**Name of Journal:** *World Journal of Critical Care Medicine*

**Manuscript NO:** 73694

**Manuscript Type:** META-ANALYSIS

**Association between early viral lower respiratory tract infections and subsequent asthma development**

Kenmoe S *et al*. Post-LRTI asthma

Sebastien Kenmoe, Etienne Atenguena Okobalemba, Guy Roussel Takuissu, Jean Thierry Ebogo-Belobo, Martin Gael Oyono, Jeannette Nina Magoudjou-Pekam, Ginette Irma Kame-Ngasse, Jean Bosco Taya-Fokou, Chris Andre Mbongue Mikangue, Raoul Kenfack-Momo, Donatien Serge Mbaga, Arnol Bowo-Ngandji, Cyprien Kengne-Ndé, Seraphine Nkie Esemu, Richard Njouom, Lucy Ndip

**Sebastien Kenmoe, Seraphine Nkie Esemu, Lucy Ndip,** Department of Microbiology and Parasitology, University of Buea, Buea 00237, Cameroon

**Sebastien Kenmoe, Richard Njouom,** Department of Virology, Centre Pasteur of Cameroon, Yaounde 00237, Cameroon

**Etienne Atenguena Okobalemba,** Faculty of Medicine and Biomedical Science, The University of Yaounde I, Yaounde 00237, Cameroon

**Guy Roussel Takuissu,** Centre of Research in Food, Food Security and Nutrition, Institute of Medical Research and Medicinal Plants Studies, Yaounde 00237, Cameroon

**Jean Thierry Ebogo-Belobo, Ginette Irma Kame-Ngasse,** Medical Research Centre, Institute of Medical Research and Medicinal Plants Studies, Yaounde 00237, Cameroon

**Martin Gael Oyono,** Laboratory of Parasitology and Ecology, The University of Yaounde I, Yaounde 00237, Cameroon

**Jeannette Nina Magoudjou-Pekam, Raoul Kenfack-Momo,** Department of Biochemistry, The University of Yaounde I, Yaounde 00237, Cameroon

**Jean Bosco Taya-Fokou, Chris Andre Mbongue Mikangue, Donatien Serge Mbaga, Arnol Bowo-Ngandji,** Department of Microbiology, The University of Yaounde I, Yaounde 00237, Cameroon

**Cyprien Kengne-Ndé,** Epidemiological Surveillance, Evaluation and Research Unit, National Aids Control Committee, Douala 00237, Cameroon

**Author contributions:** Kenmoe S, Ndip L, and Njouom R were responsible for conception and design of the study as well as project administration; Kenmoe S, Atenguena Okobalemba E, Takuissu GR, Ebogo-Belobo JT, Oyono MG, Magoudjou-Pekam JN, Kame-Ngasse GI, Taya-Fokou JB, Mbongue Mikangue CA, Kenfack-Momo R, Fall A, Mbaga DS, Bowo-Ngandji A, Kengne-Nde C, and Esemu SN were responsible for the data curation and interpretation of results; Kengne-Nde C and Kenmoe S were responsible for statistical analysis; Kenmoe S, Ndip L, and Njouom R were responsible for the project supervision; Kenmoe S wrote the original draft; All authors critically reviewed the first draft and approved the final version of the paper for submission and have read and approved the final manuscript.

**Supported by** the European Union (EDCTP2 Programme), No. TMA2019PF-2705.

**Corresponding author: Sebastien Kenmoe, PhD, Assistant Lecturer,** Department of Microbiology and Parasitology, University of Buea, Molyko to Buea Town Rd, Buea 00237, Cameroon. sebastien.kenmoe@ubuea.cm

**Received:** November 30, 2021

**Revised:** April 25, 2022

**Accepted:** **June 16, 2022**

**Published online:**

**Abstract**

BACKGROUND

The association between hospitalization for human respiratory syncytial virus (HRSV) bronchiolitis in early childhood and subsequent asthma is well established. The long-term prognosis for non-bronchiolitis lower respiratory tract infections (LRTI) caused by viruses different from HRSV and rhinovirus, on the other hand, has received less interest.

AIM

To investigate the relationship between infant LRTI and later asthma and examine the influence of confounding factors.

METHODS

The PubMed and Global Index Medicus bibliographic databases were used to search for articles published up to October 2021 for this systematic review. We included cohort studies comparing the incidence of asthma between patients with and without LRTI at ≤ 2 years regardless of the virus responsible. The meta-analysis was performed using the random effects model. Sources of heterogeneity were assessed by stratified analyses.

RESULTS

This review included 15 articles (18 unique studies) that met the inclusion criteria. LRTIs at ≤ 2 years were associated with an increased risk of subsequent asthma up to 20 years [odds ratio (OR) = 5.0, 95%CI: 3.3-7.5], with doctor-diagnosed asthma (OR = 5.3, 95%CI: 3.3-8.6), current asthma (OR = 5.4, 95%CI: 2.7-10.6), and current medication for asthma (OR = 1.2, 95%CI: 0.7-3.9). Our overall estimates were not affected by publication bias (*P* = 0.671), but there was significant heterogeneity [*I*2 = 58.8% (30.6-75.5)]. Compared to studies with hospitalized controls without LRTI, those with ambulatory controls had a significantly higher strength of association between LRTIs and subsequent asthma. The strength of the association between LRTIs and later asthma varied significantly by country and age at the time of the interview. The sensitivity analyses including only studies with similar proportions of confounding factors (gender, age at LRTI development, age at interview, gestational age, birth weight, weight, height, smoking exposure, crowding, family history of atopy, and family history of asthma) between cases and controls did not alter the overall estimates.

CONCLUSION

Regardless of the causative virus and confounding factors, viral LRTIs in children < 2 years are associated with an increased risk of developing a subsequent asthma. Parents and pediatricians should be informed of this risk.

**Key Words:** Asthma; Lower respiratory tract infections; Respiratory viruses; Long term sequelae; Children

Kenmoe S, Atenguena Okobalemba E, Takuissu GR, Ebogo-Belobo JT, Oyono MG, Magoudjou-Pekam JN, Kame-Ngasse GI, Taya-Fokou JB, Mbongue Mikangue CA, Kenfack-Momo R, Mbaga DS, Bowo-Ngandji A, Kengne-Ndé C, Esemu SN, Njouom R, Ndip L. Association between early viral lower respiratory tract infections and subsequent asthma development. *World J Crit Care Med* 2022; In press

**Core Tip:** The results of this meta-analysis confirmed that viral lower respiratory tract infections (LRTIs) in children < 2 years increase the risk of developing asthma later until the age of 20 years. This indicates that pediatricians and parents should be vigilant with anticipating asthma preventive measures in children with viral LRTIs in childhood.

**INTRODUCTION**

Asthma is a major contributor to the burden of non-communicable diseases and the most common chronic respiratory disease in the world[1]. The prevalence of asthma has increased by 12.6% in 25 years (1990-2015), and asthma causes the deaths of nearly half a million people each year[1]. Asthma also represents a considerable financial burden and costs about 19 billion Euros per year in Europe[2].

Multiple factors have been involved in the development of asthma. There is evidence that respiratory viruses, particularly human respiratory syncytial virus (HRSV)[3-7], human metapneumovirus[7-12], or rhinovirus (RV)[12-22] (including mostly the recently described RV-C), were triggers for asthma and asthma exacerbation. The data also show that air pollutants were involved in the risk of developing asthma[23].

In addition, many studies have historically suggested that neonatal bronchiolitis due to HRSV, and RV recently, is a predisposing factor for asthma development later[3,5,10,24-39]. However, the involvement of other common respiratory viruses (influenza, human coronavirus, human parainfluenza virus) and non-bronchiolitis lower respiratory tract infections (LRTI) in the subsequent risk of developing asthma has not been synthesized to date.

Conflicting findings have been reported regarding the synergistic effect of early-life bronchiolitis and personal or family history of atopic sensitization or asthma, gender, maternal smoking in the onset of asthma later[6,34,40–53]. Some authors have suggested that bronchiolitis identifies children prone to developing asthma during adolescence[26,54-59]. Therefore, the causal role of early-onset bronchiolitis and the mechanisms underlying the development of subsequent asthma remain to be clarified[3,60].

Preventing or stopping the development of predictive factors would be a possible strategy for preventing asthma[61-63]. This systematic review was conducted to describe the risk of developing asthma following viral LRTI in childhood and associated factors. Our secondary objective was to evaluate the role of confounding factors of the association of neonatal LRTI and asthma during childhood using sensitivity analyses.

**MATERIALS AND METHODS**

***Study design***

We registered the protocol of this systematic review in the PROSPERO with access number CRD42018116955. This review has been done in accordance with the Centre for Reviews and Dissemination guidelines[64] and presented in accordance with the PRISMA declaration[65] (Supplementary Table 1).

