Original Article

Association between early-life respiratory syncytial virus infection and the risk of asthma: a meta-analysis

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Background: Respiratory syncytial virus (RSV) is a common cause of lower respiratory tract infections (LRTIs) in early childhood, yet its long-term impact on asthma development remains uncertain. This meta-analysis aims to quantify the association between early-life RSV-LRTI and the subsequent risk of asthma.

Methods: A systematic search of PubMed, Embase, and Web of Science was conducted. Observational studies comparing asthma incidence between children with early-life RSV-LRTI (before 3 years of age) and those without early-life LRTI or with non-RSV LRTI were included. Risk ratios (RRs) with 95% confidence intervals (CIs) were pooled using a random-effects model to incorporate the possible influences of heterogeneity.

Results: Eighteen studies with 266,071 children were included. Compared to children without early-life LRTI, those with RSV-LRTI had a significantly higher risk of asthma (RR =1.88; 95% CI: 1.55 to 2.29; P<0.001; I^2=61%). However, no significant difference was found when comparing asthma risk between early-life RSV-LRTI and non-RSV LRTI (RR =0.81; 95% CI: 0.64 to 1.03; P=0.08; I^2=51%). Further subgroup analyses according to study design, age of RSV LRTI, age of asthma diagnosis, methods for the validation of asthma, and study quality scores showed similar results (P for subgroup difference all >0.05).

Conclusions: Early-life RSV-LRTI is associated with an increased risk of asthma compared to children without early-life LRTI. However, RSV does not appear to confer a higher risk of asthma than non-RSV LRTI in early life.

Keywords: Respiratory syncytial virus (RSV); lower respiratory tract infection (LRTI); children; asthma; meta-analysis

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Introduction

Asthma is one of the most common chronic respiratory diseases worldwide, particularly in children (1,2). It is characterized by airway inflammation, bronchial hyperresponsiveness, and features of reversible expiratory airflow obstruction, significantly impacting the quality of life and healthcare systems (3). The prevalence of childhood asthma has increased over the past few decades, with substantial variations based on geographic region and socioeconomic status (4). Asthma in early life is associated with an increased risk of persistent respiratory symptoms into adulthood, reduced lung function, and exacerbations that may lead to hospitalizations (5,6). The pathogenesis of asthma involves a complex interplay of genetic predisposition, immune dysregulation, and environmental exposures (7). A key immunological mechanism is the imbalance between T helper 17 (Th17) and regulatory T (Treg) cells, where an increase in Th17-mediated inflammation and a reduction in Treg-mediated immune tolerance contribute to airway hyperresponsiveness and chronic inflammation (8). Given the long-term burden of asthma on both individuals and society, identifying early-life risk factors is crucial for guiding preventive strategies and improving disease management.

Among the proposed risk factors, early-life lower respiratory tract infections (LRTIs) have been suggested as important contributors to asthma development (9,10). Severe viral LRTI during infancy can lead to airway remodeling, persistent inflammation, and immune dysregulation, which may predispose children to chronic respiratory diseases (11). Respiratory syncytial virus (RSV) is the most common cause of viral LRTI in infants and young children, accounting for a large proportion of pediatric hospitalizations due to bronchiolitis and pneumonia (12,13). Compared to other respiratory viruses, RSV has unique pathophysiological characteristics, including intense airway inflammation, mucus hypersecretion, and prolonged immune dysregulation, which may contribute to asthma later in life (14). Understanding the role of RSV-LRTI in asthma development is critical, given the widespread prevalence of RSV infections and the increasing availability of RSV vaccines and monoclonal antibodies for prevention (15).

Several epidemiological studies have investigated the association between early-life RSV-LRTI and subsequent asthma risk, though the results have been inconsistent (16-33). This inconsistency may be attributed to differences in study design, selection of controls, follow-up duration, definitions of asthma, and adjustment for confounding factors (34). Moreover, it remains unclear whether RSV-LRTI carries a higher risk of asthma development compared to non-RSV viral LRTI. Given these uncertainties, in this study, we performed a comprehensive meta-analysis to clarify the association between early-life RSV-LRTI and asthma incidence later in life. Specifically, we compared the asthma risk between children with early-life RSV-LRTI and those without early-life LRTI, as well as between children with RSV-LRTI and those with non-RSV LRTI. We present this article in accordance with the PRISMA reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-2025-1536/rc).

Highlight box

Key findings

- This meta-analysis of 18 observational studies involving over 266,000 children found that early-life respiratory syncytial virus (RSV) lower respiratory tract infection (LRTI) before age 3 years was significantly associated with a higher risk of developing asthma later in life [risk ratio (RR) =1.88; 95% confidence interval (CI): 1.55 to 2.29]. However, no significant difference in asthma risk was observed when comparing children with early-life RSV-LRTI to those with non-RSV LRTI (RR =0.81; 95% CI: 0.64 to 1.03).

What is known and what is new?

- It is known that early-life viral respiratory infections are associated with increased asthma risk, and RSV is a major pathogen in infantile LRTIs. Prior studies have yielded conflicting results regarding whether RSV carries a higher risk than other viruses.
- This study confirms the increased asthma risk following early-life RSV infection but shows that the risk is comparable to other viral LRTIs, suggesting that severe LRTI itself, rather than viral etiology, may be the key determinant.

What is the implication, and what should change now?

- These findings emphasize the need for early preventive strategies and close respiratory monitoring in children with a history of severe LRTI, regardless of the causative virus. While RSV vaccination and monoclonal antibody strategies may help reduce severe infections, broader approaches targeting early-life LRTI severity overall could be more impactful in lowering long-term asthma risk. Future studies should explore whether RSV-specific prevention leads to reduced asthma incidence.

Methods

The study adhered to PRISMA 2020 (35,36) and the Cochrane Handbook for Systematic Reviews and Meta-Analyses (35) guidelines for conducting this meta-analysis, including for the study protocol design, data extraction, statistical analysis, and results presentation. Additionally, the meta-analysis protocol was registered in the international prospective register of systematic reviews (PROSPERO) under registration identifier CRD42025635658.

Literature search

To identify studies pertinent to this meta-analysis, we searched the PubMed, Embase, and Web of Science databases using search strategies detailed in Appendix 1. The search was restricted to studies conducted on human subjects and included only full-length articles published in English in peer-reviewed journals. Additionally, the references of relevant original and review articles were manually screened to identify any additional eligible studies. The literature search covered the period from the inception of the databases to December 10, 2024.

