atkimson TP	2009	USA	≤ 14	18/82	21/98	IgM
[35]	Avanish K.Varshney	2009	India	5-15	33/150	2/50	IgM
[27]	Ou CY	2008	China	≤ 14	99/316	10/151	IgM
[29]	Esposito S	2008	Italy	≤ 14	16/71	6/80	Speleological diagnose
[32]	TAtkimson	2005	England	≤ 14	16/82	16/98	IgM
[5]	S Biscardi	2004	France	2-15	24/119	8/152	IgM

### *Inclusion and exclusion criteria*

Inclusion criteria: All prospective case-control studies were selected according to the following criteria: the study used the statistical method of Horwitz and Feinslein [17] with 12 standards; within detailed data list and used proper statistical methods; and both treatment and control groups were utilized. Exclusion criteria were a retrospective study design; results based solely on analyses of reviews; the use of uncertain experimental data; and the inclusion of patients with other diseases.

### *Data extraction*

Two independent researchers extracted data from all included studies, including outcome measures, inclusion and exclusion criteria, study design and population, MP detection methods, case group and control group design, the source of MP infection, study location, and the first author and year of the reference. Any disagreements or discrepancies were resolved by discussion or by consulting a committee of experts.

### *Statistical analysis*

RevMan 5.3 was used for statistical analyses. Heterogeneity was assessed using a chi-square-based Q statistic. A P-value of ≤ 0.05 was considered statistically significant. If there was significant heterogeneity, outcome data from the trials were analyzed using a random effects model [37] to estimate the pooled odds ratio (OR). In the absence of heterogeneity, a meta-analysis was performed using a fixed effects model (Mantel-Haenszel) [10]. Asthma

associated with MP infection intensity was evaluated by calculating the merged OR and 95% confidence area (confidence interval, 95% CI). The results were plotted in forest plots and a funnel plot to identify publication bias.

## **Results**

### *Search results*

A search of the PubMed, China National Knowledge Infrastructure (CNKI), EMBASE, and Cochrane databases identified 1026 articles. After reading the full-text articles and following a subgroup discussion, six theses regarding the relationship between MP infection and asthma in children were identified. Three additional publications were examined after reviewing the references and the tables within those six theses.

The search first identified 22 articles consistent with our inclusion criteria. However, seven articles were excluded due to having no control group, presenting incomplete information, or being a repetitive publication. **Figure 1** summarizes the collected articles and search process, and **Table 1** lists the characteristics included in the studies. The search ultimately identified 11 case-control studies for the meta-analysis, involving a total of 1069 patients (303 with a positive MP antibody) and 854 control cases (121 with a positive MP antibody) ( $X^2 = 55.50$ ,  $P < 0.01$ ).

### *Sensitivity analysis*

We first tested the heterogeneity between asthma and detection of the MP antibody titer: chi-

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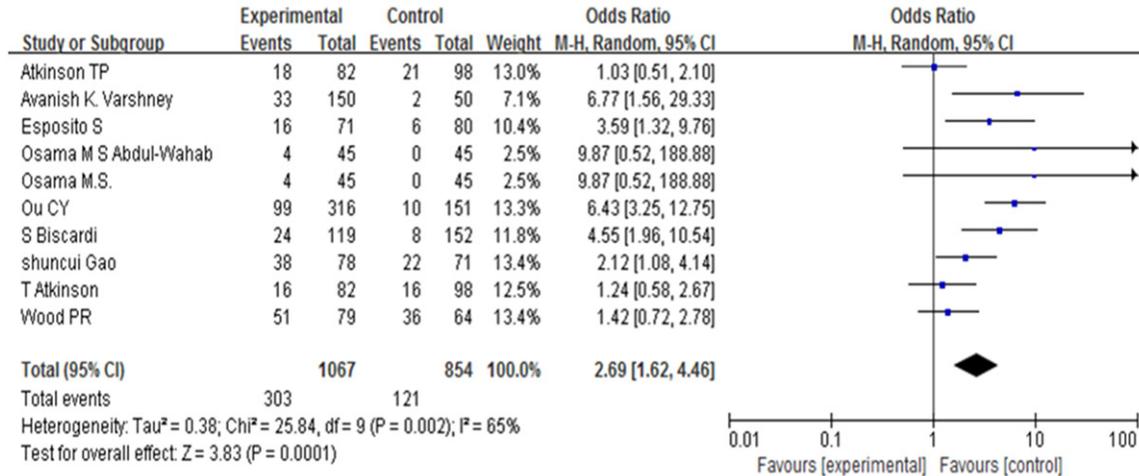


Figure 2. Sensitivity analysis.