***Inclusion and exclusion criteria***

We included cohort studies comparing the long-term asthmatic sequelae of children with and without a history of viral LRTI in childhood. The PICOs in this study were: P, children and adults of all genders with a history of viral LRTI in childhood regardless of the virus responsible; I, LRTI at ≤ 2 years; C, children and adults of all genders with no history of viral LRTI in childhood; O, the main outcome was asthma as the long-term sequelae of LRTI in infancy. This study had no temporal, geographic, or linguistic limitations. We excluded irrelevant studies, case reports, cross-sectional studies, comments, reviews, and editorials, studies that did not report outcome of interest, articles that we did not have access to full text, studies without control groups, and studies including only high-risk subjects.

***Case definition***

The definitions of LRTI have been adapted as described by the authors of the primary studies. Asthma has been defined by three or more episodes of bronchial obstruction. We did not take into account the differentiation of atopic asthma. In this systematic review, several categories of asthma definitions were considered, including: (1) Current doctor-diagnosed asthma; (2) Current self-reported asthma; (3) Current asthma; (4) Asthma in the last 12 mo; and (5) Asthma ever. The warning signs of asthma were considered: (1) Cough; (2) Night cough; and (3) Prolonged cough. The use of anti-asthma treatment was also taken into account: (1) Current medication for asthma; (2) Use of bronchodilators; and (3) Use of inhaled steroid. When a study had multiple defined asthma phenotypes for the same participants, we selected the phenotype according to the order of priority of asthma diagnosed by a doctor, most recent asthma, treatment for asthma, and asthma symptoms.

***Search strategy***

We searched for relevant articles in PubMed and Global Index Medicus until October 24, 2021. The search keywords are described in Supplementary Table 2. We conducted an additional manual search using Reference Citation Analysis (https://www.referencecitationanalysis.com/) by reviewing the list of references for included articles and relevant reviews on the subject.

***Study selection***

We (JTEB and SK) have individually reviewed the titles and abstracts of the articles identified through the electronic search in the Rayyan website[66]. We evaluated the complete texts of the eligible articles after screening titles and abstracts. These two authors discussed disagreement about the inclusion or exclusion of an article to reach consent.

***Data extraction***

Two authors (JETB and SK) independently extracted all relevant data and entered into a standardized questionnaire. The disagreements were resolved by discussion between the two investigators and consultation of a third author if an agreement could not be reached (AF). The standardized questionnaire included: (1) Title; (2) First author; (3) Year of publication; (4) Time of data collection; (5) Country; (6) Participants interview period; (7) LRTI type; (8) LRTI rank; (9) LRTI period; (10) Age at LRTI; (11) Type of infection associated with the LRTI; (12) Control age; (13) Control gender; (14) Total number of cases and controls; and (15) Numbers with asthma at follow-up and numbers of confounders in case and control groups.

***Risk of bias assessment***

We (JETB and SK) independently assessed the quality of publications using the Newcastle-Ottawa scale[67]. We assessed several potential sources of bias including patient selection in the study, comparability of groups, and outcome evaluation (Supplementary Table 3). We rated the studies as “low risk of bias” and “high risk of bias” for scores of 6-9 and 0-5, respectively.

***Statistical******analysis***

Odds ratio (OR) was used as a measure of the association between bronchiolitis potential risk factors and bronchiolitis long-term respiratory sequelae. The heterogeneity was evaluated by visual inspection of the funnel diagram, the Q test, and the *I*² statistic[68,69]. Heterogeneity between studies was considered significant for values of *P* < 0.1 and *I*² > 50%. The impact of the quality of the selected studies was evaluated by a sensitivity analysis omitting high risk of bias studies. Subgroup analysis was performed on the basis of the sampling approach, the countries, the age at LRTI development, the age at interview, the hospitalization status of the controls, the viruses responsible for LRTI, the type of LRTI, and the phenotype of asthma. Sensitivity analysis including only studies with the confounding factor proportions similar between cases and controls were carried out as described previously[70].

**RESULTS**

***Overview of included studies***

As shown in Figure 1, 875 articles were found in PubMed and Global Index Medicus. A total of 733 publications were excluded after selection according to titles and abstracts. Of the remaining 162 articles, 147 articles were eliminated for multiple reasons (no LRTI negative group, no data on asthma, wrong study design, not viral laboratory confirmed LRTI, and not LRTI, Supplementary Table 4). Based on the inclusion criteria, 15 comparative publications (18 unique studies) were finally selected for this systematic review[71–85].

***Study characteristics***

The characteristics and risk of bias of the 18 unique studies are summarized in Supplementary Tables 5-7. All studies were published from 1982 to 2018 and were conducted on children and adults between < 9 mo and 20 years of age. LRTIs were dominated by bronchiolitis (83.3%) and were recorded between 1967 and 2005. The authors of 61.1% of the studies reported that children had their first episode of LRTI and all children with LRTI were hospitalized. The majority of children recruited in the studies were < 2 years or < 1 year at the time of the LRTI in childhood (88.9%). Most studies presented a low risk of bias (77.8%) and were conducted in Europe (88.9%) with prospective follow-up (94.4%) of children included. All included articles were written in English and from high-income countries. The virus mainly reported in the studies was HRSV (83.3%).

***Overall prevalence and sensitivity analysis of asthma in the LRTI group and controls***

Compared to controls, most children in the LRTI group had subsequent asthma [OR = 5.0, 95%CI: 3.3-7.5], including doctor-diagnosed asthma (OR = 5.3, 95%CI: 3.3-8.6), current asthma (OR = 5.4, 95%CI: 2.7-10.6), and current medication for asthma (OR = 1.2, 95%CI: 0.7-3.9) (Figure 2). Sensitivity analyses including studies based on the first episode of LRTI (OR = 4.6, 95%CI: 2.6-8.1), doctor-diagnosed asthma (OR = 5.3, 95%CI: 3.3-8.6), and studies with low risk of bias (OR = 4.5, 95%CI: 2.9-7.2) showed conclusions consistent with overall analyses (Table 1). For the studies that reported confounding factors, we illustrated the definitions in Supplementary Tables 8 and 9. Qualitative confounders included gender, preterm birth, smoking exposure, crowding, family history of atopy, and family history of asthma. Quantitative confounders included age at LRTI development, age at interview, birth weight, gestational age, number of siblings, weight, and height. The association between LRTI and subsequent asthma was also maintained in all sensitivity analyses including more than two studies with confounding factor proportions similar between cases and controls, notably for male gender, weight, height, age, presence of pets in the home, family history of atopy, family history of asthma, and exposure to smoke.

***Subgroup analysis***

The subgroup analyses are displayed in Supplementary Table 10. The strength of the association between LRTI and asthma was significantly stronger for studies with probabilistic than non-probabilistic recruitment [OR = 4.5 (3.0-6.8) *vs* OR = 12.5 (4.9-31.9), *P* = 0.048]. The strength of association between LRTI and subsequent asthma also varied significantly among countries (*P* < 0.001). Age at follow-up was related to the strength of the association between LRTI in childhood and the development of asthma later (*P* = 0.005). The association of asthma with LRTI in childhood was higher in studies with hospitalized controls (OR = 14.2, 95%CI: 6.7-30.1) compared to studies with ambulatory controls (OR = 3.9, 95%CI: 2.3-6.6) and was statistically significant (*P* = 0.006). Other parameters including the age of LRTI development, the virus detected in children with LRTI, the type of LRTI, and the phenotype of asthma did not significantly influence the strength of the association between LRTI and subsequent asthma.

***Heterogeneity and publication bias***

Using visual inspection, the asymmetry distribution of the funnel graph was used to check for publication bias. We observed no publication bias by the funnel graph (Supplementary Figure 1). The *P* = 0.671 of the Egger regression test also indicated an absence of publication bias. We recorded a substantial heterogeneity [*I*2 = 58.8 (30.6-75.5)] in the overall estimates (Table 1).

**DISCUSSION**

We have two main results in this meta-analysis: (1) By taking into account multiple confounding factors including gender, age at LRTI development, age at interview, gestational age, birth weight, weight, height, smoking exposure, overcrowding, and family history of atopy/asthma, this meta-analysis suggests that LRTI due to several viruses in children < 2 years is significantly associated with an increased risk of asthma up to 20 years later; and (2) This increased risk of developing asthma was present regardless of the virus detected in LRTI and the type of LRTI.