Inclusion and exclusion criteria

The inclusion criteria for potential studies were defined according to the PICOS framework:

- ❖ P (patients): children with or without LRTI diagnosed before 3 years of age.
- ❖ I (exposure): children with early-life RSV-associated LRTI before 3 years of age, such as those with RSV bronchiolitis or pneumonia.
- ❖ C (comparison): children without early-life LRTI (healthy controls), or children with early-life non-RSV LRTI, such as LRTI caused by other viruses, such as rhinovirus, adenovirus, and influenza, before 3 years of age.
- ❖ O (outcome): incidence of asthma diagnosed later in life. The diagnosis of asthma is consistent with the criteria used in the original studies.
- ❖ S (study design): observational studies with longitudinal follow-up, such as cohort studies, nested case-control studies, or post-hoc analyses of clinical trials.

Studies were excluded if they were reviews, editorials, meta-analyses, preclinical research, cross-sectional studies, studies without an early-life RSV-LRTI as exposure, or did not report the outcome of asthma incidence later in life. For studies with overlapping populations, the one with the largest sample size was included in the meta-analysis.

Study quality assessment and data extraction

The literature search, study selection, quality assessment, and data extraction were independently performed by two authors, with discrepancies resolved through discussion with the corresponding author. Study quality was assessed using the Newcastle-Ottawa Scale (NOS) (37), which evaluates selection, control of confounding factors, and outcome measurement and analysis, with scores ranging from 1 to 9, where a score of 9 indicates the highest quality. Studies with NOS scores of 7 or above are considered of high quality. Data extracted for analysis included study characteristics (author, year, country, and design), number of the included children in each study, methods for validating the early-life RSV-LRTI, number of children with early-life RSV-LRTI, definition of controls (healthy controls or children with early-life non-RSV LRTI), mean ages of asthma diagnosis, the proportion of male participants, methods for the diagnosis of asthma, the number of participants who developed asthma during follow-up, and variables adjusted for or controlled when the association between early-life RSV-LRTI and the incidence of asthma was evaluated.

Statistical analyses

The primary outcome of this study was to compare the incidence of asthma between children with early-life (before 3 years of age) RSV LRTI and those without early-life LRTI. The secondary outcome was to compare the incidence of asthma between children with early-life RSV LRTI and those with non-RSV LRTI. The results were summarized as risk ratios (RRs) with 95% confidence intervals (CIs). RRs and their standard errors were derived from 95% CIs or P values and subsequently log-transformed to stabilize variance and achieve a normalized distribution (35). To assess heterogeneity, we used the Cochrane *Q* test and I^2 statistics (38), with I^2<25%, 25–75%, and >75% indicating mild, moderate, and substantial heterogeneity among the included studies. A random-effects model was applied to integrate the results, accounting for study variability (35). By excluding individual studies sequentially, a sensitivity analysis was performed to evaluate the robustness of the findings. In addition, subgroup analyses according to study design (prospective or retrospective), age at diagnosis of RSV LRTI, mean ages for the diagnosis of asthma, methods for the diagnosis of asthma, and NOS scores were also performed. Publication bias was evaluated using funnel plots and visual inspection for asymmetry, supplemented by Egger's regression test (39). A P value <0.05 indicates statistical significance. Analyses were performed using RevMan (version 5.1; Cochrane Collaboration, Oxford, UK) and Stata software (version 12.0; Stata Corporation, College Station, TX, USA).

Results

Study identification

The study selection process is summarized in *Figure 1*. A total of 2467 potentially relevant records were initially identified from the three databases searched, with 532 duplicates removed. Screening of titles and abstracts resulted in the further exclusion of 1,894 articles that did

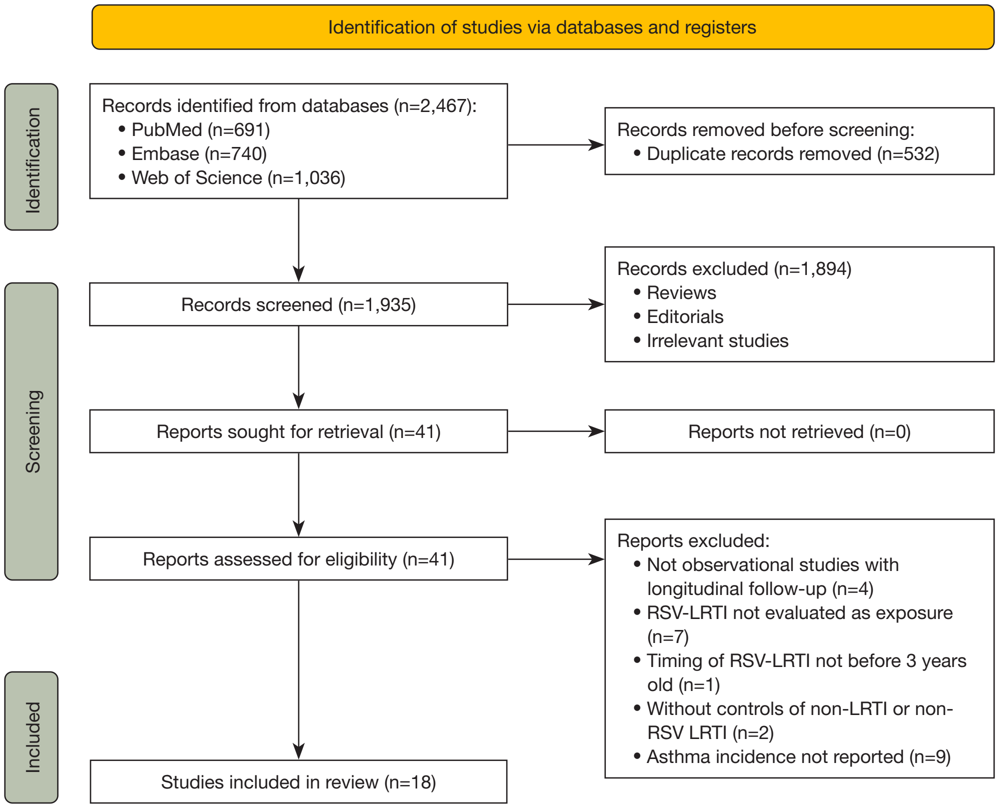

Figure 1 Flowchart of database search and study inclusion. LRTI, lower respiratory tract infection; RSV, respiratory syncytial virus.

not meet the objectives of the meta-analysis. The full texts of the remaining 41 articles were independently reviewed by two authors, leading to the exclusion of 23 studies for various reasons detailed in *Figure 1*. Ultimately, 18 studies were included in the quantitative analysis (16-33).

