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Review Article

Early-life respiratory infections are pivotal in the progression of asthma-a systematic review and meta-analysis

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Abstract: Background: To perform a systematic review and meta-analysis of case-control and cohort studies assessing the association of early-life respiratory infections with the risk of asthma. Methods: Relevant studies were identified by a search of PubMed, Cochrane Library, ScienceDirect, Springer, China National Knowledge Infrastructure (CNKI), WANFANG and VIP before April 2016 with no restrictions. We included studies that reported odds ratio (OR) estimates with 95% confidence intervals (CIs) for the association between early-life respiratory infection and the risk of asthma. Results: Thirteen studies involving 9172 participants from several countries were included in the meta-analysis. In a pooled analysis of all studies, respiratory infection was associated with an increased risk of asthma (OR: 1.62; 95% CI: 1.52-1.74). Childhood asthma was significantly correlated with respiratory tract infections among children who acquired infections within 6 months (OR: 1.47; 95% CI: 1.20-1.80), 8 months (OR: 2.00; 95% CI: 1.34-2.99), 12 month (OR: 2.72; 95% CI: 2.18-3.40) and 24 months (OR: 2.41; 95% CI: 1.74-3.34) of life. Asthma was significantly positively correlated with both human rhinovirus infection (OR: 2.88; 95% CI: 1.79-4.64) and respiratory syncytial virus infection (OR: 1.61; 95% CI: 1.44-1.80) and significantly negatively correlated with herpes simplex virus infection (OR: 0.48; 95% CI: 0.26-0.89), but was not significantly correlated with coronavirus infection (OR: 1.97; 95% CI: 0.75-5.19) or measles virus infection (OR: 0.63; 95% CI: 0.08-4.90). Conclusions: Early-life respiratory infections are positively associated with the risk of asthma.

Keywords: Respiratory infections, virus, asthma

Introduction

Asthma is a frequent chronic respiratory disease causing enormous economic burdens for the country, the society and the families of patients. Many recent studies revealed that there were a series of changes in the composition of the lower respiratory tract microbiome in asthmatic patients compared with healthy people. Specifically, the distribution of proteobacteria (e.g., pseudomonas, hemophilus) is dominant in asthmatic patients [1-4]. In 1989, the British scholar Strachan proposed the hygiene hypothesis, which states that infection may be related to the occurrence of allergic diseases in early life. It was demonstrated that the number and frequency of natural killer (NK) cells increased in the lung and colonic mucosa lamina of germ-free animals, and this may be related to the occurrence and development of allergic diseases, such as asthma [5]. Some studies show a “window period” in early life, in which the colonization of various microflora can appropriately modulate the immune response and respiratory tractinfections in early life may stimulate epithelial immune damage, chronic airway inflammation and airway hyper-responsiveness which will leading to recurrent wheeze and asthma later in childhood [6-10]. Therefore, changes in the microbial community in early life may affect the development of asthma. However, the relationship between respiratory tractinfections and subsequent development of asthma is still controversial. This study aims to assess the association of early-life respiratory infections with the risk of asthma by performing a systematic review and meta-analysis of case-control and cohort studies.

Materials and methods

Search strategy

We searched PubMed, Cochrane Library, ScienceDirect, Springer, China National Knowle-

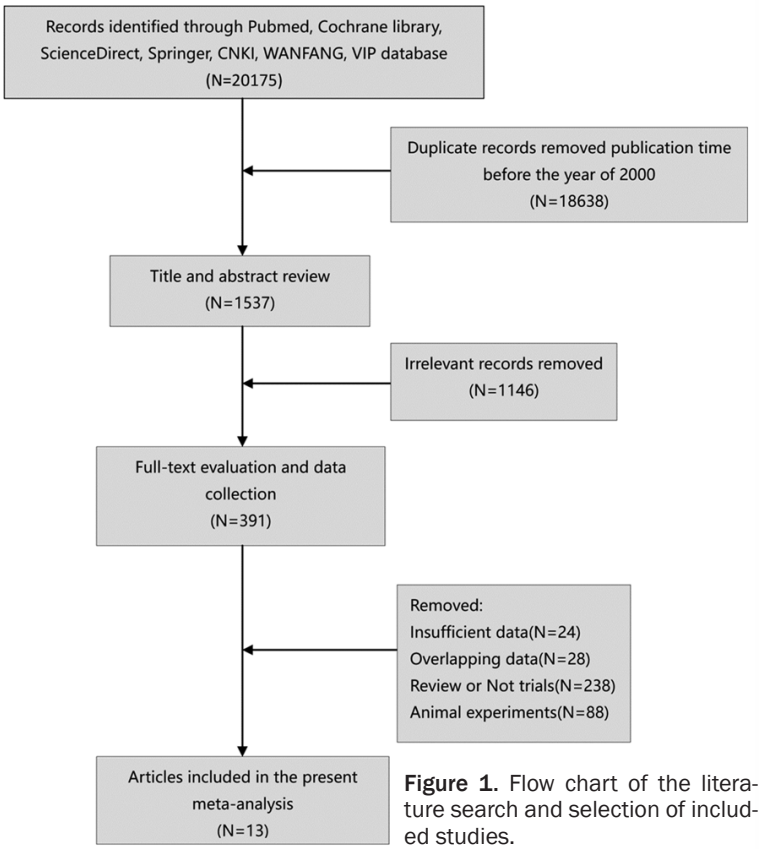


Figure 1. Flow chart of the literature search and selection of included studies.