Our findings are correlated with similar systematic reviews previously conducted[44,86-89]. Kneyber *et al*[44] reported in a quantitative analysis in 2001 the increased risk of asthma in hospitalized children for bronchiolitis episodes due to HRSV at less than 1 year compared to controls. The systematic review by Pérez-Yarza *et al*[88] analyzed 8 published studies from 1985 to 2006 and found a positive association between HRSV respiratory infections at less than 3 years of age and the risk of subsequent physician-diagnosed asthma development. Régnier *et al*[89] in 2013 showed in a review of 15 studies published from 1977 to 2012 that hospitalizations with HRSV at less than 3 years were correlated significantly with a risk of developing a parent or physician-diagnosed asthma in the 12 mo preceding follow-up. Fauroux *et al*[86], in a systematic review without meta-analysis conducted in 2017 on studies published between 1995 and 2015 and conducted in Western countries, also reported increased risk of developing asthma following hospitalizations due to severe HRSV LRTI registered at less than 3 years. Liu *et al*[87] also reported in 2017 in a review of 15 studies published between 1988 and 2017 that wheezing due to RV predisposed children at high risk of asthma later[87]. In this study, the definitions of asthma were prioritized in order of decreasing priority: doctor-diagnosed asthma *vs* parent-diagnosed asthma and current asthma *vs* asthma during the previous year *vs* asthma at any time.

In a review published by Edmond *et al*[90] in 2012, no association was observed between childhood pneumonia and the development of subsequent asthma. Most studies on the association between viral LRTIs and the subsequent development of asthma have focused primarily on bronchiolitis such as LRTI. Early studies show that HRSV infections were associated with increased risk of asthma[44,86,88,89]. In this systematic review, regardless of the virus responsible for bronchiolitis in childhood, the association remained with asthma later. The risk was higher in non-HRSV viruses and more specifically in human metapneumovirus and RV, suggesting that the development of asthma after bronchiolitis in childhood is not different depending on the type of virus detected in the LRTI. This result is consistent with the meta-analysis of Liu *et al*[87], who had shown that childhood RV infections predisposed to the risk of developing asthma later. The systematic review by Fauroux *et al*[86] found that infections with non-HRSV respiratory viruses (influenza A, human bocavirus, human parainfluenza virus-3, human adenovirus, human metapneumovirus, and unknown etiology) were associated with a higher risk of subsequent asthma than HRSV.

The attribution of the causal role of preschool or adult asthma to bronchiolitis remains a subject of debate[91]. Several other factors such as female sex, passive smoking, overweight, low weight at birth, premature birth, or family history of atopy have been proposed as factors associated with asthma at school age[24,92-97]. Breastfeeding was also reported as a protective factor against asthma as a result of bronchiolitis in childhood[58,98]. These multiple other risk factors could interact additively with bronchiolitis to promote the development of asthma[45]. This meta-analysis appropriately assessed for the first time the confounders of the relationship between bronchiolitis in childhood and asthma later. This meta-analysis revealed that bronchiolitis is independently associated with subsequent asthma.

In this systematic review, we followed a rigorous methodology according to the PRISMA guidelines and applied a very sensitive research strategy accompanied by a very intensive manual search. We carefully collected and shared the individual data from the included studies and gave the individual reasons for exclusion of all articles examined entirely. We have explored and explained almost all sources of heterogeneity. The multiple sensitivity analyses gave consistent results with the overall results.

However, some methodological weaknesses must be considered in interpreting the results of this study and in future research on the subject. First, some subgroup analyses were probably limited by the small number of studies, particularly the non-bronchiolitis and non-HRSV studies. Apart from these areas eligible for improvement, future work should focus on assessing the sequelae of non-bronchiolitis LRTI with non-HRSV etiology, particularly in low income countries (Africa and Southeast Asia) where the data suggested that asthma could be associated with a significant burden[99]. Another potential limitation of this review would be the absence of data in the included studies concerning the type of asthma observed, which could be allergic asthma or not.

**CONCLUSION**

In conclusion, the current meta-analysis has shown that viral LRTI at ≤ 2 years, independently of the detected virus, is a predictive factor of asthma sequelae up to the age of 20. Health care workers and parents should be aware of these findings when managing viral LRTI in childhood.

**ARTICLE HIGHLIGHTS**

***Research background***

We performed a literature search in PubMed and Global Index Medicus in December 2019 using keywords covering low respiratory tract infections AND common respiratory viruses AND asthma. The results of our research depicted in original articles, narrative reviews, and systematic reviews suggesting that human respiratory syncytial virus (HRSV) and rhinovirus (RV) bronchiolitis in childhood are associated with an increased risk of asthma later. This research also identified conflicting data on the influence of confounding factors on the high risk of developing asthma after bronchiolitis in childhood. It has also emerged from this research that the involvement of lower respiratory tract infections (LRTI) other than bronchiolitis and respiratory viruses other than HRSV and RV in the subsequent risk of asthma remains hypothetical to date.

***Research motivation***

Taking into account confounding factors, the influence of respiratory infections other than bronchiolitis in childhood and respiratory viruses other than HRSV and RV should be weighed against the risk of developing subsequent asthma.

***Research objectives***

This study was conducted to assess the influence of viral LRTI at < 2 years on the risk of subsequent asthma development.

***Research methods***

This meta-analysis included cohort studies with viral LRTI at < 2 years as exposure and asthma as outcome. R software version 4.1.0 was used to calculate the odds ratios and their 95%CI using a random-effects model.

***Research results***

This study included 15 articles and demonstrated the implications of childhood viral LRTI in the risk of subsequent asthma development up to the age of 20 (odds ratio = 5.0, 95%CI: 3.3-7.5). This risk of developing asthma was not influenced in sensitivity analyses including only confounding factors with similar proportions between exposed and unexposed. The estimates were not affected by publication bias, but there was significant heterogeneity.

***Research conclusions***

Childhood viral LRTIs, primarily HRSV bronchiolitis, are significantly associated with a risk of developing asthma later in life.

***Research perspectives***

To curb the heavy burden of asthma in patients of all ages, we hope that the results of this review will encourage the implementation of a sensitization program for this association of viral LRTI in childhood and the subsequent asthma risk. Interventional studies are needed to involve the causality relationship between neonatal viral LRTI and the subsequent risk of asthma.

**REFERENCES**

1 **GBD 2015 Chronic Respiratory Disease Collaborators**. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Respir Med* 2017; **5**: 691-706 [PMID: 28822787 DOI: 10.1016/S2213-2600(17)30293-X]

2 **Domínguez-Ortega J**, Phillips-Anglés E, Barranco P, Quirce S. Cost-effectiveness of asthma therapy: a comprehensive review. *J Asthma* 2015; **52**: 529-537 [PMID: 25539023 DOI: 10.3109/02770903.2014.999283]

3 **Bartlett NW**, McLean GR, Chang YS, Johnston SL. Genetics and epidemiology: asthma and infection. *Curr Opin Allergy Clin Immunol* 2009; **9**: 395-400 [PMID: 19644362 DOI: 10.1097/ACI.0b013e32833066fa]

4 **Brunetti L**, Colazzo D, Francavilla R, Tesse R, De Sario V, Lorè M, Armenio L. The role of pulmonary infection in pediatric asthma. *Allergy Asthma Proc* 2007; **28**: 190-193 [PMID: 17479603 DOI: 10.2500/aap.2007.28.2964]

5 **Busse WW**, Lemanske RF Jr, Gern JE. Role of viral respiratory infections in asthma and asthma exacerbations. *Lancet* 2010; **376**: 826-834 [PMID: 20816549 DOI: 10.1016/S0140-6736(10)61380-3]

6 **Emuzyte R**, Firantiene R, Petraityte R, Sasnauskas K. Human rhinoviruses, allergy, and asthma: a clinical approach. *Medicina (Kaunas)* 2009; **45**: 839-847 [PMID: 20051716]

7 **Gavala ML**, Bertics PJ, Gern JE. Rhinoviruses, allergic inflammation, and asthma. *Immunol Rev* 2011; **242**: 69-90 [PMID: 21682739 DOI: 10.1111/j.1600-065X.2011.01031.x]

8 **Gern JE**. Rhinovirus and the initiation of asthma. *Curr Opin Allergy Clin Immunol* 2009; **9**: 73-78 [PMID: 19532096 DOI: 10.1097/ACI.0b013e32831f8f1b]

9 **Heymann PW**, Platts-Mills TA, Johnston SL. Role of viral infections, atopy and antiviral immunity in the etiology of wheezing exacerbations among children and young adults. *Pediatr Infect Dis J* 2005; **24**: S217-S222, discussion S220-discussion S221 [PMID: 16378049 DOI: 10.1097/01.inf.0000188164.33856.f9]

10 **Jackson DJ**. The role of rhinovirus infections in the development of early childhood asthma. *Curr Opin Allergy Clin Immunol* 2010; **10**: 133-138 [PMID: 19996738 DOI: 10.1097/ACI.0b013e3283352f7c]

