

# World Journal of *Critical Care Medicine*

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## Contents

Bimonthly Volume 11 Number 4 July 9, 2022

## REVIEW

- 201 Effects of nutrients on immunomodulation in patients with severe COVID-19: Current knowledge  
*Costa BTD, Araújo GRL, da Silva Júnior RT, Santos LKS, Lima de Souza Gonçalves V, Lima DBA, Cuzzuol BR, Santos Apolonio J, de Carvalho LS, Marques HS, Silva CS, Barcelos IS, Oliveira MV, Freire de Melo F*

## MINIREVIEWS

- 219 Challenges in hyperglycemia management in critically ill patients with COVID-19  
*Kethireddy R, Gandhi D, Kichloo A, Patel L*
- 228 Medicinal nicotine in COVID-19 acute respiratory distress syndrome, the new corticosteroid  
*Ahmad F*
- 236 Health-related quality-of-life and health-utility reporting in critical care  
*Lau VI, Johnson JA, Bagshaw SM, Rewa OG, Basmaji J, Lewis KA, Wilcox ME, Barrett K, Lamontagne F, Lauzier F, Ferguson ND, Oczkowski SJW, Fiest KM, Niven DJ, Stelfox HT, Alhazzani W, Herridge M, Fowler R, Cook DJ, Rochwerg B, Xie F*

## ORIGINAL ARTICLE

## Observational Study

- 246 Septic shock 3.0 criteria application in severe COVID-19 patients: An unattended sepsis population with high mortality risk  
*Cidade JP, Coelho L, Costa V, Morais R, Moniz P, Morais L, Fidalgo P, Tralhão A, Paulino C, Nora D, Valério B, Mendes V, Tapadinhas C, Póvoa P*
- 255 Development and pilot implementation of a patient-oriented discharge summary for critically ill patients  
*Shahid A, Sept B, Kupsch S, Brundin-Mather R, Piskulic D, Soo A, Grant C, Leigh JP, Fiest KM, Stelfox HT*

## SYSTEMATIC REVIEWS

- 269 Immunomodulatory therapy for the management of critically ill patients with COVID-19: A narrative review  
*Andaluz-Ojeda D, Vidal-Cortes P, Aparisi Sanz Á, Suberviola B, Del Río Carbajo L, Nogales Martín L, Prol Silva E, Nieto del Olmo J, Barberán J, Cusacovich I*

## META-ANALYSIS

- 298 Association between early viral lower respiratory tract infections and subsequent asthma development  
*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, Njoum R, Ndip L*

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

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### 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  $\leq 2$  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  $\leq 2$  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

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**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.

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## 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[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 PICO 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  $\leq 2$  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 (JETB 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.

**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, <i>n</i>	LRTI cases, <i>n</i>	Controls, <i>n</i>	H (95%CI)	<i>I</i> <sup>2</sup> (95%CI)	<i>P</i> value, heterogeneity	<i>P</i> 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



	5.8)								
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

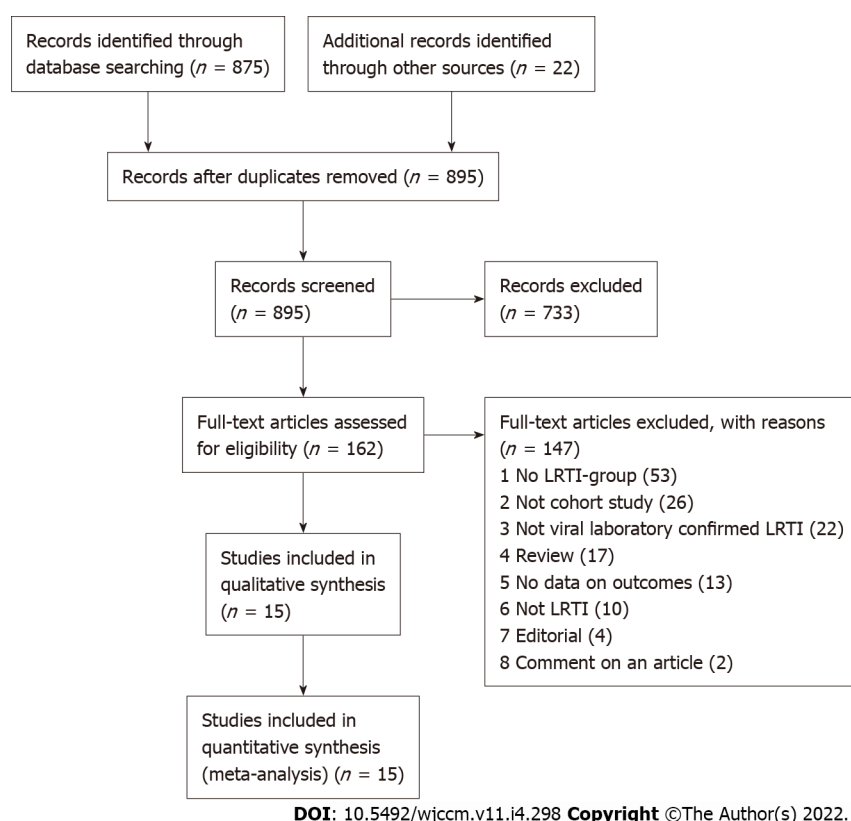
LRTI: Lower respiratory tract infection; OR: Odds ratio; NA: Not applicable.

