

Review Article

Association between Respiratory Syncytial Virus Infection in Infancy and Subsequent Asthma: A Meta-Analysis of Observational Studies

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OPEN ACCESS**Keywords**

- Respiratory syncytial virus infection
- Bronchiolitis
- Asthma
- Systematic review
- Meta-analysis

Abstract

Background: It has been shown that respiratory syncytial virus (RSV) bronchiolitis in infancy can increase the risk of asthma. This review will aim to describe the association between RSV bronchiolitis in infancy and subsequent asthma.

Methodology: Relevant articles were retrieved from PubMed and Web of Science. A random effect meta-analysis was done using the Open Meta Analyst software to evaluate the influence of RSV bronchiolitis as a risk factor of subsequent asthma.

Results: Five studies met the inclusion criteria and showed that people who had suffered RSV bronchiolitis in infancy had a higher risk to develop asthma (OR: 4.03; 95% confidence interval (CI): 2.23 to 8.31, p-value<0.001) comparing to those who did not have bronchiolitis in infancy.

The heterogeneity of this meta-analysis was moderate ($Q=11.28$, p-value <0.024, $I^2=64.56\%$). Two outlying studies were found that had results that diverged with the rest of the studies. After removing these two outlying studies, the heterogeneity of the study becomes null ($I^2=0$) and the asthma risk in the RSV group becomes higher (OR=8.01; 95% CI: 4.30 to 14.93, p-value <0.001).

Conclusion: The results from this meta-analysis suggest that RSV bronchiolitis in infancy can precipitate subsequent asthma. Further studies are needed to confirm this association. However, prevention of RSV bronchiolitis is suggested to be able to decrease the risk of asthma.

ABBREVIATIONS

CI: Confidence Interval; MOOSE: Meta-analysis of Observational Studies; OR: Odds Ratio; RSV: Respiratory Syncytial Virus

INTRODUCTION

Asthma is one of the most important non communicable diseases in childhood with an estimated prevalence ranging from 6% to 13%, depending on geographical areas [1-3]. This disease is characterized by reversible airflow obstruction, non-specific bronchial hyper-reactivity and chronic airway inflammation [4]. These histologic modifications can explain subsequent symptoms like cough, wheezing, breathlessness, and chest pain [5,6].

Respiratory syncytial virus (RSV) is the leading cause of bronchiolitis worldwide with an estimated overall incidence of 48.5% per 1000 per year in children aged <1 year [7]. Many studies found an association between RSV bronchiolitis and asthma [8-17].

Therefore, a meta-analysis was performed to determine the association between RSV bronchiolitis in infancy and subsequent asthma.

MATERIAL AND METHODS

This article was conducted according to the MOOSE guidelines [18].

Publication search and study selection

A systematic literature search was done with the electronic database of PubMed and Web of Science. In PubMed, the following keywords were used in the title field to include as many articles as possible: "Respiratory syncytial virus or Bronchiolitis OR RSV and asthma". In Web of Science the key words "respiratory syncytial virus and asthma" were used in the title field. Last search was updated in February 2017. This meta-analysis was restricted to articles written in English and French. However there was no time restriction on the publications.

All titles and abstracts from the preliminary electronic search for pertinent studies were assessed. The full texts of the retrieved studies were then studied to determine whether the study met the inclusion criteria or not. The inclusion criteria for studies included in this meta-analysis were:

- (1) Study design: cohort study, case-control study
- (2) Population: children under 36 months without asthma
- (3) Exposure: RSV bronchiolitis
- (4) Comparison: children without RSV bronchiolitis
- (5) Outcome: OR with a 95% CI of Asthma in the overall population.

Systematic reviews and meta-analysis were excluded.

Data extraction

Full articles were reviewed and the following data was extracted: Study authors, the year of publication, country of publication, timeframe of the study, study population, the number of cases of RSV bronchiolitis, the sample size of the control group and the number of people who developed asthma.

Statistical considerations

A random effect meta-analysis was performed using the Open Meta Analyst software to synthesize effect estimates of studies. The Der Simonian-Laird random-effects model meta-analysis was used to define the weight of each individual study [19]. Heterogeneity was assessed using the Cochrane's Q test and quantified its magnitude using I^2 .

RESULTS

Study characteristics

A total of 264 publications were identified. After removal of duplicates and assessment of the remaining publications, 8 studies met the inclusion criteria. 3 supplementary studies were removed because they were based on the same cohort even though the outcome was assessed in different years. Two

studies were done in Finland, 1 in Sweden, 1 in the UK and 1 in Spain (Table 1). Figure (1) shows the flow diagram for the study selection process.