11 **Kalina WV**, Gershwin LJ. Progress in defining the role of RSV in allergy and asthma: from clinical observations to animal models. *Clin Dev Immunol* 2004; **11**: 113-119 [PMID: 15330446 DOI: 10.1080/10446670410001722131]

12 **Kumar A**, Grayson MH. The role of viruses in the development and exacerbation of atopic disease. *Ann Allergy Asthma Immunol* 2009; **103**: 181-6; quiz 186-7, 219 [PMID: 19788013 DOI: 10.1016/S1081-1206(10)60178-0]

13 **Garcia-Garcia ML**, Calvo Rey C, Del Rosal Rabes T. Pediatric Asthma and Viral Infection. *Arch Bronconeumol* 2016; **52**: 269-273 [PMID: 26766408 DOI: 10.1016/j.arbres.2015.11.008]

14 **Message SD**, Johnston SL. Viruses in asthma. *Br Med Bull* 2002; **61**: 29-43 [PMID: 11997297 DOI: 10.1093/bmb/61.1.29]

15 **Miller EK**, Mackay IM. From sneeze to wheeze: what we know about rhinovirus Cs. *J Clin Virol* 2013; **57**: 291-299 [PMID: 23714395 DOI: 10.1016/j.jcv.2013.04.015]

16 **Papadopoulos NG**, Kalobatsou A. Respiratory viruses in childhood asthma. *Curr Opin Allergy Clin Immunol* 2007; **7**: 91-95 [PMID: 17218817 DOI: 10.1097/ACI.0b013e328013d501]

17 **Piedimonte G**. Respiratory syncytial virus and asthma: speed-dating or long-term relationship? *Curr Opin Pediatr* 2013; **25**: 344-349 [PMID: 23657245 DOI: 10.1097/MOP.0b013e328360bd2e]

18 **Proud D**. Role of rhinovirus infections in asthma. *Asian Pac J Allergy Immunol* 2011; **29**: 201-208 [PMID: 22053589]

19 **Rossi GA**, Colin AA. Infantile respiratory syncytial virus and human rhinovirus infections: respective role in inception and persistence of wheezing. *Eur Respir J* 2015; **45**: 774-789 [PMID: 25359340 DOI: 10.1183/09031936.00062714]

20 **Singh AM**, Moore PE, Gern JE, Lemanske RF Jr, Hartert TV. Bronchiolitis to asthma: a review and call for studies of gene-virus interactions in asthma causation. *Am J Respir Crit Care Med* 2007; **175**: 108-119 [PMID: 17053206 DOI: 10.1164/rccm.200603-435PP]

21 **Song DJ**. Rhinovirus and childhood asthma: an update. *Korean J Pediatr* 2016; **59**: 432-439 [PMID: 27895690 DOI: 10.3345/kjp.2016.59.11.432]

22 **Tan WC**. Viruses in asthma exacerbations. *Curr Opin Pulm Med* 2005; **11**: 21-26 [PMID: 15591884 DOI: 10.1097/01.mcp.0000146781.11092.0d]

23 **Arruda LK**, Solé D, Baena-Cagnani CE, Naspitz CK. Risk factors for asthma and atopy. *Curr Opin Allergy Clin Immunol* 2005; **5**: 153-159 [PMID: 15764906 DOI: 10.1097/01.all.0000162308.89857.6c]

24 **Goksör E**, Amark M, Alm B, Gustafsson PM, Wennergren G. Asthma symptoms in early childhood--what happens then? *Acta Paediatr* 2006; **95**: 471-478 [PMID: 16720497 DOI: 10.1080/08035250500499440]

25 **Henry RL**, Hodges IG, Milner AD, Stokes GM. Respiratory problems 2 years after acute bronchiolitis in infancy. *Arch Dis Child* 1983; **58**: 713-716 [PMID: 6625633 DOI: 10.1136/adc.58.9.713]

26 **Hyvärinen M**, Piippo-Savolainen E, Korhonen K, Korppi M. Teenage asthma after severe infantile bronchiolitis or pneumonia. *Acta Paediatr* 2005; **94**: 1378-1383 [PMID: 16263629 DOI: 10.1080/08035250510046812]

27 **Hyvärinen MK**, Kotaniemi-Syrjänen A, Reijonen TM, Korhonen K, Korppi MO. Teenage asthma after severe early childhood wheezing: an 11-year prospective follow-up. *Pediatr Pulmonol* 2005; **40**: 316-323 [PMID: 16082689 DOI: 10.1002/ppul.20273]

28 **Jartti T**, Korppi M. Rhinovirus-induced bronchiolitis and asthma development. *Pediatr Allergy Immunol* 2011; **22**: 350-355 [PMID: 21535176 DOI: 10.1111/j.1399-3038.2011.01170.x]

29 **Koponen P**, Helminen M, Paassilta M, Luukkaala T, Korppi M. Preschool asthma after bronchiolitis in infancy. *Eur Respir J* 2012; **39**: 76-80 [PMID: 21700604 DOI: 10.1183/09031936.00040211]

30 **Korppi M**, Reijonen T, Pöysä L, Juntunen-Backman K. A 2- to 3-year outcome after bronchiolitis. *Am J Dis Child* 1993; **147**: 628-631 [PMID: 8506829 DOI: 10.1001/archpedi.1993.02160300034017]

31 **Kotaniemi-Syrjänen A**, Reijonen TM, Korhonen K, Korppi M. Wheezing requiring hospitalization in early childhood: predictive factors for asthma in a six-year follow-up. *Pediatr Allergy Immunol* 2002; **13**: 418-425 [PMID: 12485317 DOI: 10.1034/j.1399-3038.2002.02091.x]

32 **Lauhkonen E**, Koponen P, Nuolivirta K, Paassilta M, Toikka J, Korppi M. Lung function by impulse oscillometry at age 5-7 years after bronchiolitis at age 0-6 months. *Pediatr Pulmonol* 2015; **50**: 389-395 [PMID: 24668616 DOI: 10.1002/ppul.23039]

33 **Lemanske RF Jr**. The childhood origins of asthma (COAST) study. *Pediatr Allergy Immunol* 2002; **13**: 38-43 [PMID: 12688623 DOI: 10.1034/j.1399-3038.13.s.15.8.x]

34 **Piippo-Savolainen E**, Korppi M. Wheezy babies--wheezy adults? Review on long-term outcome until adulthood after early childhood wheezing. *Acta Paediatr* 2008; **97**: 5-11 [PMID: 18052998 DOI: 10.1111/j.1651-2227.2007.00558.x]

35 **Reijonen TM**, Korppi M, Kuikka L, Savolainen K, Kleemola M, Mononen I, Remes K. Serum eosinophil cationic protein as a predictor of wheezing after bronchiolitis. *Pediatr Pulmonol* 1997; **23**: 397-403 [PMID: 9220520 DOI: 10.1002/(sici)1099-0496(199706)23:6<397::aid-ppul1>3.0.co;2-g]

36 **Stern DA**, Morgan WJ, Halonen M, Wright AL, Martinez FD. Wheezing and bronchial hyper-responsiveness in early childhood as predictors of newly diagnosed asthma in early adulthood: a longitudinal birth-cohort study. *Lancet* 2008; **372**: 1058-1064 [PMID: 18805334 DOI: 10.1016/S0140-6736(08)61447-6]

37 **Törmänen S**, Lauhkonen E, Saari A, Koponen P, Korppi M, Nuolivirta K. Excess weight in preschool children with a history of severe bronchiolitis is associated with asthma. *Pediatr Pulmonol* 2015; **50**: 424-430 [PMID: 24753502 DOI: 10.1002/ppul.23053]

38 **Valkonen H**, Waris M, Ruohola A, Ruuskanen O, Heikkinen T. Recurrent wheezing after respiratory syncytial virus or non-respiratory syncytial virus bronchiolitis in infancy: a 3-year follow-up. *Allergy* 2009; **64**: 1359-1365 [PMID: 19416146 DOI: 10.1111/j.1398-9995.2009.02022.x]

39 **Wennergren G**, Kristjánsson S. Relationship between respiratory syncytial virus bronchiolitis and future obstructive airway diseases. *Eur Respir J* 2001; **18**: 1044-1058 [PMID: 11829086 DOI: 10.1183/09031936.01.00254101]

40 **Almqvist C**, Worm M, Leynaert B; working group of GA2LEN WP 2.5 Gender. Impact of gender on asthma in childhood and adolescence: a GA2LEN review. *Allergy* 2008; **63**: 47-57 [PMID: 17822448 DOI: 10.1111/j.1398-9995.2007.01524.x]