dge Infrastructure (CNKI), WANFANG and VIP for studies on associations between early respiratory infections and the risk of asthma published before April 2016. The following key words were used in searching: "asthma" and "early/childhood or respiratory infection/illness or viral and bacterial infections or bronchiolitis or pneumonia". Moreover, we explored these key words in titles and abstracts and manually searched the references cited in the selected articles and relevant reviews. The published studies were sought with no restrictions of languages or the minimum number of patients. The titles and abstracts were screened to identify related studies, and full texts were evaluated carefully.

Eligibility criteria

The following inclusion criteria were used: a case-control or cohort study design; published before April 2016; respiratory infection found within 24 months after birth in case-control studies; data extracted in the time from respiratory tract infection to asthma, with the shortest follow-up period of 1 month; provision of odds ratios (OR) or relative risks (RR) with confidence intervals (CI) or data necessary to calculate them; study objects being asthmatic patients, and asthma being defined as physician-diagnosed asthma. All the included studies provided the sources of subjects from the case-control and cohort studies. If data sets were overlapped or duplicated, only the most recent information was included in this meta-analysis. All identified studies were reviewed by two authors independently for eligibility.

Data extraction

Data were extracted by two researchers independently, and any disagreement between them was resolved by discussion and consensus. The following information was recorded from 13 studies: first name of the study, publication year, study period, country of origin, study design, sample size (numbers of patients and controls or cohort size), types of early infections, age at infection, pathogens causing the infections, and OR with 95% CI for each category. The primary authors were contacted to retrieve additional information, if necessary.

Statistical analysis

Statistical analysis was conducted using STATA 14.0 (STATA Corp, College Station, TX) and Revman 5.2 (Cochrane Collaboration, Copenhagen) [11]. Study-specific OR estimates and were combined using a random-effects model, which considers both within-study and between-study variations. Log transformation was adopted in the combination. By convention, a pooled OR not equal to 1 indicated a difference between subjects with and without early respiratory infections. The effect of early respiratory infections on asthma was considered to be significant when the 95% CI for the overall OR did not overlap 1. Statistical heterogeneity among the studies was evaluated with

Table 1. Characteristics of prospective studies on respiratory infection and asthma

Study	Year	Location	Study period	Study design	No. of participants	OR (95% CI)	NOS
Haby M	2001	Australia	1995.05-1995.06	Case-control	974	2.41 (1.74, 3.34)	6
Yuan C	2012	China	2010.01-2011.06	Case-control	375	2.96 (1.57, 5.56)	6
QingYan H	2012	China	2009.01-2011.12	Case-control	634	2.82 (2.03, 3.93)	7
JiangYa L	2011	China	2008.01-2009.12	Case-control	602	1.30 (0.80, 1.40)	7
Jeng M J	2015	China	2000-2010	Cohort	21971	1.46 (1.32, 1.62)	8
BønnelykkeK	2015	Finland/Denmark	1998-2008	Cohort	313	1.43 (1.26, 1.61)	8
Illi S	2001	Germany	1990-1997	Cohort	939	4.51 (2.59, 7.85)	8
Kusel M M H	2007	UK	2000-2005	Cohort	198	3.90 (1.40, 10.50)	6
Nafstad P	2005	Norway	1992-2002	Cohort	2540	2.10 (1.30, 3.00)	8
Puig C	2010	UK/Spain/Germany	1996-2004	Cohort	368	3.03 (1.39, 6.61)	8
Ramsey C D	2006	American	1994-2003	Cohort	440	1.74 (0.90, 3.35)	8
Jackson D J	2008	American	1998-2006	Cohort	259	2.80 (1.60, 4.90)	8
Nafstad P	2000	Norway	1992-1996	Cohort	2531	3.40 (2.30, 7.00)	8

Q and I^2 statistics, with the significance level set at P<0.05 [12]. If there was significant heterogeneity among the studies, the random effects model was used to combine the OR estimates, and these studies were divided by different factors into specific subgroups [13]. The stability of the results was evaluated using sensitivity analysis. Subgroup analysis was performed by geographic area, pathogens causing the infections, and initial time of infection. The influence of the individual data set on the pooled ORs was evaluated by deleting one included study at a time. The potential publication bias was estimated by funnel plots, which express the SE of the log(OR) of each study against its log(OR). Funnel plot asymmetry was assessed by Egger's linear regression test on the natural logarithm scale of the OR [14]. An asymmetrical plot indicated a possible publication bias. The significance of the intercept was determined by the t-test suggested by Egger (*P*<0.05 was considered significant publication bias, which would be corrected by the trim and fill method [15]).