Overview of the study characteristics

Table 1 shows the summarized characteristics of the studies included in the meta-analysis. Overall, eight prospective (16,18,20,21,25,27,32,33) and 10 retrospective cohort studies (17,19,22-24,26,28-31) were included in the meta-analysis. These were published from 2000 to 2024, and were conducted in Sweden, Norway, the United Kingdom, Spain, Finland, China, France, Denmark, Israel, and the United States. A total of 266,071 children were included, and 29,478 (11.1%) of them had early-life RSV LRTI, which were defined as RSV LRTI-related hospitalization before the age of 6 months (20,29), 1 year (16-18,21,25,28,30,32), 2 years (19,22,24,26,27,31,33), or 3 years (23), respectively. Twelve of the included studies compared the incidence of asthma later in life between children with early-life RSV LRTI and those without early-life LRTI (16-19,21,26-29,31-33), and 10 studies compared the incidence of asthma between children with early-life RSV LRTI and those with early-life non-RSV LRTI (17,19,20,22-25,28,30,33). The mean ages for the diagnosis of asthma varied from 3.9 to 26.5 years. The validation for the diagnosis of asthma was via clinical diagnosis by a physician in 12 studies (16,17,19-22,25-27,30,32,33), via self-reported doctor-diagnosed asthma in four studies (18,23,24,28), and by the International Classification of Diseases (ICD) codes in another two studies (29,31). Accordingly, 14,600 (5.5%) of the included children developed asthma later in life. Multivariate analyses were performed in 17 of the included studies when the association between early-life RSV LRTI and the risk of asthma was reported, at least adjusted for age and sex (16-22,24-33), while univariate analysis was performed in the remaining study (23). The NOS scores of the included studies ranged from five to nine, reflecting a generally moderate to high quality of methodology and reporting (*Table 2*).

Table 1 Characteristics of the included studies

Study	Location	Design	No. of participants	Definition of early childhood RSV-LRTI	No. of subjects with childhood RSV-LRTI	Definition of controls	Mean age at asthma diagnosis (years)	Male (%)	Methods for the diagnosis of asthma	No. of subjects with asthma	Variables adjusted or controlled
Sigurs (16), 2000	Sweden	PC	140	Infantile (aged <1 year) hospitalization for RSV bronchiolitis	47	Birth date and sex matched subjects without infantile bronchiolitis	7.5	45	Clinical diagnosis by physician	17	Age, sex, family history of asthma, smoking in the family, presence of indoor furred animals, and history of pertussis
Fjaerli (17), 2005	Norway	RC	121	Infantile (aged <1 year) hospitalization for RSV bronchiolitis	35	Subjects with infantile non-RSV bronchiolitis, and subjects without infantile bronchiolitis	7	56.2	Clinical diagnosis by physician	34	Age, sex, and parent smoking
Henderson (18), 2005	UK	PC	8,112	Infantile (aged <1 year) hospitalization for RSV bronchiolitis	73	Subjects without infantile bronchiolitis	7.6	51.7	Self-reported doctor-diagnosed asthma	1,641	Age, sex, birth weight, pre-term delivery, season of birth, duration of breast feeding, maternal parity, maternal age, maternal educational qualifications, housing tenure during pregnancy, maternal smoking during pregnancy and maternal history of asthma
García-García (19), 2007	Spain	RC	85	Early childhood (aged <2 years) hospitalization for RSV bronchiolitis	32	Subjects with early childhood non-RSV bronchiolitis, and subjects without infantile bronchiolitis	3.9	51.8	Clinical diagnosis by physician	40	Age, sex, prematurity, parental smoking, family history of asthma, and furred animals at home
Koponen (20), 2012	Finland	PC	166	Infantile (aged <6 months) hospitalization for RSV bronchiolitis	117	Subjects with infantile non-RSV bronchiolitis	6.5	52	Clinical diagnosis by physician	21	Age, sex, atopic dermatitis at <12 months of age, and maternal asthma

Table 1 (*continued*)

Table 1 (*continued*)

Study	Location	Design	No. of participants	Definition of early childhood RSV-LRTI	No. of subjects with childhood RSV-LRTI	Definition of controls	Mean age at asthma diagnosis (years)	Male (%)	Methods for the diagnosis of asthma	No. of subjects with asthma	Variables adjusted or controlled
Zomer-Kooijker (21), 2014	Finland	PC	708	Infantile (aged <1 year) hospitalization for RSV bronchiolitis	159	Subjects without infantile bronchiolitis	6	49.7	Clinical diagnosis by physician	121	Age, sex, birth weight, birth season, smoke exposure during pregnancy and during life, breastfeeding, daycare, siblings, maternal atopy, ethnicity, year of birth, and maternal educational level
Del Rosal (22), 2016	Spain	RC	80	Early childhood (aged <2 years) hospitalization for RSV bronchiolitis	70	Subjects with early childhood non-RSV bronchiolitis	6	57.5	Clinical diagnosis by physician	59	Age, sex, prematurity, parental smoking, and family history of asthma
Ding (23), 2020	China	RC	246	Early childhood (aged <3 years) hospitalization for RSV LRTI	199	Subjects with early childhood non-RSV LRTI	NR (up to 10.3 years after discharge for LRTI)	71.1	Self-reported doctor-diagnosed asthma	11	None
Garcia-Garcia (24), 2020	Spain	RC	247	Early childhood (aged <2 years) hospitalization for RSV bronchiolitis	117	Subjects with early childhood non-RSV bronchiolitis	6.6	56.3	Self-reported doctor-diagnosed asthma	52	Age, sex, ICU admission in bronchiolitis, and parental asthma
Magnier (25), 2021	France	PC	68	Infantile (aged <1 year) hospitalization for RSV bronchiolitis	52	Subjects with infantile non-RSV bronchiolitis	7	63.3	Clinical diagnosis by physician	15	Age and sex
Ruotsalainen (27), 2022	Finland	PC	114	Early childhood (aged <2 years) hospitalization for RSV LRTI	14	Subjects without early childhood LRTI	26.5	66	Clinical diagnosis by physician	11	Age, sex, overweight, smoking and allergic rhinitis
Sørensen (28), 2022	Norway	RC	392	Infantile (aged <1 year) hospitalization for RSV bronchiolitis	128	Subjects with infantile non-RSV bronchiolitis, and subjects without infantile bronchiolitis	19.3	50.8	Self-reported doctor-diagnosed asthma	141	Age, sex, GA at birth, birth weight, household smoking ever, atopic dermatitis, and family history of atopy