All those studies were published between 2005 and 2013 with a median follow-up of 15 years. The sum of all participants was 8 612 among which 210 infants with RSV bronchiolitis and 8 402 controls. All the participants were recruited when they were younger than 3 years. The prevalence of asthma in the RSV group ranged from 27.1% [20] to 62.5% [21] and in the control group from 8.6% [17] to 20% [22].

Study quality

The quality of the studies was evaluated with the Newcastle-Ottawa scale for cohort studies and it was concluded that all were of good quality (Table 2).

Meta-analysis results

A meta-analysis (Binary random-effect model) was conducted to derive a pooled or for asthma in 5 studies. The meta-analysis across all these studies showed that the asthma risk in people suffered of RSV bronchiolitis in infancy was a statistically difference higher than in people who didn't have bronchiolitis in infancy (OR: 4.03; 95% confidence interval (CI): 2.23 to 8.31, p -value<0.001, see Figure 2). The study of Henderson et al [22]. had the one with the biggest weights (27.86%) whereas the study of Ruotsalainen et al [23]. Had the one with the lesser weights (17.02%).

The heterogeneity of this meta-analysis was moderate ($Q=11.28$, p -value<0.024, $I^2=64.56\%$). Two outlying studies were found (Henderson et al. [22], and Backman et al. [20].) that had results that diverged with the rest of the studies. After removing these two studies, the heterogeneity becomes null ($I^2=0$) and the asthma risk in the RSV group becomes higher (OR=8.01; 95% CI: 4.30 to 14.93, p -value <0.001, see Figure 3).

DISCUSSION AND CONCLUSION

The aim of this systematic review was to measure the degree of association between RSV bronchiolitis in infancy and subsequent

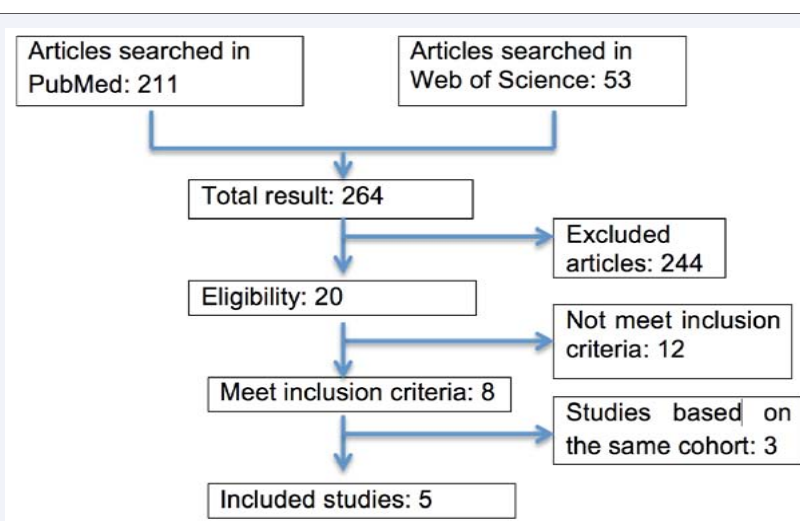


Figure 1 Flowchart for the study selection process.

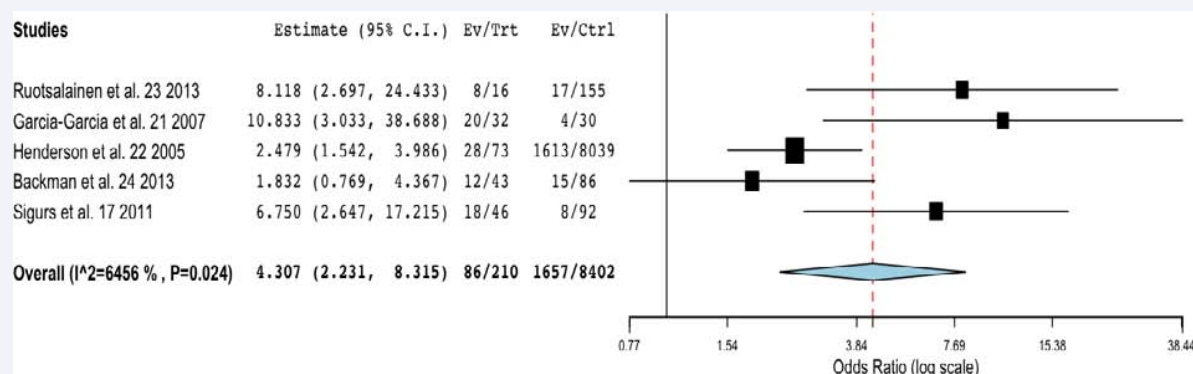


Figure 2 Forest plot of pooled OR of asthma with 95% CI.