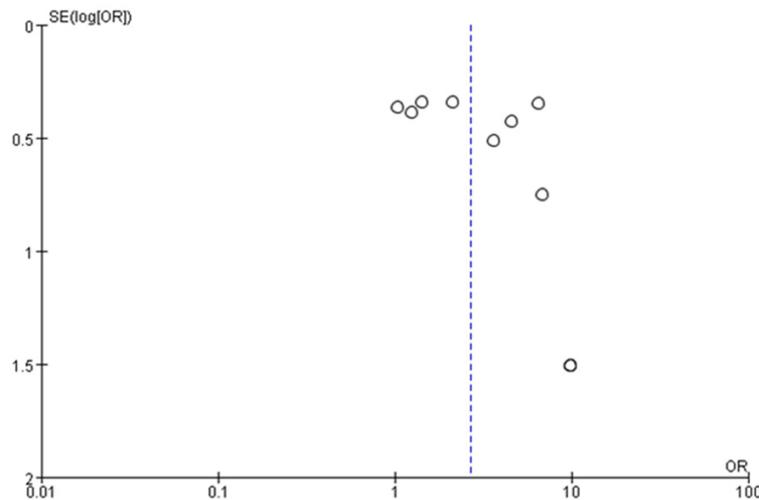


Figure 3. The publication bias in the estimates.

square = 13.14,  $d_f = 9$ ,  $P < 0.01$ ,  $I^2 = 0.29$ . These results indicated that the random effects model could be used for the meta-analysis. Second, with regard to the risk analysis, we found that: OR = 2.69, 95% CI = 1.62-4.46, Z = 3.83,  $P < 0.01$ . There was a significant difference between these two groups. Furthermore, we determined that the level of the MP antibody titer was 2.69 times higher in asthma patients than in the control group. Among the studies, Wood [39] and Shuncui [30] had the highest degree, which showed in Figure 2.

### Publication bias

Publication bias was estimated using RevMan 5.3 statistical software. A funnel plot was

drawn for the relationship between asthma and MP infection. Because the plot had a symmetrical shape, we concluded that there was no publication bias (Figure 3).

### Discussion

MP generally causes upper and lower respiratory tract infections. In particular, it can lead to serious complications in immunocompromised populations (e.g., young babies and elderly people), which include pharyngitis, [33] otitis, [34] tracheobronchitis, [2] and community-acquired pneumonia [41]. However, it sometimes remains totally asymptomatic.

An increasing number of studies have focused on persistent MP infection; most have been performed on humans or animal models. According to Tang [31], MP induces the aggregation and activation of eosinophils in the body, which are closely associated with lymphocytes in BALF. However, susceptible populations have immature or aging lymphocytes.

Some studies have determined that the percentage of MP infection is significantly higher in asthmatic patients than in non-asthmatic controls [12, 18].

Some retrospective analyses have reported that the use of macrolide for the treatment of asthma usually induces a favorable clinical response [3, 24]. However, increasing numbers of cases of macrolide-resistant MP have been found in clinics, however, there is no direct evidence of a relationship between MP and asthma and role of MP in asthma remains elusive.

Our meta-analysis identified an association between MP infection and asthma. More specifically, we found that MP antibody titer was 2.69 times higher in the asthmatic group than in the control group.

Asthma is the result of chronic inflammation of the conducting zone of the airways (particularly the bronchi and bronchioles), which subsequently results in increased contractibility of the surrounding smooth muscles. This, among other factors, leads to bouts of narrowing of the airway and the classic symptoms of wheezing [40].

Watanabe [38] determined that it was difficult to cure patients with a history of asthma concurrently infected with MP. MP infection can aggravate the structures and functions of the respiratory epithelium cilia, as well as induce chronic inflammation of respiratory tracts. Furthermore, it causes local smooth muscle contraction, leads to the aggregation of cytokines, and produces specific antibodies in the respiratory tract, resulting in exacerbated airway hyperresponsiveness [11, 14, 20, 22].

Therefore, in the clinical health setting, MP infection status should be evaluated in asthmatic patients using serological or molecular diagnoses.

There were some limitations to this study. First, we only examined case-control studies. In addition, asthma is also caused by other factors such as genetics, the environment, other infections, and individual differences. However, our results still provide convincing evidence that MP infection and asthma are closely related.

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### Disclosure of conflict of interest

None.

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