Table 1 (*continued*)

Table 1 (*continued*)

Study	Location	Design	No. of participants	Definition of early childhood RSV-LRTI	No. of subjects with childhood RSV-LRTI	Definition of controls	Mean age at asthma diagnosis (years)	Male (%)	Methods for the diagnosis of asthma	No. of subjects with asthma	Variables adjusted or controlled
van Wijhe (29), 2022	Denmark	RC	38,300	Infantile (aged <6 months) hospitalization for RSV LRTI	20,920	Subjects without infantile LRTI	6	54.3	ICD codes	2,604	Age at inclusion, sex, hospital length of stay, maternal smoking, 5-minute Apgar score, prematurity, and congenital risk factors
Be'er (26), 2022	Israel	RC	129	Early childhood (aged <2 years) hospitalization for RSV LRTI	63	Subjects without early childhood LRTI	NR (3–10 years)	50.4	Clinical diagnosis by physician	39	Age, sex, GA at birth, and birthweight
Mansbach (30), 2023	USA	RC	779	Infantile (aged <1 year) hospitalization for RSV bronchiolitis	644	Subjects with infantile non-RSV bronchiolitis	6	58.9	Clinical diagnosis by physician	239	Age, sex, race, preterm birth, maternal history of asthma, ICU admission, and IgE
Muñoz-Quiles (31), 2023	Spain	RC	214,303	Early childhood (aged <2 year) hospitalization for RSV bronchiolitis	5,813	Subjects without early childhood bronchiolitis	NR (5 years or older)	49.3	ICD codes	9,268	Age, sex, prematurity, antibiotic consumption in the first year of life, vaccination against pneumococcus, health department, and year and month of birth
Rosas-Salazar (32), 2023	USA	PC	1,946	Infantile (aged <1 year) with RSV bronchiolitis	944	Subjects without RSV infection in infancy	5	52	Clinical diagnosis by physician	230	Age, sex, race and ethnicity, any breastfeeding, daycare attendance during infancy, exposure to second-hand smoke in utero or during early infancy, and maternal asthma
Myklebust (33), 2024	Finland	PC	135	Early childhood (aged <2 years) hospitalization for RSV LRTI	51	Subjects with early childhood non-RSV bronchiolitis, and subjects without early childhood bronchiolitis	9.3	62.2	Clinical diagnosis by physician	57	Age, sex, prematurity, parental smoking, and family history of asthma

GA, gestational age; ICD, International Classification of Diseases; ICU, intensive care unit; IgE, immunoglobulin E; LRTI, lower respiratory tract infection; NR, not reported; PC, prospective cohort; RC, retrospective cohort; RSV, respiratory syncytial virus.

Table 2 Study quality evaluation via the NOS

Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome not present at baseline	Control for age	Control for other confounding factors	Assessment of outcome	Enough long follow-up duration	Adequacy of follow-up of cohorts	Total
Sigurs (16), 2000	1	1	1	1	1	1	1	1	1	9
Fjaerli (17), 2005	0	1	1	1	1	1	1	1	1	8
Henderson (18), 2005	1	1	1	1	1	1	0	1	1	8
García-García (19), 2007	0	1	1	1	1	1	1	0	1	7
Koponen (20), 2012	1	1	1	1	1	1	1	1	1	9
Zomer-Kooijker (21), 2014	1	1	1	1	1	1	1	1	1	9
Del Rosal (22), 2016	0	1	1	1	1	1	1	1	1	8
Ding (23), 2020	0	1	1	1	0	0	0	1	1	5
Garcia-Garcia (24), 2020	0	1	1	1	1	1	0	1	1	7
Magnier (25), 2021	1	1	1	1	1	0	1	1	0	7
Ruotsalainen (27), 2022	1	1	1	1	1	1	1	1	0	8
Sørensen (28), 2022	0	1	1	1	1	1	0	1	1	7
van Wijhe (29), 2022	0	1	0	1	1	1	0	1	1	6
Be’er (26), 2022	0	1	1	1	1	1	1	1	1	8
Mansbach (30), 2023	0	1	1	1	1	1	1	1	1	8
Muñoz-Quiles (31), 2023	0	1	0	1	1	1	0	1	1	6
Rosas-Salazar (32), 2023	1	1	1	1	1	1	1	1	1	9
Myklebust (33), 2024	1	1	1	1	1	1	1	1	1	9

NOS, Newcastle-Ottawa Scale.

Comparing asthma incidence between children with early-life RSV LRTI and those without early-life LRTI

The pooled results of 12 studies (16-19,21,26-29,31-33), all with multivariate analysis, showed that, compared to those without early-life LRTI, children with early-life RSV LRTI diagnosed before 3 years of age had a higher incidence of asthma later in life (RR =1.88; 95% CI: 1.55 to 2.29; P<0.001; I^2=61%; *Figure 2A*). The sensitivity analysis by excluding one study at a time did not significantly change the results (RR =1.76 to 1.99, P all <0.05). Subsequent subgroup analyses suggested that the results were similar between prospective and retrospective studies (P for subgroup difference =0.31; *Figure 2B*), in children with RSV LRTI before 6 months, 1 year, and 2 years of age (P for subgroup difference =0.44; *Figure 2C*), in participants with asthma diagnosed <7 years, between 7 and 18 years, and after 18 years of age (for subgroup difference =0.21; *Figure 3A*), in studies with asthma diagnosis validated by clinical evaluation and self-report or ICD codes (P for subgroup difference =0.23; *Figure 3B*), and in studies with NOS scores <7 or ≥7 (P for subgroup difference =0.45; *Figure 3C*).

Comparing asthma incidence between children with early-life RSV and non-RSV LRTI

The meta-analysis of 10 studies (17,19,20,22-25,28,30,33) did not show a significant difference of asthma incidence between children with early-life RSV and non-RSV LRTI (RR =0.81; 95% CI: 0.64 to 1.03; P=0.08; I^2=51%; *Figure 4A*). The sensitivity analysis by omitting one study at a time did not significantly change the results (RR =0.75 to 0.86, P all >0.05). In particular, the sensitivity analysis excluding the only study with univariate analysis (23) also showed similar results (RR =0.82; 95% CI: 0.64 to 1.05; P=0.11; I^2=56%). Further subgroup analyses according to study design (P for subgroup difference =0.53; *Figure 4B*), the age of RSV infection (P for subgroup difference =0.07; *Figure 4C*), the age for the diagnosis of asthma (P for subgroup difference =0.95; *Figure 5A*), the methods for the validation of asthma diagnosis (P for subgroup difference =0.31; *Figure 5B*), or the NOS scores (P for subgroup difference =0.76; *Figure 5C*) did not significantly affect the results.