### 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](#)).



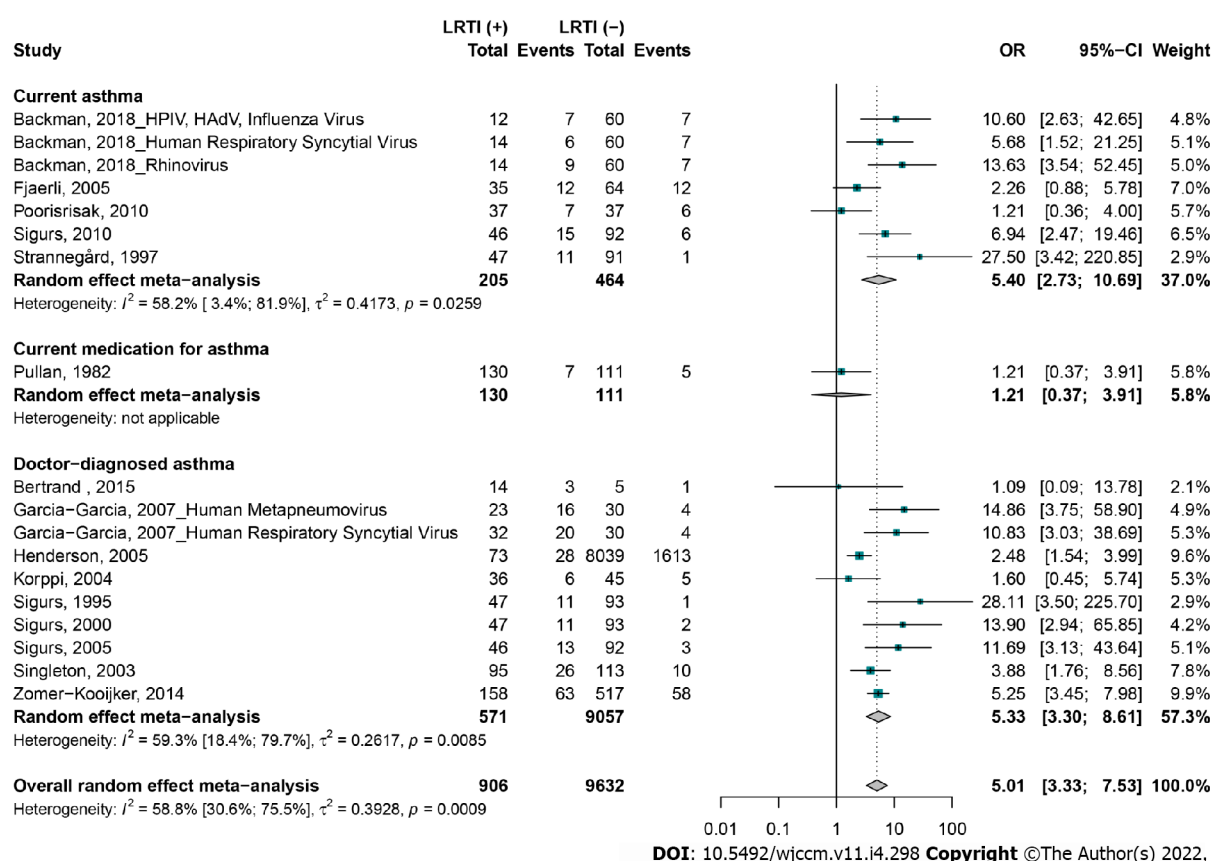
**Figure 1 Study selection.** LRTI: Lower respiratory tract infection.

## 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



**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.

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  $\leq 2$  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.

## FOOTNOTES

**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.

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