Results

A flow diagram of our literature search is shown in **Figure 1**. The initial search yielded 20,175 entries. After the removal of 18,638 duplicates, 1537 titles and abstracts were assessed, of which 1146 articles were potentially irrelevant for this review. Finally, the full texts of 391 studies were evaluated. Of them, 377 articles were excluded because of no original data or insufficient data (n=24); overlapped data from the same study population or no specific follow-up time and control group (n=28); the study design being comments, reviews or meta-analysis (n=238); and animal experiments (n=88). Among the remaining 13 studies, 4 were case-control studies [16-19] and 9 were cohort studies [20-28]. Of these studies, 6 studies were conducted in Europe [20, 22, 25-27], 4 in China [21, 16-18], 1 in Australia [19] and 2 in America [23, 24]. The sample sizes ranged from 198 to 2531. Of the studies, 9 studies reported the age at initial respiratory infection [16-19, 22-24, 26, 28], and 6 studies analyzed the type of infection and provided stratified analysis of the pathogen causing the infection [20, 21, 23-25, 27] (**Table 1**).

Relationship between asthma and respiratory infections

The random effects model shows a significant relationship between childhood asthma and respiratory tract infection (OR: 1.62; 95% CI: 1.52-1.74; P<0.05) (**Figure 2**). Subgroup analysis by study design, including case-control studies (OR: 2.02; 95% CI: 1.70-2.40; P<0.05) and cohort studies (OR: 1.56; 95% CI: 1.45-1.68; P<0.05), yields similar results about the relationship between respiratory infections and asthma (**Figure 3A**; **Table 2**). We also performed subgroup analysis on geographic areas to further explain the results of this meta-analysis. A significant relationship between respiratory infection and asthma is found in studies from Europe (OR: 1.64; 95% CI: 1.46-1.83; P<0.05), China (OR, 0.52; 95% CI, 0.35-0.69), Australia (OR: 2.41; 95% CI: 1.74-3.34; P<0.05) and America (OR: 2.30; 95% CI: 1.50-3.51; P<0.05) (**Figure 3B**; **Table 2**).

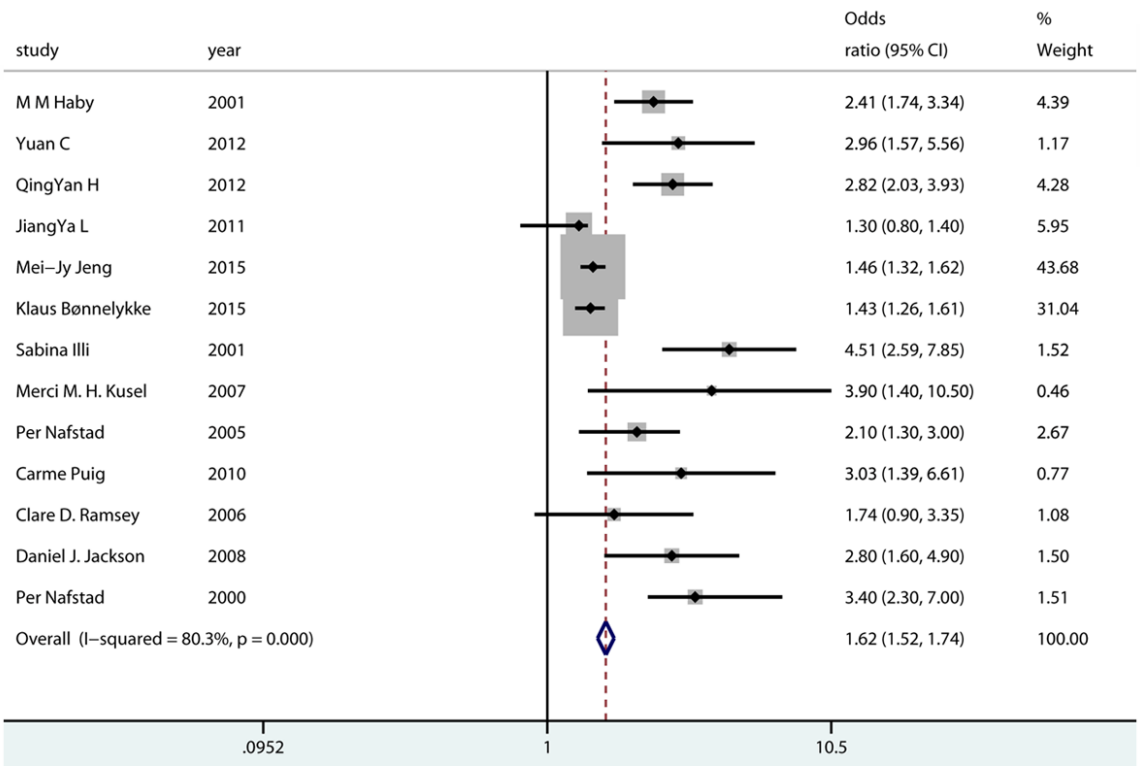


Figure 2. Forest plot (random-effects model) of respiratory tract infection and childhood asthma.