Publication bias

The funnel plots for the meta-analyses comparing the incidence of asthma between children with early-life RSV LRTI to those without early-life LRTI or with early-life non-RSV LRTI are shown in *Figure 6A,6B*. Visual inspection of the plots reveals symmetry, indicating a low risk of publication bias. These findings are further supported by Egger's regression analyses, which did not suggest a significant publication bias (P=0.32 and 0.61, respectively).

Discussion

This meta-analysis demonstrated that children who experienced RSV-LRTI before the age of three had a significantly higher risk of developing asthma later in life compared to those without early-life LRTI. However, when comparing RSV-LRTI to non-RSV LRTI, no significant difference in asthma risk was observed. These findings suggest that while early-life severe LRTI itself is a strong predictor of asthma development, the specific viral etiology—RSV versus non-RSV—may not substantially alter the long-term risk. The results remained robust across multiple sensitivity analyses and subgroup evaluations, indicating consistency in the association between early-life LRTI and subsequent asthma risk.

Several mechanisms may explain the increased asthma risk following early-life RSV-LRTI. Severe RSV infection in infancy has been associated with persistent airway inflammation, epithelial damage, and structural remodeling, which may contribute to long-term airway hyperresponsiveness and recurrent wheezing (40-42). Additionally, RSV is known to induce an exaggerated type 2 immune response, with increased production of interleukin (IL)-4, IL-5, and IL-13, which are implicated in eosinophilic airway inflammation and asthma pathogenesis (43,44). This immune dysregulation may lead to a heightened predisposition to atopic diseases, particularly in genetically susceptible individuals. Furthermore, early-life RSV infection can disrupt normal lung development and impair immune responses to subsequent infections, increasing susceptibility to asthma (45). The lack of a significant difference in asthma risk between RSV-LRTI and non-RSV LRTI suggests that the severity of early-life LRTI, rather than the specific viral pathogen, may be the key determinant of long-term respiratory outcomes. Other respiratory viruses, such as rhinovirus and adenovirus, have also been implicated in asthma pathogenesis and may exert similar effects on airway inflammation and remodeling (46,47). From a clinical perspective, these findings highlight

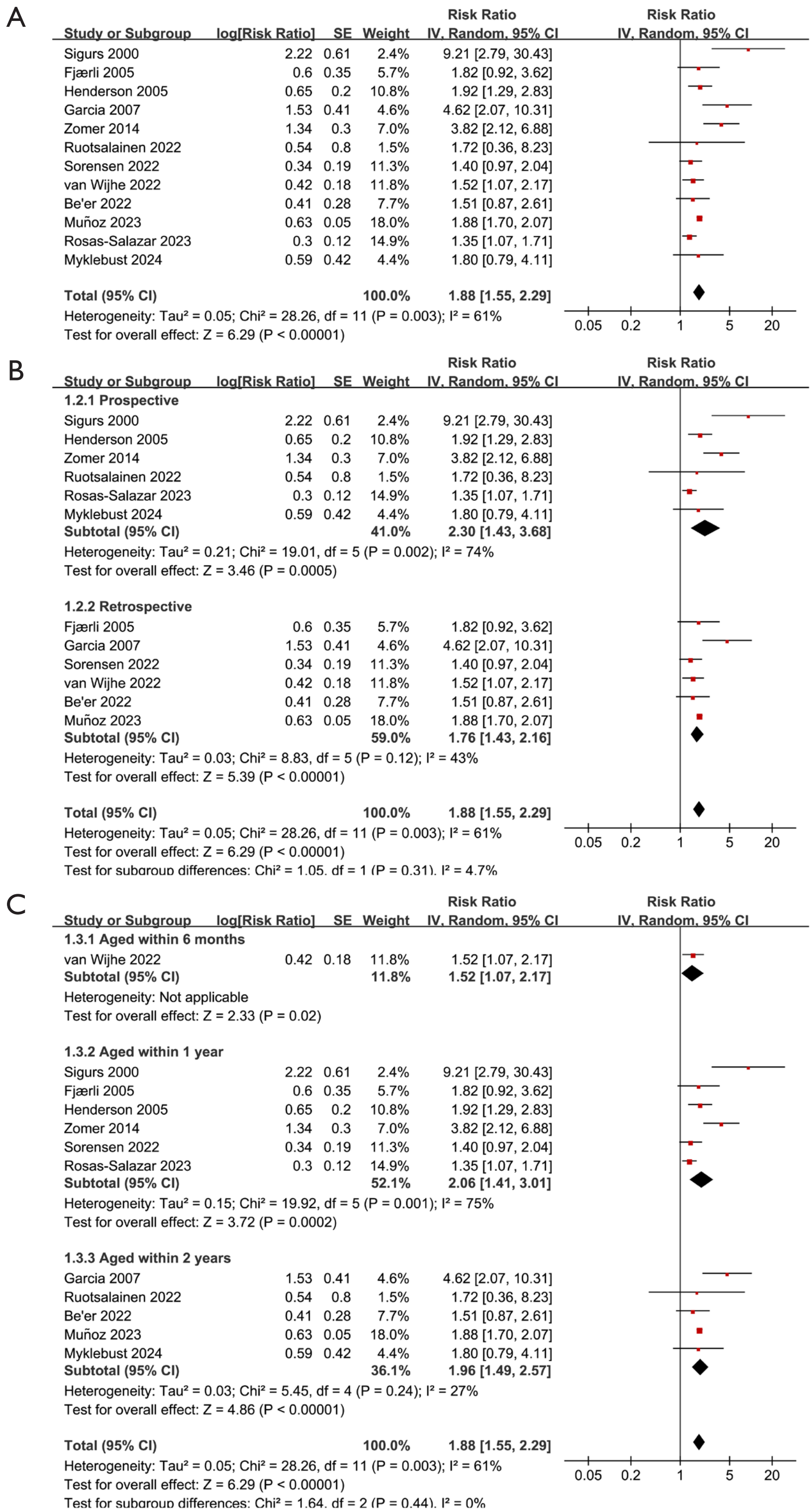

Figure 2 Forest plots for the meta-analysis comparing the incidence of asthma between children with early-life RSV LRTI and those without early-life LRTI. (A) Overall meta-analysis; (B) subgroup analysis according to the study design; (C) subgroup analysis according to the age at diagnosis of RSV LRTI. CI, confidence interval; IV, inverse variance; LRTI, lower respiratory tract infection; RSV, respiratory syncytial virus; SE, standard error.