41 **Bont L**, Aalderen WM, Kimpen JL. Long-term consequences of respiratory syncytial virus (RSV) bronchiolitis. *Paediatr Respir Rev* 2000; **1**: 221-227 [PMID: 12531083 DOI: 10.1053/prrv.2000.0052]

42 **Everard ML**. The relationship between respiratory syncytial virus infections and the development of wheezing and asthma in children. *Curr Opin Allergy Clin Immunol* 2006; **6**: 56-61 [PMID: 16505613 DOI: 10.1097/01.all.0000200506.62048.06]

43 **Holt PG**, Strickland DH, Sly PD. Virus infection and allergy in the development of asthma: what is the connection? *Curr Opin Allergy Clin Immunol* 2012; **12**: 151-157 [PMID: 22356945 DOI: 10.1097/ACI.0b013e3283520166]

44 **Kneyber MCJ**, Steyerberg EW, de Groot R, Moll HA. Long-term effects of respiratory syncytial virus (RSV) bronchiolitis in infants and young children: a quantitative review. *Acta Paediatr* 2000; **89**: 654-660 [PMID: 10914957 DOI: 10.1080/080352500750043945]

45 **Kusel MM**, de Klerk NH, Kebadze T, Vohma V, Holt PG, Johnston SL, Sly PD. Early-life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma. *J Allergy Clin Immunol* 2007; **119**: 1105-1110 [PMID: 17353039 DOI: 10.1016/j.jaci.2006.12.669]

46 **Le Souëf PN**. Gene-environmental interaction in the development of atopic asthma: new developments. *Curr Opin Allergy Clin Immunol* 2009; **9**: 123-127 [PMID: 19295429 DOI: 10.1097/ACI.0b013e3283292283]

47 **Lemanske RF**. Viral infections and asthma inception. *J Allergy Clin Immunol* 2004; 114: 1023-1026 [PMID: 15536404 DOI: 10.1016/j.jaci.2004.08.031]

48 **Lemanske RF Jr**. Issues in understanding pediatric asthma: epidemiology and genetics. *J Allergy Clin Immunol* 2002; **109**: S521-S524 [PMID: 12063507 DOI: 10.1067/mai.2002.124564]

49 **Martinez FD**. Development of wheezing disorders and asthma in preschool children. *Pediatrics* 2002; **109**: 362-367 [PMID: 11826251]

50 **Puddu M**, Fanos V. Respiratory syncytial virus infection and recurrent wheezing: what next? *J Chemother* 2007; **19 Suppl 2**: 8-11 [PMID: 18073170 DOI: 10.1080/1120009x.2007.11782434]

51 **Saglani S**. Viral infections and the development of asthma in children. *Ther Adv Infect Dis* 2013; **1**: 139-150 [PMID: 25165549 DOI: 10.1177/2049936113497202]

52 **Sly PD**, Kusel M, Holt PG. Do early-life viral infections cause asthma? *J Allergy Clin Immunol* 2010; **125**: 1202-1205 [PMID: 20304476 DOI: 10.1016/j.jaci.2010.01.024]

53 **Soto-Quiros M**, Avila L, Platts-Mills TA, Hunt JF, Erdman DD, Carper H, Murphy DD, Odio S, James HR, Patrie JT, Hunt W, O'Rourke AK, Davis MD, Steinke JW, Lu X, Kennedy J, Heymann PW. High titers of IgE antibody to dust mite allergen and risk for wheezing among asthmatic children infected with rhinovirus. *J Allergy Clin Immunol* 2012; **129**: 1499-1505.e5 [PMID: 22560151 DOI: 10.1016/j.jaci.2012.03.040]

54 **Godfrey S**. Bronchiolitis and asthma in infancy and early childhood. *Thorax* 1996; **51 Suppl 2**: S60-S64 [PMID: 8869355 DOI: 10.1136/thx.51.suppl\_2.s60]

55 **Mikalsen IB**, Halvorsen T, Eide GE, Øymar K. Severe bronchiolitis in infancy: can asthma in adolescence be predicted? *Pediatr Pulmonol* 2013; **48**: 538-544 [PMID: 22976850 DOI: 10.1002/ppul.22675]

56 **Rhodes HL**, Thomas P, Sporik R, Holgate ST, Cogswell JJ. A birth cohort study of subjects at risk of atopy: twenty-two-year follow-up of wheeze and atopic status. *Am J Respir Crit Care Med* 2002; **165**: 176-180 [PMID: 11790650 DOI: 10.1164/ajrccm.165.2.2104032]

57 **Rhodes HL**, Sporik R, Thomas P, Holgate ST, Cogswell JJ. Early life risk factors for adult asthma: a birth cohort study of subjects at risk. *J Allergy Clin Immunol* 2001; **108**: 720-725 [PMID: 11692095 DOI: 10.1067/mai.2001.119151]

58 **Rylander E**, Eriksson M, Freyschuss U. Risk factors for occasional and recurrent wheezing after RSV infection in infancy. *Acta Paediatr Scand* 1988; **77**: 711-715 [PMID: 3201977 DOI: 10.1111/j.1651-2227.1988.tb10735.x]

59 **Wennergren G**, Amark M, Amark K, Oskarsdóttir S, Sten G, Redfors S. Wheezing bronchitis reinvestigated at the age of 10 years. *Acta Paediatr* 1997; **86**: 351-355 [PMID: 9174218 DOI: 10.1111/j.1651-2227.1997.tb09021.x]

60 **Walton RP**, Johnston SL. Role of respiratory viral infections in the development of atopic conditions. *Curr Opin Allergy Clin Immunol* 2008; **8**: 150-153 [PMID: 18317024 DOI: 10.1097/ACI.0b013e3282f889df]

61 **Simoes EA**, Groothuis JR, Carbonell-Estrany X, Rieger CH, Mitchell I, Fredrick LM, Kimpen JL; Palivizumab Long-Term Respiratory Outcomes Study Group. Palivizumab prophylaxis, respiratory syncytial virus, and subsequent recurrent wheezing. *J Pediatr* 2007; **151**: 34-42, 42.e1 [PMID: 17586188 DOI: 10.1016/j.jpeds.2007.02.032]

62 **Yoshihara S**, Kusuda S, Mochizuki H, Okada K, Nishima S, Simões EA; C-CREW Investigators. Effect of palivizumab prophylaxis on subsequent recurrent wheezing in preterm infants. *Pediatrics* 2013; **132**: 811-818 [PMID: 24127479 DOI: 10.1542/peds.2013-0982]

63 **Edell D**, Khoshoo V, Ross G, Salter K. Early ribavarin treatment of bronchiolitis: effect on long-term respiratory morbidity. *Chest* 2002; **122**: 935-939 [PMID: 12226035 DOI: 10.1378/chest.122.3.935]

64 **Centers for Reviews and Dissemination**. CRD’s guidance for undertaking reviews in 301 healthcare: centers for reviews and dissemination. England: York Associates

65 **Moher D**, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**: e1000097 [PMID: 19621072 DOI: 10.1371/journal.pmed.1000097]

66 **Ouzzani M**, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 2016; **5**: 210 [PMID: 27919275 DOI: 10.1186/s13643-016-0384-4]

67 **Hoy D**, Brooks P, Woolf A, Blyth F, March L, Bain C, Baker P, Smith E, Buchbinder R. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. *J Clin Epidemiol* 2012; **65**: 934-939 [PMID: 22742910 DOI: 10.1016/j.jclinepi.2011.11.014]

68 **Higgins JP**, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**: 1539-1558 [PMID: 12111919 DOI: 10.1002/sim.1186]

69 **Cochran WG**. The Combination of Estimates from Different Experiments. *Biometrics* 1954; **10**: 101–129 [DOI: 10.2307/3001666]

70 **Kenmoe S**, Bowo-Ngandji A, Kengne-Nde C, Ebogo-Belobo JT, Mbaga DS, Mahamat G, Demeni Emoh CP, Njouom R. Association between early viral LRTI and subsequent wheezing development, a meta-analysis and sensitivity analyses for studies comparable for confounding factors. *PLoS One* 2021; **16**: e0249831 [PMID: 33857215 DOI: 10.1371/journal.pone.0249831]

71 **Backman K**, Ollikainen H, Piippo-Savolainen E, Nuolivirta K, Korppi M. Asthma and lung function in adulthood after a viral wheezing episode in early childhood. *Clin Exp Allergy* 2018; **48**: 138-146 [PMID: 29143374 DOI: 10.1111/cea.13062]