Relationship between different ages at onset of infection and asthma

One purpose of our meta-analysis was to find whether asthmatic children had respiratory infection within 24 months and we found a similar result in different age groups. Specifically, childhood asthma and respiratory tract infections are significantly related in the groups in which children acquired infection within 6 months (OR: 1.47; 95% CI: 1.20-1.80; P<0.05), 8 months (OR: 2.00; 95% CI: 1.34-2.99; P< 0.05), 12 months (OR: 2.72; 95% CI: 2.18-3.40; P<0.05) and 24 months (OR: 2.41; 95% CI: 1.74-3.34; P<0.05) of life (**Figure 4A**).

Relationships between different viral infections and asthma

To extend the results of our meta-analysis, we performed subgroup analysis on different virus types. The occurrence of asthma is significantly positively related to human rhinovirus (HRV) infection (OR: 2.88; 95% CI: 1.79-4.64; P<0.05) and respiratory syncytial virus (RSV) infection (OR: 1.61; 95% CI: 1.44-1.80; P<0.05) and significantly negatively related to herpes simplex virus (HSV) infection (OR: 0.48; 95% CI: 0.26-0.89; P<0.05). However, there was no significant relationship with coronavirus (CV) infection (OR: 1.97; 95% CI: 0.75-5.19; P=0.17) or measles virus (MV) infection (OR: 0.63; 95% CI: 0.08-4.90; P=0.659) (**Figure 4B**).

Publication bias and sensitivity analysis

There was significant heterogeneity among all studies (I^2=80.3%, P<0.01), even after subgroup analysis. For this reason, we performed sensitivity analysis. The results showed that deletion of any study did not impact the final results, and this result was robust. However, the Egger tests show publication bias (P<0.1) for the included studies in the analysis of the association between respiratory infections and asthma. But there was no obvious asymmetry in the funnel plots after modification with trim and fill method, which suggesting no publication bias (**Figure 5**).

Discussion

Developments in biological science and technology allow us to detect microorganisms in different parts of the human body. Some studies of the lower respiratory tract show a strong cor-