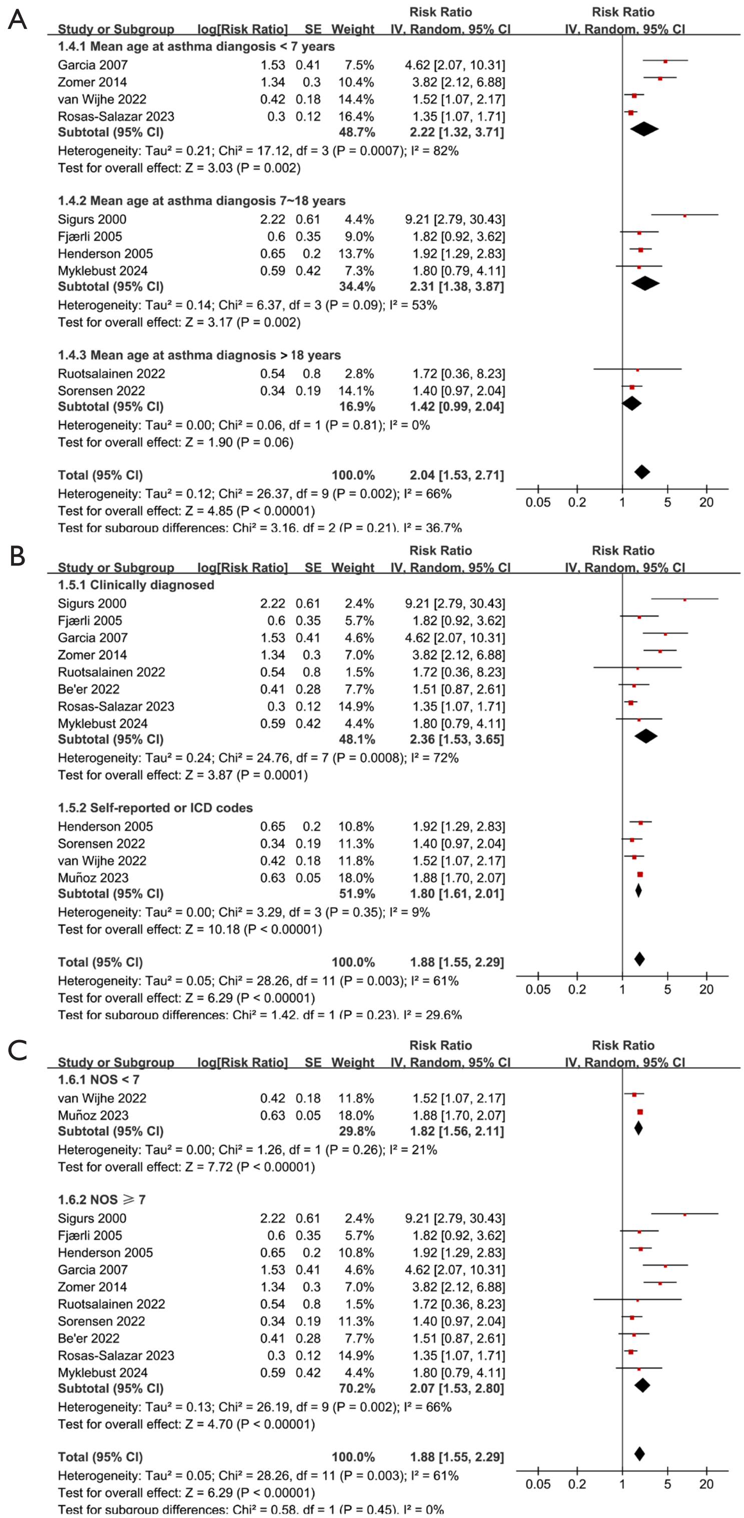

Figure 3 Forest plots for the subgroup analyses comparing the incidence of asthma between children with early-life RSV LRTI and those without early-life LRTI. (A) Subgroup analysis according to the age of asthma diagnosis; (B) subgroup analysis according to the methods for validation of asthma diagnosis; (C) subgroup analysis according to the NOS scores. CI, confidence interval; ICD, International Classification of Diseases; IV, inverse variance; LRTI, lower respiratory tract infection; NOS, Newcastle-Ottawa Scale; RSV, respiratory syncytial virus; SE, standard error.