72 **Bertrand P**, Lay MK, Piedimonte G, Brockmann PE, Palavecino CE, Hernández J, León MA, Kalergis AM, Bueno SM. Elevated IL-3 and IL-12p40 levels in the lower airway of infants with RSV-induced bronchiolitis correlate with recurrent wheezing. *Cytokine* 2015; **76**: 417-423 [PMID: 26299549 DOI: 10.1016/j.cyto.2015.07.017]

73 **Fjaerli HO**, Farstad T, Rød G, Ufert GK, Gulbrandsen P, Nakstad B. Acute bronchiolitis in infancy as risk factor for wheezing and reduced pulmonary function by seven years in Akershus County, Norway. *BMC Pediatr* 2005; **5**: 31 [PMID: 16109158 DOI: 10.1186/1471-2431-5-31]

74 **García-García ML**, Calvo C, Casas I, Bracamonte T, Rellán A, Gozalo F, Tenorio T, Pérez-Breña P. Human metapneumovirus bronchiolitis in infancy is an important risk factor for asthma at age 5. *Pediatr Pulmonol* 2007; **42**: 458-464 [PMID: 17427899 DOI: 10.1002/ppul.20597]

75 **Henderson J**, Hilliard TN, Sherriff A, Stalker D, Al Shammari N, Thomas HM. Hospitalization for RSV bronchiolitis before 12 months of age and subsequent asthma, atopy and wheeze: a longitudinal birth cohort study. *Pediatr Allergy Immunol* 2005; **16**: 386-392 [PMID: 16101930 DOI: 10.1111/j.1399-3038.2005.00298.x]

76 **Korppi M**, Piippo-Savolainen E, Korhonen K, Remes S. Respiratory morbidity 20 years after RSV infection in infancy. *Pediatr Pulmonol* 2004; **38**: 155-160 [PMID: 15211700 DOI: 10.1002/ppul.20058]

77 **Poorisrisak P**, Halkjaer LB, Thomsen SF, Stensballe LG, Kyvik KO, Skytthe A, Schioetz PO, Bisgaard H. Causal direction between respiratory syncytial virus bronchiolitis and asthma studied in monozygotic twins. *Chest* 2010; **138**: 338-344 [PMID: 20435661 DOI: 10.1378/chest.10-0365]

78 **Pullan CR**, Hey EN. Wheezing, asthma, and pulmonary dysfunction 10 years after infection with respiratory syncytial virus in infancy. *Br Med J (Clin Res Ed)* 1982; **284**: 1665-1669 [PMID: 6805648 DOI: 10.1136/bmj.284.6330.1665]

79 **Sigurs N**, Bjarnason R, Sigurbergsson F, Kjellman B, Björkstén B. Asthma and immunoglobulin E antibodies after respiratory syncytial virus bronchiolitis: a prospective cohort study with matched controls. *Pediatrics* 1995; **95**: 500-505 [PMID: 7700748]

80 **Sigurs N**, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. *Am J Respir Crit Care Med* 2000; **161**: 1501-1507 [PMID: 10806145 DOI: 10.1164/ajrccm.161.5.9906076]

81 **Sigurs N**, Aljassim F, Kjellman B, Robinson PD, Sigurbergsson F, Bjarnason R, Gustafsson PM. Asthma and allergy patterns over 18 years after severe RSV bronchiolitis in the first year of life. *Thorax* 2010; **65**: 1045-1052 [PMID: 20581410 DOI: 10.1136/thx.2009.121582]

82 **Sigurs N**, Gustafsson PM, Bjarnason R, Lundberg F, Schmidt S, Sigurbergsson F, Kjellman B. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. *Am J Respir Crit Care Med* 2005; **171**: 137-141 [PMID: 15516534 DOI: 10.1164/rccm.200406-730OC]

83 **Singleton RJ**, Redding GJ, Lewis TC, Martinez P, Bulkow L, Morray B, Peters H, Gove J, Jones C, Stamey D, Talkington DF, DeMain J, Bernert JT, Butler JC. Sequelae of severe respiratory syncytial virus infection in infancy and early childhood among Alaska Native children. *Pediatrics* 2003; **112**: 285-290 [PMID: 12897275 DOI: 10.1542/peds.112.2.285]

84 **Strannegård O**, Cello J, Bjarnason R, Sigurbergsson F, Sigurs N. Association between pronounced IgA response in RSV bronchiolitis and development of allergic sensitization. *Pediatr Allergy Immunol* 1997; **8**: 1-6 [PMID: 9260211 DOI: 10.1111/j.1399-3038.1997.tb00134.x]

85 **Zomer-Kooijker K**, van der Ent CK, Ermers MJ, Uiterwaal CS, Rovers MM, Bont LJ; RSV Corticosteroid Study Group. Increased risk of wheeze and decreased lung function after respiratory syncytial virus infection. *PLoS One* 2014; **9**: e87162 [PMID: 24498037 DOI: 10.1371/journal.pone.0087162]

86 **Fauroux B**, Simões EAF, Checchia PA, Paes B, Figueras-Aloy J, Manzoni P, Bont L, Carbonell-Estrany X. The Burden and Long-term Respiratory Morbidity Associated with Respiratory Syncytial Virus Infection in Early Childhood. *Infect Dis Ther* 2017; **6**: 173-197 [PMID: 28357706 DOI: 10.1007/s40121-017-0151-4]

87 **Liu L**, Pan Y, Zhu Y, Song Y, Su X, Yang L, Li M. Association between rhinovirus wheezing illness and the development of childhood asthma: a meta-analysis. *BMJ Open* 2017; **7**: e013034 [PMID: 28373249 DOI: 10.1136/bmjopen-2016-013034]

88 **Pérez-Yarza EG**, Moreno A, Lázaro P, Mejías A, Ramilo O. The association between respiratory syncytial virus infection and the development of childhood asthma: a systematic review of the literature. *Pediatr Infect Dis J* 2007; **26**: 733-739 [PMID: 17848887 DOI: 10.1097/INF.0b013e3180618c42]

89 **Régnier SA**, Huels J. Association between respiratory syncytial virus hospitalizations in infants and respiratory sequelae: systematic review and meta-analysis. *Pediatr Infect Dis J* 2013; **32**: 820-826 [PMID: 23518824 DOI: 10.1097/INF.0b013e31829061e8]

90 **Edmond K**, Scott S, Korczak V, Ward C, Sanderson C, Theodoratou E, Clark A, Griffiths U, Rudan I, Campbell H. Long term sequelae from childhood pneumonia; systematic review and meta-analysis. *PLoS One* 2012; **7**: e31239 [PMID: 22384005 DOI: 10.1371/journal.pone.0031239]

91 **Kuehni CE**, Spycher BD, Silverman M. Causal links between RSV infection and asthma: no clear answers to an old question. *Am J Respir Crit Care Med* 2009; **179**: 1079-1080 [PMID: 19498062 DOI: 10.1164/rccm.200904-0567ED]

92 **Flaherman V**, Rutherford GW. A meta-analysis of the effect of high weight on asthma. *Arch Dis Child* 2006; **91**: 334-339 [PMID: 16428358 DOI: 10.1136/adc.2005.080390]

93 **Goksör E**, Amark M, Alm B, Gustafsson PM, Wennergren G. The impact of pre- and post-natal smoke exposure on future asthma and bronchial hyper-responsiveness. *Acta Paediatr* 2007; **96**: 1030-1035 [PMID: 17498194 DOI: 10.1111/j.1651-2227.2007.00296.x]

94 **Lin HW**, Lin SC. Environmental factors association between asthma and acute bronchiolitis in young children--a perspective cohort study. *Eur J Pediatr* 2012; **171**: 1645-1650 [PMID: 22777642 DOI: 10.1007/s00431-012-1788-3]

95 **Sears MR**, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, Cowan JO, Herbison GP, Silva PA, Poulton R. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med* 2003; **349**: 1414-1422 [PMID: 14534334 DOI: 10.1056/NEJMoa022363]

96 **Sears MR**, Holdaway MD, Flannery EM, Herbison GP, Silva PA. Parental and neonatal risk factors for atopy, airway hyper-responsiveness, and asthma. *Arch Dis Child* 1996; **75**: 392-398 [PMID: 8957951 DOI: 10.1136/adc.75.5.392]