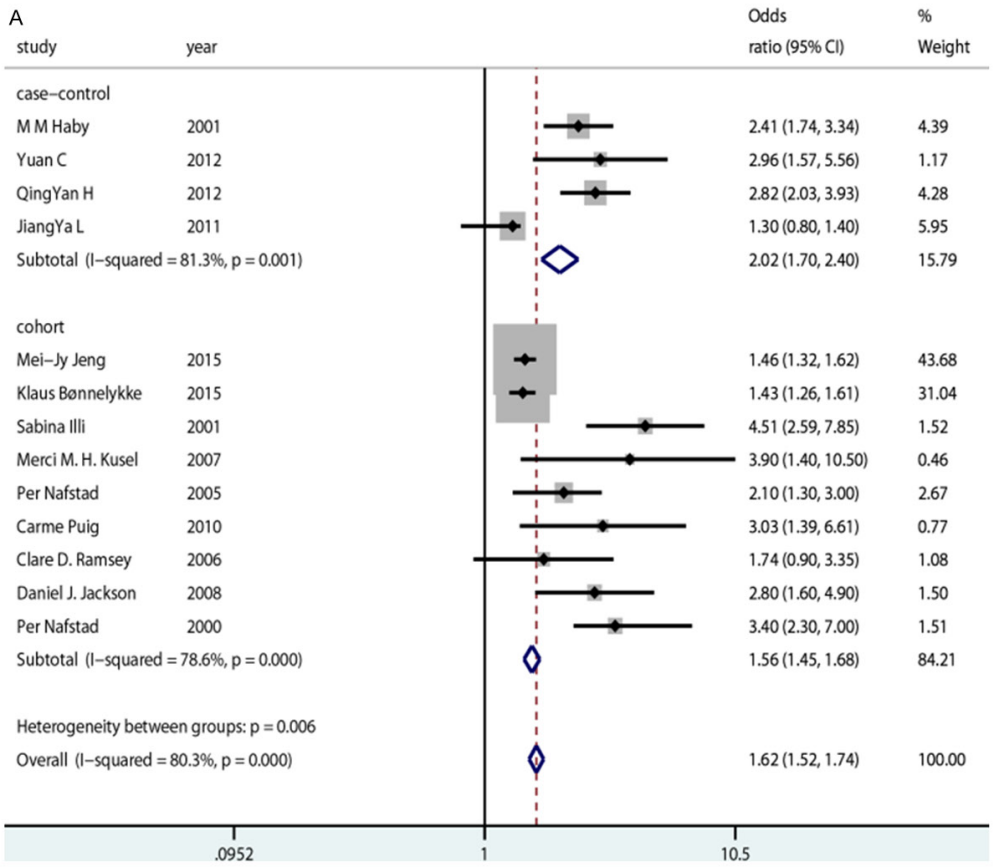

A
study
year
Odds ratio (95% CI)
% Weight
case–control
M M Haby 2001 2.41 (1.74, 3.34) 4.39
Yuan C 2012 2.96 (1.57, 5.56) 1.17
QingYan H 2012 2.82 (2.03, 3.93) 4.28
JiangYa L 2011 1.30 (0.80, 1.40) 5.95
Subtotal (I–squared = 81.3%, p = 0.001) 2.02 (1.70, 2.40) 15.79
cohort
Mei–Jy Jeng 2015 1.46 (1.32, 1.62) 43.68
Klaus Bønnelykke 2015 1.43 (1.26, 1.61) 31.04
Sabina Illi 2001 4.51 (2.59, 7.85) 1.52
Merci M. H. Kusel 2007 3.90 (1.40, 10.50) 0.46
Per Nafstad 2005 2.10 (1.30, 3.00) 2.67
Carme Puig 2010 3.03 (1.39, 6.61) 0.77
Clare D. Ramsey 2006 1.74 (0.90, 3.35) 1.08
Daniel J. Jackson 2008 2.80 (1.60, 4.90) 1.50
Per Nafstad 2000 3.40 (2.30, 7.00) 1.51
Subtotal (I–squared = 78.6%, p = 0.000) 1.56 (1.45, 1.68) 84.21
Heterogeneity between groups: p = 0.006
Overall (I–squared = 80.3%, p = 0.000) 1.62 (1.52, 1.74) 100.00
.0952
1
10.5
B
study
year
Odds ratio (95% CI)
% Weight
Australia
M M Haby 2001 2.41 (1.74, 3.34) 4.39
Subtotal (I–squared = .%, p = .) 2.41 (1.74, 3.34) 4.39
China
Yuan C 2012 2.96 (1.57, 5.56) 1.17
QingYan H 2012 2.82 (2.03, 3.93) 4.28
JiangYa L 2011 1.30 (0.80, 1.40) 5.95
Mei–Jy Jeng 2015 1.46 (1.32, 1.62) 43.68
Subtotal (I–squared = 84.6%, p = 0.000) 1.54 (1.40, 1.69) 55.08
Europe
Klaus Bønnelykke 2015 1.43 (1.26, 1.61) 31.04
Sabina Illi 2001 4.51 (2.59, 7.85) 1.52
Merci M. H. Kusel 2007 3.90 (1.40, 10.50) 0.46
Per Nafstad 2005 2.10 (1.30, 3.00) 2.67
Carme Puig 2010 3.03 (1.39, 6.61) 0.77
Per Nafstad 2000 3.40 (2.30, 7.00) 1.51
Subtotal (I–squared = 83.7%, p = 0.000) 1.64 (1.46, 1.83) 37.95
American
Clare D. Ramsey 2006 1.74 (0.90, 3.35) 1.08
Daniel J. Jackson 2008 2.80 (1.60, 4.90) 1.50
Subtotal (I–squared = 15.0%, p = 0.278) 2.30 (1.50, 3.51) 2.58
Heterogeneity between groups: p = 0.024
Overall (I–squared = 80.3%, p = 0.000) 1.62 (1.52, 1.74) 100.00
.0952
1
10.5

Figure 3. Forest plot (random-effects model) of respiratory tract infection and childhood asthma: A. Study design; B. Geographic areas.

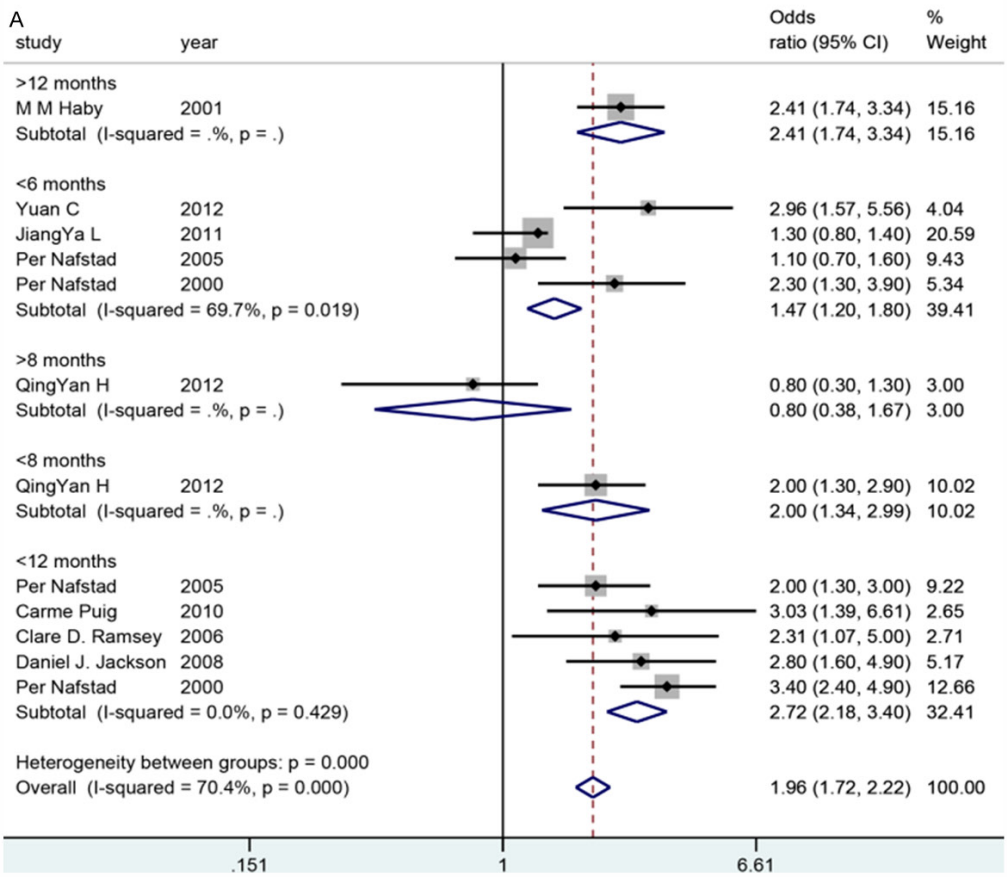
Table 2. A summary of OR for the overall and subgroup analyses of respiratory infection and asthma