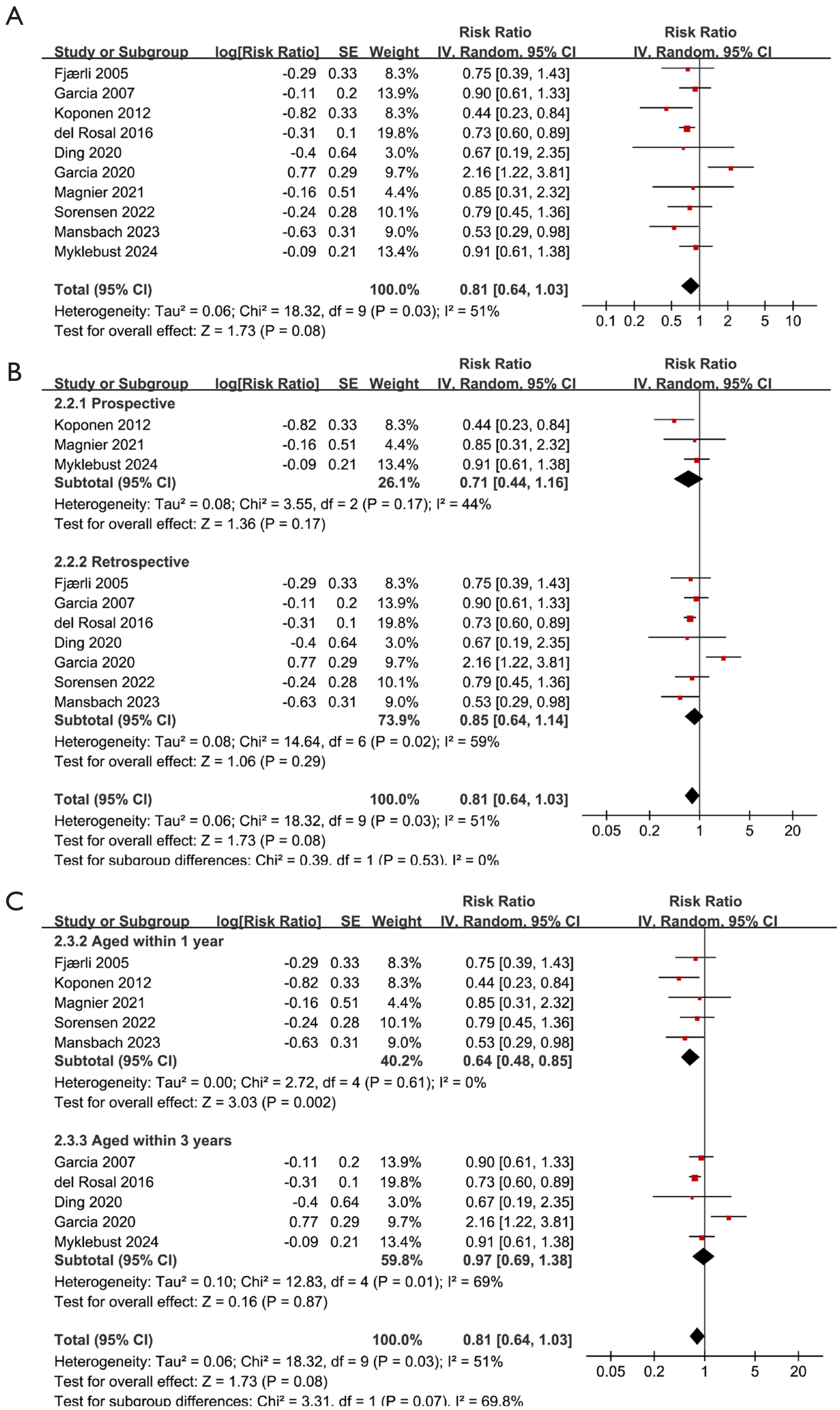

Figure 4 Forest plots for the meta-analysis comparing the incidence of asthma between children with early-life RSV and non-RSV LRTI. (A) Overall meta-analysis; (B) subgroup analysis according to the study design; (C) subgroup analysis according to the age of RSV LRTI. CI, confidence interval; IV, inverse variance; LRTI, lower respiratory tract infection; RSV, respiratory syncytial virus; SE, standard error.

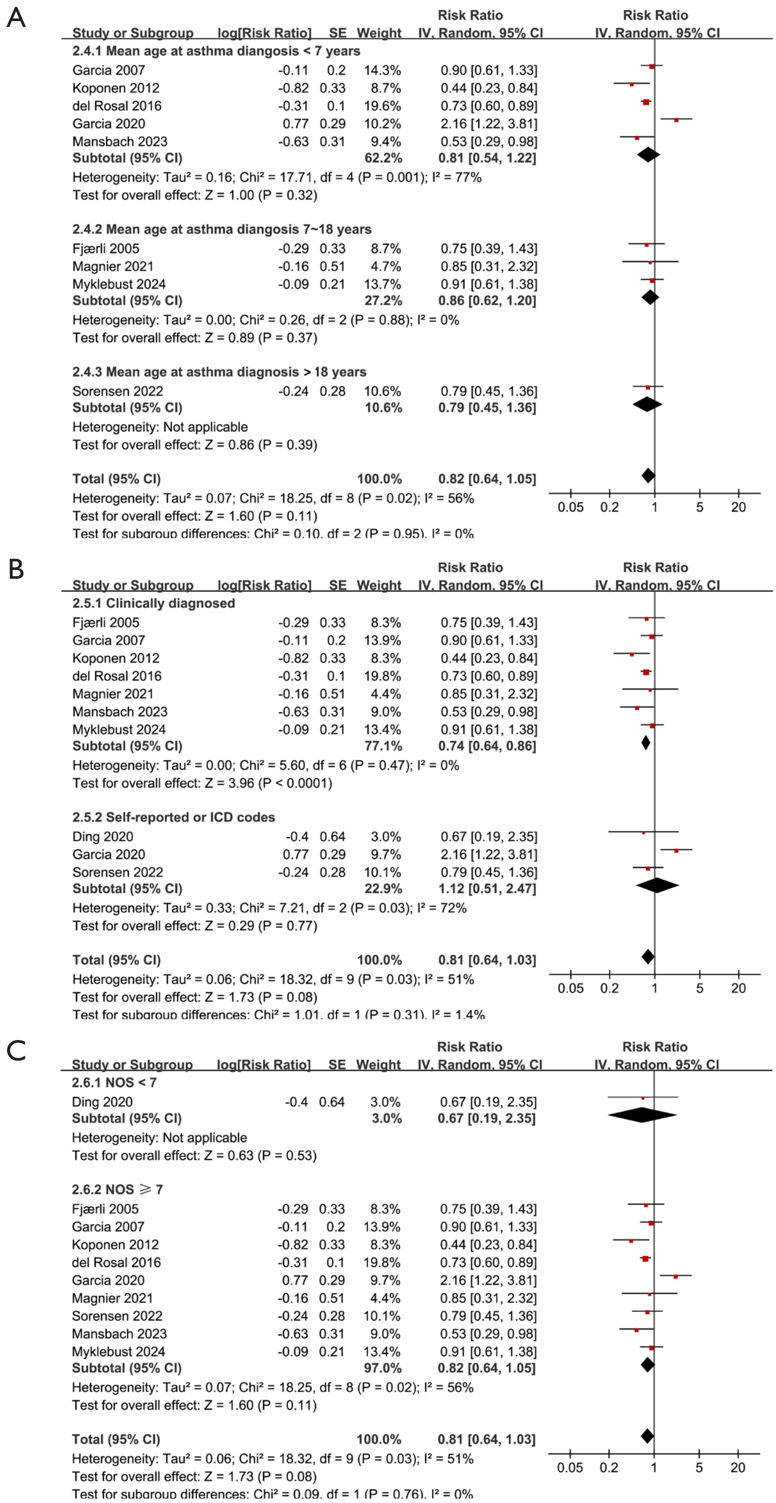

Figure 5 Forest plots for the subgroup analyses comparing the incidence of asthma between children with early-life RSV and non-RSV LRTI. (A) Subgroup analysis according to the age of asthma diagnosis; (B) subgroup analysis according to the methods for validation of asthma diagnosis; (C) subgroup analysis according to the NOS scores. CI, confidence interval; ICD, International Classification of Diseases; IV, inverse variance; LRTI, lower respiratory tract infection; NOS, Newcastle-Ottawa Scale; RSV, respiratory syncytial virus; SE, standard error.

