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

Kenmoe S *et al.* Post-LRTI asthma

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Abstract

BACKGROUND

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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.

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AIM

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

METHODS

The PubMed² 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 patients¹ with and without LRTI at ≤ 2 years⁴ regardless of the virus responsible. The meta-analysis was performed using 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 years¹ 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 controls⁴ had a significantly higher strength of association between LRTIs and subsequent asthma. The strength of the association between LRTIs and later asthma¹ 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)⁵ between cases and controls¹ did not alter the overall estimates.

CONCLUSION

Regardless of the causative virus and confounding factors, viral LRTIs¹ 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

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Core Tip: The results of this meta-analysis confirmed that ⁸ 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 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 (HMPV)^[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 (HPIV)...] 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 neonatal LRTI and asthma during childhood using sensitivity analyses.

MATERIALS AND METHODS

Study design

We registered ¹¹ the protocol of this systematic review in the PROSPERO ² 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].

Inclusion and exclusion criteria

We included cohort ² studies comparing the long-term asthmatic sequelae of children with and without a history of viral LRTI in childhood. ² The PICO in this study were: P, children and adults of all gender with a history of viral LRTI in childhood regardless of the virus responsible; I, LRTI at ≤ 2 years; C, children and adults of all gender 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

¹ 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: ¹² (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; and (2) night cough; and 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 1. We conducted an additional manual search by reviewing the list of references for included articles and relevant reviews on the subject.

Study selection

We (JTEB and SK) have individually ² reviewed the titles and abstracts of the articles identified through the electronic in 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) 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 2). 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

² 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, ³ 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 analyzes 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 ³ viruses responsible for LRTI, the type of LRTI, and the phenotype of asthma. Sensitivity analyzes including only studies with the confounding factors 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 3). 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 4-6. 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 reported mainly in the studies was HRSV (83.3%).

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

Compared to controls, significantly 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 7 and 8. Qualitative confounders include gender, preterm birth, smoking exposure, crowding, family history of atopy, family history of asthma. Quantitative confounders include 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 factors 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 9. The strength of the association between LRTI and asthma was significantly stronger for studies with probabilistic than non-probabilistic recruitment [OR = 4.5 (3-6.8) *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) 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; (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 one year compared to controls. Pérez-Yarza *et al*^[88] systematic review out of 8 published studies from 1985 to 2006 had shown 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 had shown 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 had also reported increased risk of developing asthma following hospitalizations due to severe HRSV LRTI registered at less than 3 years. Liu also reported in 2017 reported 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 a study by Liu *et al*^[87], 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 HMPV and rhinovirus, 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 ² 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. ² The systematic review by Fauroux *et al*^[86] found that infections with non-HRSV respiratory viruses (influenza A, human bocavirus, HPIV-3, human adenovirus, HMPV and unknown etiology) were associated with a higher risk of subsequent asthma than HRSV.

The attribution of the causal role of pre-school or adult asthma to bronchiolitis remains a subject of debate up to date^[97]. 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^[24,98-103]. Breastfeeding has also reported as a protective factor against asthma as a result of bronchiolitis in childhood^[58,104]. 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 reveals 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 analyzes 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 South-east Asia) where the

data suggested that asthma could be associated with a significant burden^[105]. 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.

⁶ *Research objectives*

This study was conducted to assess the influence of ² 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 ⁴ odds ratios (OR) and their 95%CI using a random-effects model.

Research results

This study included 15 articles and demonstrated the implications of ² childhood viral LRTI in the risk of subsequent asthma development up to the age of 20 (OR = 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 ¹ LRTI in childhood and the subsequent asthma risk. ⁹ Interventional studies are needed to involve the causality relationship between neonatal viral LRTI and the subsequent risk of asthma.

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- 1 Sebastien Kenmoe, Arnol Bowo-Ngandji, Cyprien Kengne-Nde, Jean Thierry Ebogo-Belobo et al. 183 words — 5%
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- 2 Sebastien Kenmoe, Cyprien Kengne-Nde, Abdou Fatawou Modiyinji, Jean Joel Bigna, Richard Njouom. 150 words — 4%
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