		No. of studies	OR	95% CI	Heterogeneity (I^2)
Overall		13	1.62	1.52-1.74	0.80
Study design	Case-control	4	2.02	1.70-2.40	0.81
	Cohort	9	1.56	1.45-1.68	0.79
Geographic areas	Australia	1	2.41	1.74-3.34	0.00
	China	4	1.54	1.40-1.69	0.85
	Europe	6	1.64	1.46-1.83	0.84
	American	2	2.30	1.50-3.51	0.15
Age	<6 months	4	1.47	1.20-1.80	0.70
	<8 months	1	2.00	1.34-2.99	0.00
	<12 months	5	2.72	2.18-3.40	0.00
	<24 months	1	2.41	1.74-3.34	0.00
Virus	RSV	6	1.61	1.44-1.80	0.00
	HRV	3	2.88	1.79-4.64	0.00
	CV	1	1.97	0.75-5.19	0.00
	HSV	1	0.48	0.26-0.89	0.00
	MV	1	0.63	0.08-4.90	0.00

relation between the microbiome and respiratory diseases [2, 29-36] Emerging data suggest that the composition of the airway microbiome in early life is an important determinant of future asthma [37]. The current meta-analysis summarizes the results of cohort studies and case-control studies involving a total of 9172 patients. Our meta-analysis is based on published data and performed on different subgroups. To the best of our knowledge, this is the first meta-analysis to focus on the association between early-life respiratory infection and asthma. Our results indicate that the early-life respiratory infections are positively associated with asthma risk for different types of infection and different ages at onset of infection. Most children who have a history of asthma and impaired lung function at school age have a history of respiratory infection in early life [23, 25, 38]. It is hypothesized that if severe respiratory infection causes future asthma by inducing airway epithelial injury and promoting the appropriate proinflammatory allergenic milieu, a subsequent allergen exposure within a suitable time could result in allergic airway inflammation and asthma.

The experiments in mice demonstrated that the level of IgE in serum increased in the early stage of the germ-free mice, being about 3-4 weeks after birth, which coincided with the time of weaning. This shows that the immune response of the host is affected by the changes of microbiome in intestinal tract [5]. Meanwhile, the higher level of IgE is consistent with the increase of eosinophils in circulating blood which will release IL-4 to regulate the lung's NK cells and enhance the expression of CCL11, IL-5, IL-9 and IL-13. These cytokines will aggravate inflammation of airway [39, 40]. Another possible mechanism was demonstrated that when neonatal mice exposed to house dust mite (HDM) allergen after birth, Th2-type inflammation and airway hyper-responsiveness in mice were enhanced. With their airway microbiome matured, the bacterial burden increases and a community shift from predominance of Proteobacteria and Firmicutes to Bacteroidetes phyla and the response to HDM diminished [41].

In our study, we found that the risk of asthma is significantly and positively correlated with infections with some particular viruses (HRV, RSV). For HSV, we obtained the opposite result. Meanwhile, CV and MV were not significantly correlated with the risk of asthma. Much research has focused on the role of early-life RSV and HRV infections in asthma incidence. A recent prospective European study demonstrates the high risk of asthma following serious RSV infection among children at age 6, with an incidence of 21% compared with 5% in the control cohort [42]. However, when the common RSV infection is evaluated, the link between the virus and asthma is weakened and even becomes meaningless [9]. The number of respiratory tract infections (RTIs) in early life, but not the specific viral trigger, is associated with the development of asthma at school age [20]. In addition, in our study, RSV also shows


A
study
year
Odds ratio (95% CI)
% Weight
>12 months
M M Haby 2001 2.41 (1.74, 3.34) 15.16
Subtotal (I-squared = .%, p = .) 2.41 (1.74, 3.34) 15.16
<6 months
Yuan C 2012 2.96 (1.57, 5.56) 4.04
JiangYa L 2011 1.30 (0.80, 1.40) 20.59
Per Nafstad 2005 1.10 (0.70, 1.60) 9.43
Per Nafstad 2000 2.30 (1.30, 3.90) 5.34
Subtotal (I-squared = 69.7%, p = 0.019) 1.47 (1.20, 1.80) 39.41
>8 months
QingYan H 2012 0.80 (0.30, 1.30) 3.00
Subtotal (I-squared = .%, p = .) 0.80 (0.38, 1.67) 3.00
<8 months
QingYan H 2012 2.00 (1.30, 2.90) 10.02
Subtotal (I-squared = .%, p = .) 2.00 (1.34, 2.99) 10.02
<12 months
Per Nafstad 2005 2.00 (1.30, 3.00) 9.22
Carme Puig 2010 3.03 (1.39, 6.61) 2.65
Clare D. Ramsey 2006 2.31 (1.07, 5.00) 2.71
Daniel J. Jackson 2008 2.80 (1.60, 4.90) 5.17
Per Nafstad 2000 3.40 (2.40, 4.90) 12.66
Subtotal (I-squared = 0.0%, p = 0.429) 2.72 (2.18, 3.40) 32.41
Heterogeneity between groups: p = 0.000
Overall (I-squared = 70.4%, p = 0.000) 1.96 (1.72, 2.22) 100.00
.151
1
6.61