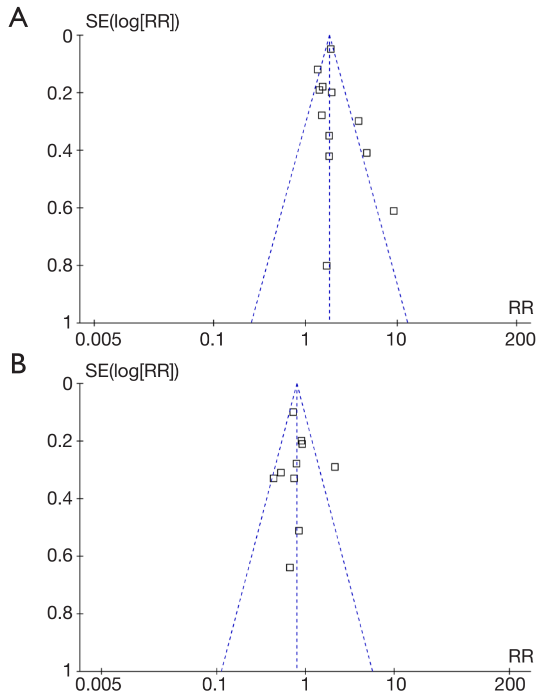

Figure 6 Funnel plots for estimating the potential publication biases underlying the meta-analyses. (A) Funnel plots for the meta-analysis comparing the incidence of asthma between children with early-life RSV LRTI and those without early-life LRTI; (B) funnel plots for the meta-analysis comparing the incidence of asthma between children with early-life RSV and non-RSV LRTI. LRTI, lower respiratory tract infection; RR, risk ratio; RSV, respiratory syncytial virus; SE, standard error.

the importance of preventing and managing severe LRTI in early childhood, regardless of the causative virus. While RSV has received significant attention due to its high burden of hospitalization in infants, other viral LRTIs may also contribute to asthma development, suggesting that broader strategies for reducing the severity of early-life respiratory infections could be beneficial. The results also emphasize the need for close respiratory follow-up in children with a history of severe LRTI, particularly those requiring hospitalization. Given the increasing availability of RSV vaccines and monoclonal antibodies, further research should explore whether RSV prevention strategies help reduce the long-term risk of asthma (48). An alternative explanation for the observed association is that severe early-life LRTI may not directly induce asthma, but rather identify children who are inherently predisposed to airway disease. Infants with atopic predisposition, hyper-reactive airways, or structurally smaller and more compliant airways may be more vulnerable to both severe viral infections and later asthma development (49). In this view, severe LRTI may be more of a marker of underlying susceptibility rather than a causal driver of asthma. This possibility underscores the need for future studies incorporating genetic, immunologic, and airway structural assessments to disentangle host predisposition from infection-related effects.

The subgroup and sensitivity analyses further support the robustness of our findings. The increased asthma risk associated with RSV-LRTI was consistent across study designs, different ages of developing RSV infection, and various asthma diagnosis methods. The similar asthma risk between RSV-LRTI and non-RSV LRTI was also stable across subgroups, suggesting that our results are not driven by specific study characteristics. However, it is important to note that all subgroup analyses were based on study-level data rather than individual patient data, limiting our ability to account for patient-level variations, such as genetic predisposition, atopy status, and environmental exposures.

There are several strengths in this meta-analysis. We conducted an extensive literature search across multiple databases and included only longitudinal studies, ensuring that asthma outcomes were assessed after RSV exposure. The majority of included studies used multivariate analysis to adjust for potential confounders, enhancing the validity of our findings. Additionally, multiple sensitivity and subgroup analyses confirmed the consistency of the results, reducing the likelihood of bias from study heterogeneity. However, some limitations should be acknowledged. First, since all included studies were observational, a causal relationship between early-life RSV-LRTI and asthma cannot be established. Despite multivariate adjustments, residual confounding from unmeasured factors, such as genetic susceptibility, household allergens, and parental smoking, cannot be ruled out. Second, we relied on study-level data rather than individual patient data, limiting our ability to evaluate the influence of participant characteristics on asthma risk. Future meta-analyses incorporating individual participant data may provide a more detailed assessment of effect modifiers. Third, while the subgroup analyses were informative, they were also based on study-level characteristics and should be interpreted with caution. Another limitation is that we could not perform a subgroup analysis stratified by atopy status, as only two of the included studies (20,28) provided models adjusted for atopy. Their results were inconsistent, with one suggesting a reduced asthma risk for RSV-LRTI compared with non-RSV LRTI (20) and the other showing no significant differences of asthma risk between children with RSV-LRTI *vs.* those without LRTI or with non-RSV LRTI (28). The limited and heterogeneous evidence prevents firm conclusions regarding the modifying role of atopy. Lastly, variations in asthma diagnosis criteria across studies could introduce some heterogeneity, although our subgroup analysis suggested that the results were consistent across different diagnostic methods.

The clinical implications of these findings are particularly relevant given the recent advancements in RSV prevention. The development of RSV vaccines and monoclonal antibody therapies raises the question of whether preventing RSV-LRTI in early life could reduce long-term asthma risk (50). Although our results suggest that the overall burden of early-life LRTI, rather than RSV specifically, is the primary driver of asthma development, reducing RSV infections may still be beneficial by preventing severe respiratory disease in infancy. Future studies should assess whether RSV prevention strategies translate into a lower incidence of asthma and other chronic respiratory conditions.

Conclusions

In conclusion, this meta-analysis provides robust evidence that early-life RSV-LRTI is associated with an increased risk of asthma compared to children without early-life LRTI. However, RSV does not appear to confer a higher risk than non-RSV LRTI, suggesting that early-life LRTI severity may be a more critical determinant of long-term respiratory outcomes than the specific viral etiology. These findings underscore the need for strategies to prevent and manage severe LRTI in infancy and highlight the importance of ongoing research into RSV vaccines and targeted interventions for reducing asthma risk in high-risk populations.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-2025-1536/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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