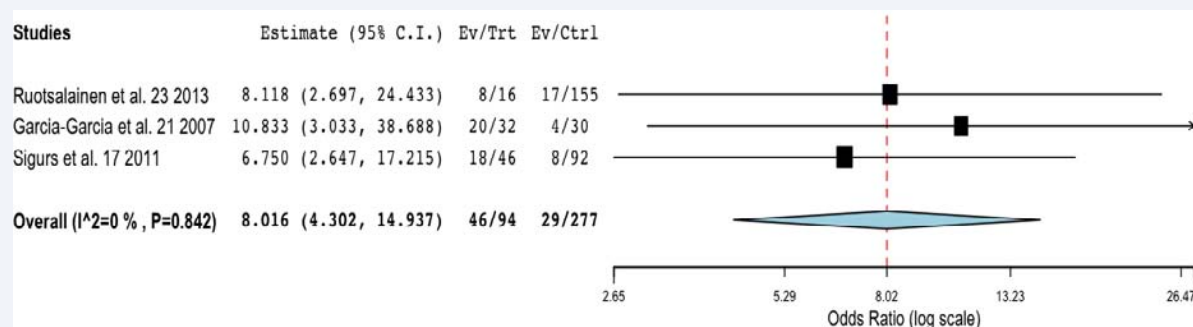


Figure 3 Forest plot of pooled OR of asthma with 95% CI after excluding outlying studies.

Table 1: Baseline characteristics of included studies.

Reference, study design	Year	Region	Sample size (Exposure)	Years of follow-up	Confounding variables
Ruotsalainen et al. [23] Cohort study	2013	Finland	171 (16)	16	Age, sex, presence of asthma in parents, atopic dermatitis in infancy, blood eosinophilia on admission, and presence of specific IgE to at least one allergen tested at <24 months of age
García-García et al. [21] Cohort study	2007	Spain	62 (32)	5	Allergic rhinitis, Prematurity, Siblings with atopy, Smoking by mother
Henderson et al. [22] Cohort study	2005	UK	8,112(73)	7	Birth weight, sex of the child, season of birth and mother's age at delivery obtained from birth records, maternal parity, maternal smoking during pregnancy, maternal history of asthma or eczema, highest maternal educational qualification and housing tenure
Backman et al. [20] Cohort study	2014	Finland	129 (43)	30	Age, sex, current daily smoking and clinical atopy
Sigurs et al. [17] Cohort study	2011	Sweden	138 (46)	18	Gender, domestic furred pets in the first year of life, parental smoking in the first year of life, own smoking at age 18, current Allergic rhino-conjunctivitis (ARC) of the subjects themselves, physician-diagnosed parental ARC and physician-diagnosed parental asthma

asthma. Based on the 5 articles included in this review, the odds of asthma in infants who suffered of RSV bronchiolitis was 4-fold higher than infants who did not get bronchiolitis.

Some studies had revealed some degree of genetic correlation between RSV infection and subsequent asthma [11,24]. Even though it is somehow hard to study the mechanical link between RSV respiratory infection and asthma in human due to ethical constraints, this link has been studied in animal models using mice, cows and rats. Post-RSV sequels, due to histologic,

anatomical, and immunological modifications, such as airway dysfunction and immune deviation can explain the mechanical link between these two diseases in mice models [25].

The strength of this review is that it has integrated statistical tools to resume the overall effect. Moreover, the electronic database search was done meticulously and the selection criteria were well-defined and stringent. The exposure was compared to a well-chosen control group in all 5 studies.

Table 2: Newcastle-Ottawa scale for bias of included studies.

First authors	Source of bias								Total
	Selection Bias				Confound- ing bias	Measurements bias			
	The cohort of RSV infection was representative	The cohort of control group was drawn from the same community with the exposure group	RSV infection was ascertain	Asthma was not present at start of study	Asthma prevalence was adjusted for confounding factors	Asthma was validated	Mean follow-up of at least 5 years	<20% of patients were lost of follow-up	
Ruotsalainen et al.[23]	*	*	*	*	**	*	*	NA	8
García-García et al.[21]	*	*	*	*	**	*	NA	NA	7
Henderson et al. [22]	*	*	*	*	**	*	*	NA	8
Backman et al. [20]	*	*	*	*	**	*	*	NA	8
Sigurs et al. [17]	*	*	*	*	**	*	*	*	9

The limitations of this review were firstly the fact that it was a meta-analysis based on observational studies. Secondly, articles included did not have the advantages of randomized control trials when it comes to allocating the intervention. The exclusion of articles not written in English or in French may also introduce some selection bias in this review. Moreover, this meta-analysis suffers of publication bias because we did not include unpublished studies.

Proper elucidation of the association between these two diseases can result in prevention of RSV infection, resulting in a decrease in the incidence of asthma.

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