97 **Sonnenschein-van der Voort AM**, Arends LR, de Jongste JC, Annesi-Maesano I, Arshad SH, Barros H, Basterrechea M, Bisgaard H, Chatzi L, Corpeleijn E, Correia S, Craig LC, Devereux G, Dogaru C, Dostal M, Duchen K, Eggesbø M, van der Ent CK, Fantini MP, Forastiere F, Frey U, Gehring U, Gori D, van der Gugten AC, Hanke W, Henderson AJ, Heude B, Iñiguez C, Inskip HM, Keil T, Kelleher CC, Kogevinas M, Kreiner-Møller E, Kuehni CE, Küpers LK, Lancz K, Larsen PS, Lau S, Ludvigsson J, Mommers M, Nybo Andersen AM, Palkovicova L, Pike KC, Pizzi C, Polanska K, Porta D, Richiardi L, Roberts G, Schmidt A, Sram RJ, Sunyer J, Thijs C, Torrent M, Viljoen K, Wijga AH, Vrijheid M, Jaddoe VW, Duijts L. Preterm birth, infant weight gain, and childhood asthma risk: a meta-analysis of 147,000 European children. *J Allergy Clin Immunol* 2014; **133**: 1317-1329 [PMID: 24529685 DOI: 10.1016/j.jaci.2013.12.1082]

98 **Oddy WH**, de Klerk NH, Sly PD, Holt PG. The effects of respiratory infections, atopy, and breastfeeding on childhood asthma. *Eur Respir J* 2002; **19**: 899-905 [PMID: 12030731 DOI: 10.1183/09031936.02.00103602]

99 **Østergaard MS**, Nantanda R, Tumwine JK, Aabenhus R. Childhood asthma in low income countries: an invisible killer? *Prim Care Respir J* 2012; **21**: 214-219 [PMID: 22623048 DOI: 10.4104/pcrj.2012.00038]

**Footnotes**

**Conflict-of-interest statement:** The authors deny any conflict of interest.

**PRISMA 2009 Checklist statement:** The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** November 30, 2021

**First decision:** April 19, 2022

**Article in press:**

**Specialty type:** Respiratory system

**Country/Territory of origin:** Cameroon

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

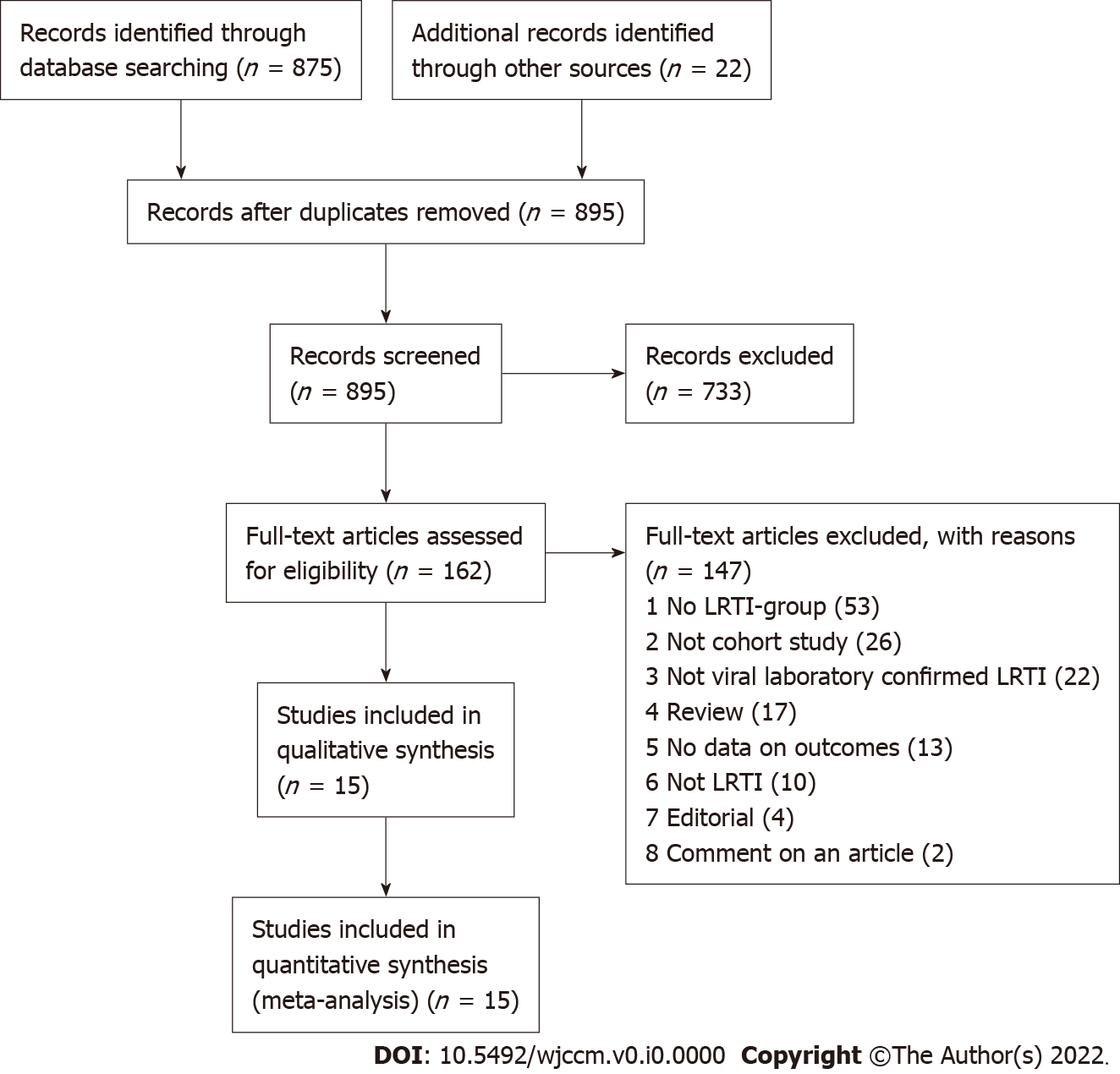
Grade C (Good): 0

Grade D (Fair): 0

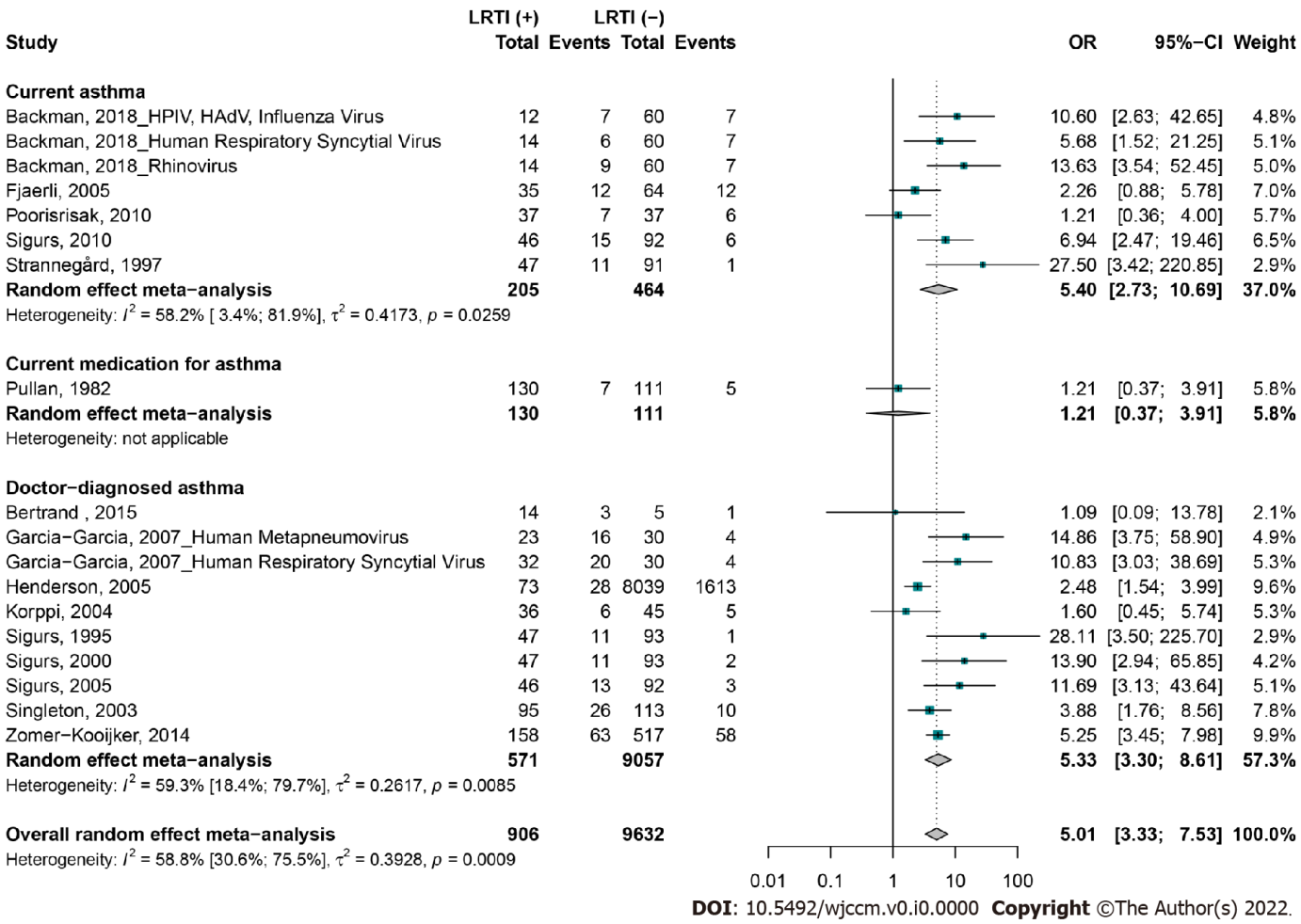
Grade E (Poor): 0

**P-Reviewer:** Alberca RW, Brazil **S-Editor:** Zhang H **L-Editor:** Filipodia CL **P-Editor:** Zhang H

**Figure Legends**

****

**Figure 1 Study selection.** LRTI: Lower respiratory tract infection.

****

**Figure 2 Forest plot of asthma in children with and without viral** **lower respiratory tract infections in infancy.** LRTI: Lower respiratory tract infection; OR: Odds ratio.