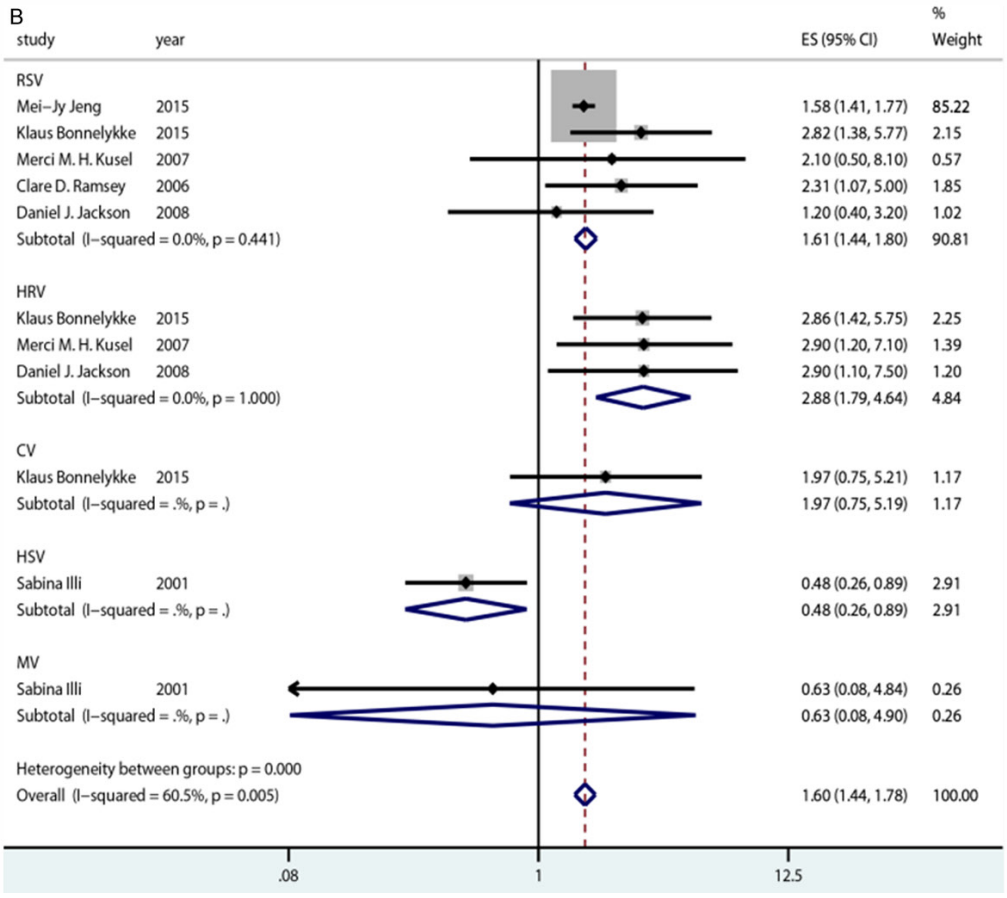

B
study
year
ES (95% CI)
% Weight
RSV
Mei-Jy Jeng 2015 1.58 (1.41, 1.77) 85.22
Klaus Bonnelykke 2015 2.82 (1.38, 5.77) 2.15
Merci M. H. Kusel 2007 2.10 (0.50, 8.10) 0.57
Clare D. Ramsey 2006 2.31 (1.07, 5.00) 1.85
Daniel J. Jackson 2008 1.20 (0.40, 3.20) 1.02
Subtotal (I-squared = 0.0%, p = 0.441) 1.61 (1.44, 1.80) 90.81
HRV
Klaus Bonnelykke 2015 2.86 (1.42, 5.75) 2.25
Merci M. H. Kusel 2007 2.90 (1.20, 7.10) 1.39
Daniel J. Jackson 2008 2.90 (1.10, 7.50) 1.20
Subtotal (I-squared = 0.0%, p = 1.000) 2.88 (1.79, 4.64) 4.84
CV
Klaus Bonnelykke 2015 1.97 (0.75, 5.21) 1.17
Subtotal (I-squared = .%, p = .) 1.97 (0.75, 5.19) 1.17
HSV
Sabina Illi 2001 0.48 (0.26, 0.89) 2.91
Subtotal (I-squared = .%, p = .) 0.48 (0.26, 0.89) 2.91
MV
Sabina Illi 2001 0.63 (0.08, 4.84) 0.26
Subtotal (I-squared = .%, p = .) 0.63 (0.08, 4.90) 0.26
Heterogeneity between groups: p = 0.000
Overall (I-squared = 60.5%, p = 0.005) 1.60 (1.44, 1.78) 100.00
.08
1
12.5

Figure 4. Forest plot (random-effects model) of respiratory tract infection and childhood asthma: A. Age; B. Virus.

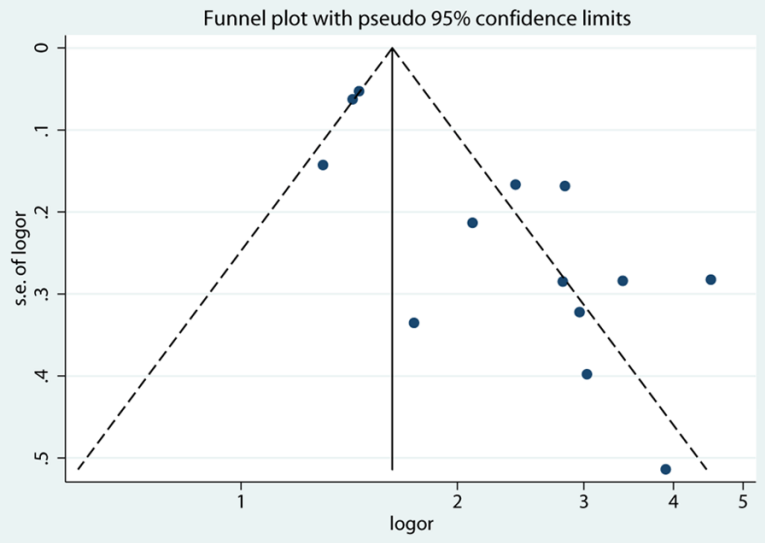


Figure 5. Funnel plot designed to visualize a potential publication bias on odds ratio of all studies.

a strong positive correlation with asthma. Early-life HRV-associated lower respiratory tract infections (LRTIs) are a significant predictor of asthma at age 6 [23] and of pulmonary function impairment at age 5-8 [43]. Moreover, the highest risk for future asthma was detected among children with genetic variants in an asthma-associated gene locus on chromosome 17 (17q21) who experienced early-life HRV-associated lower respiratory tract infections (LRTIs) [43]. By synthesizing all previous studies, we further confirm the association of asthma with RSV and HRV. Studies about the relationship among HSV, CV, MV and asthma are still rare. Besides, the relationship among them is controversial [44, 45]. And there are only two cohort studies of these viruses in our meta-analysis. We did not have enough evidence to demonstrate the role of HSV, CV and MV in asthma.

Clarifying whether early respiratory tract infection is a risk factor for asthma is important for the prevention of asthma. This meta-analysis synthesizes all relevant studies to show that early-life respiratory infections (within 24 months) are significantly associated with asthma and will increase the risk of asthma. Given the strong associations between early-life respiratory infection and subsequent asthma, asthma risk may be reduced through strategies that either prevent the development of earlylife respiratory infections or attenuate the severity of infection and the consequences of the immune response to the pathogen.

Limitations

This study has some limitations. First, only case control studies and cohort studies, but not randomized controlled trials (RCTs), are included here. Four of the 13 included studies were conducted to analyze the potential confounding factors of all experimental groups, including gender, breastfeeding, and women's childbearing age. For the main confounding factors, such as exposure to tobacco, parental history of asthma, and history of pet feeding, only 3 cohort studies were performed with multi-factor analysis. We only obtained a portion of the experimental data from the original texts. As a result, we are unable to obtain information regarding the main confounding factors for most of the studies. Thus, the results of this meta-analysis should be used with caution by considering the impact of confounding factors. Despite the performance of stratified analysis in some studies, the factors of stratification are different and the data are not complete, so these studies could not be included in the subgroup analysis. Therefore, we used a random effect model to merge these studies to further reduce the errors caused by statistics. Finally, the significant heterogeneity and possible publication bias of these studies must be considered. There is a large degree of heterogeneity ($P<0.01$, $I^2=79.8$). However, the removal of individual studies did not affect the final results after sensitivity analysis, suggesting that the results of the analysis are robust. To further explain the source of heterogeneity, we performed a series of subgroup analyses of these studies. The heterogeneity was reduced after subgroup analysis of different viruses and study design. We tested the publication bias in the included articles. Egger's test showed publication bias ($P<0.1$), But there

was no obvious asymmetry in the funnel plots after modification with trim and fill method, which suggesting no publication bias.

Conclusions

Overall, respiratory tract infection in early life is associated with asthma, and there is an increased risk of asthma in children who have respiratory tract infections in early life. Nevertheless, the incidence of asthma is also related to age, gender, genetic history of asthma, and exposure to tobacco. However, given the limitations mentioned above, these findings should be treated with caution when applied to clinical practice. More prospective cohort studies with large samples are needed to further demonstrate the association between early-life respiratory infection and the risk of asthma.

Acknowledgements

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Disclosure of conflict of interest

None.

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