**Table 1 Asthma in children with and without viral lower respiratory tract infections in infancy and control without respiratory diseases**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Asthma** | **OR (95%CI)** | **95% prediction interval** | **Studies, *n*** | **LRTI cases, *n*** | **Controls, *n*** | **H (95%CI)** | **I² (95%CI)** | ***P* value, heterogeneity** | ***P* value, Egger’s test** |
| Overall | 5 (3.3-7.5) | (1.2-20.3) | 18 | 906 | 9632 | 1.6 (1.2-2.0) | 58.8 (30.6-75.5) | 0.001 | 0.671 |
| Sensitivity analyses |  |  |  |  |  |  |  |  |  |
| First episode of LRTI | 4.6 (2.6-8.1) | (0.8-27.1) | 11 | 725 | 9199 | 1.7 (1.3-2.4) | 67 (37.7-82.5) | 0.001 | 0.974 |
| Doctor-diagnosed asthma | 5.3 (3.3-8.6) | (1.4-19.7) | 10 | 571 | 9057 | 1.6 (1.1-2.2) | 59.3 (18.4-79.7) | 0.008 | 0.822 |
| Low risk of bias | 4.5 (2.9-7.2) | (1.1-18.2) | 14 | 732 | 1441 | 1.5 (1.1-2.0) | 54.5 (16.9-75.1) | 0.007 | 0.873 |
| Asthma in father | 12.5 (4.9-31.9) | NA | 2 | 55 | 60 | 1 | 0 | 0.741 | NA |
| Asthma in mother | 12.5 (4.9-31.9) | NA | 2 | 55 | 60 | 1 | 0 | 0.741 | NA |
| Asthma in parents | 10.6 (5.4-20.9) | (2.4-47.1) | 4 | 186 | 370 | 1 (1.0-2.6) | 0 (0-84.7) | 0.653 | 0.034 |
| Asthma in siblings | 12.5 (4.9-31.9) | NA | 2 | 55 | 60 | 1 | 0 | 0.741 | NA |
| Atopy in father | 12.5 (4.9-31.9) | NA | 2 | 55 | 60 | 1 | 0 | 0.741 | NA |
| Atopy in mother | 6.1 (4.1-8.9) | (0.5-72.6) | 3 | 213 | 577 | 1.2 (1.0-3.7) | 30.6 (0-92.8) | 0.237 | 0.358 |
| Atopy in parents | 9.1 (4.7-17.5) | (3.1-26.4) | 5 | 200 | 375 | 1.1 (1.0-2.3) | 11.2 (0-81.5) | 0.342 | 0.233 |
| Atopy in siblings | 14.9 (3.7-58.9) | NA | 1 | 23 | 30 | NA | NA | 1 | NA |
| Current allergy | 2.3 (0.9-5.8) | NA | 1 | 35 | 64 | NA | NA | 1 | NA |
| Current eczema | 2.3 (0.9-5.8) | NA | 1 | 35 | 64 | NA | NA | 1 | NA |
| Family history of asthma | 14.9 (4.9-45.4) | NA | 2 | 93 | 183 | 1 | 0 | 0.496 | NA |
| Family history of atopy | 14.9 (4.9-45.4) | NA | 2 | 93 | 183 | 1 | 0 | 0.496 | NA |
| Family smoking | 14.6 (5.9-36.2) | (0-5178.5) | 3 | 140 | 278 | 1 (1.0-3.1) | 0 (0-89.6) | 0.781 | 0.349 |
| Father smoking | 12.5 (4.9-31.9) | NA | 2 | 55 | 60 | 1 | 0 | 0.741 | NA |
| Father smoking, time of study | 1.2 (0.4-3.9) | NA | 1 | 130 | 111 | NA | NA | 1 | NA |
| Heredity for asthma | 13.9 (2.9-65.8) | NA | 1 | 47 | 93 | NA | NA | 1 | NA |
| Heredity for atopy | 13.9 (2.9-65.8) | NA | 1 | 47 | 93 | NA | NA | 1 | NA |
| History of atopic dermatitis | 1.2 (0.4-4.0) | NA | 1 | 37 | 37 | NA | NA | 1 | NA |
| Male gender | 5.3 (3.9-7.2) | (3.6-7.8) | 8 | 451 | 945 | 1.3 (1.0-2.0) | 44.3 (0-75.3) | 0.084 | 0.913 |
| Mother smoking | 12.5 (4.9-31.9) | NA | 2 | 55 | 60 | 1 | 0 | 0.741 | NA |
| Mother smoking, 10 yr before | 1.2 (0.4-3.9) | NA | 1 | 130 | 111 | NA | NA | 1 | NA |
| Parental smoking | 2.3 (0.9-5.8) | NA | 1 | 35 | 64 | NA | NA | 1 | NA |
| Pets at home | 6.5 (3.9-11.0) | (1.8-24.3) | 7 | 482 | 965 | 1.4 (1.0-2.2) | 50.8 (0-79.1) | 0.058 | 0.934 |
| Positive airway responsiveness | 1.2 (0.4-4.0) | NA | 1 | 37 | 37 | NA | NA | 1 | NA |
| Positive skin prick test | 1.2 (0.4-4.0) | NA | 1 | 37 | 37 | NA | NA | 1 | NA |
| Prematurity | 10.8 (3.0-38.7) | NA | 1 | 32 | 30 | NA | NA | 1 | NA |
| Running water | 3.9 (1.8-8.6) | NA | 1 | 95 | 113 | NA | NA | 1 | NA |
| Siblings in the house | 2.3 (0.9-5.8) | NA | 1 | 35 | 64 | NA | NA | 1 | NA |
| Single heredity for asthma | 28.1 (3.5-225.7) | NA | 1 | 47 | 93 | NA | NA | 1 | NA |
| Single heredity for atopy | 28.1 (3.5-225.7) | NA | 1 | 47 | 93 | NA | NA | 1 | NA |
| Smoke exposure | 5.1 (3.6-7.2) | (0.5-49.0) | 3 | 299 | 722 | 1 (1.0-3.1) | 0 (0-89.6) | 0.665 | 0.801 |
| Wheeze the first 5 yr of life | 1.2 (0.4-4.0) | NA | 1 | 37 | 37 | NA | NA | 1 | NA |
| Age at interview (yr) | 1.1 (0.1-13.8) | NA | 1 | 14 | 5 | NA | NA | 1 | NA |
| Age at recruitment (mo) | 12.5 (4.9-31.9) | NA | 2 | 55 | 60 | 1 | 0 | 0.741 | NA |
| Gestational age (wk) | 5.2 (3.4-8.0) | NA | 1 | 158 | 517 | NA | NA | 1 | NA |
| Height at age 6 (cm) | 5.2 (3.4-8.0) | NA | 1 | 158 | 517 | NA | NA | 1 | NA |
| Height at interview (cm) | 9.4 (4.6-19.3) | (0.1-1002.0) | 3 | 139 | 277 | 1 (1.0-3.1) | 0 (0-89.6) | 0.711 | 0.194 |
| Number of siblings | 17.9 (5.1-62.2) | NA | 2 | 94 | 186 | 1 | 0 | 0.596 | NA |
| Weight at age 6 (kg) | 5.2 (3.4-8.0) | NA | 1 | 158 | 517 | NA | NA | 1 | NA |
| Weight at interview (kg) | 14.6 (5.9-36.2) | (0-5178.5) | 3 | 140 | 278 | 1 (1.0-3.1) | 0 (0-89.6) | 0.781 | 0.349 |

LRTI: Lower respiratory tract infection; OR: Odds ratio; NA: Not applicable.