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REVIEW

The Burden and Long-term Respiratory Morbidity Associated with Respiratory Syncytial Virus Infection in Early Childhood

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ABSTRACT

Introduction: The REGAL (RSV Evidence—a Geographical Archive of the Literature) series provide a comprehensive review of the published evidence in the field of respiratory syncytial virus (RSV) in Western countries over the last 20 years. The objective of this fifth publication was to determine the long-term respiratory morbidity associated with RSV lower respiratory tract infection (RSV LRTI) in early life.

Methods: A systematic review was undertaken for articles published between January 1, 1995 and December 31, 2015. This was supplemented by inclusion of papers published whilst drafting the manuscript. Studies reporting data on the incidence and long-term wheezing and asthma following RSV LRTI in early life were included. Study quality and strength of evidence (SOE) were graded using recognized criteria.

Results: A total of 2337 studies were identified of which 74 were included. Prospective, epidemiologic studies consistently demonstrated that RSV LRTI is a significant risk factor for on-going respiratory morbidity characterized by transient early wheezing and recurrent wheezing and asthma within the first decade of life and possibly into adolescence and adulthood

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(high SOE). RSV LRTI was also associated with impaired lung function in these children (high SOE). Respiratory morbidity has been shown to result in reduced quality of life and increased healthcare resource use (moderate SOE). The mechanisms through which RSV contributes to wheezing/asthma development are not fully understood, but appear to relate to the viral injury, preexisting abnormal lung function and/or other factors that predispose to wheezing/asthma, including genetic susceptibility, altered immunology, eosinophilia, and associated risk factors such as exposure to environmental tobacco smoke (high SOE).

Conclusion: There is growing evidence that RSV LRTI in early childhood is associated with long-term wheezing and asthma and impaired lung function. Future research should aim to fully elucidate the pathophysiological mechanisms through which RSV causes recurrent wheezing/asthma.

Keywords: Asthma; Bronchial hyperreactivity; Bronchiolitis; Lower respiratory tract infection; Lung function; Recurrent wheezing; Respiratory morbidity; Sensitization; Wheezing

INTRODUCTION

Respiratory syncytial virus (RSV) is a leading cause of lower respiratory tract infection (LRTI) in children worldwide, with severe infection resulting in hospitalization and considerable morbidity [1, 2]. Previous infection with RSV does not convey persistent immunity and reinfection is common, though the severity of infection tends to decrease with increasing age [3]. There are well-characterized risk factors for RSV hospitalization (RSVH) including prematurity, chronic lung disease (CLD) and congenital heart disease (CHD) [4–8]; however, the majority of children hospitalized for RSV LRTI are previously healthy and have no risk factors for severe disease [7, 9]. In addition to the acute burden of RSV, epidemiological data suggest that RSV infection in the first 3 years of life is associated with long-term respiratory morbidity, such as recurrent wheezing and asthma, decreased lung function, and possibly allergic sensitization [10–12]. Such respiratory morbidity may persist into early adulthood [12, 13]. These long-term effects may reduce quality of life (QoL) and increase healthcare resource utilization [14, 15].

The etiological link between RSV infection and the development of asthma has long been debated. It is unclear whether severe RSV LRTI causes wheezing, or if genetic predisposition or other environmental risk factors increase the propensity for an exaggerated response to RSV [16]. It has been proposed that both of these pathways may be relevant, and that there may be differential effects based on the child's atopic predisposition and the specific viral genotype [2]. It remains unclear, however, which children hospitalized for severe RSV infection will develop recurrent wheezing and/or asthma later in life. Predicting which children are at risk for long-term respiratory problems could identify specific populations who would benefit from early targeted interventions.

The primary objective of REGAL (RSV Evidence—a Geographical Archive of the Literature) was to carry out a series of systematic reviews and then to assess, quantify, summarize and grade the evidence base for severe RSV infection in Western societies over the past 20 years [17–20]. REGAL was undertaken by an expert panel, comprising neonatologists, pediatricians, pediatric infectious disease specialists, pediatric cardiologists and pediatric pulmonologists from the United States, Canada and Europe. This paper, which represents the fifth in a series of seven publications covering a range of topics on RSV disease, identifies and describes the incidence, risk factors and long-term effects of respiratory morbidity and allergic sensitization after RSV LRTI in early life.

METHODS

The primary objective of REGAL was to address seven specific research questions relating to RSV covering: epidemiology [17]; premature infants [18]; CLD [19]; CHD [20]; special populations (e.g. Down syndrome); prevention and future management; and long-term respiratory morbidity, the focus of this paper. The systematic

reviews undertaken to answer each research question all used the same broad methodology, which has been described elsewhere [17]. The full protocol and generic search terms for the systematic reviews are available as part of the online supplement. To ensure that the literature search was manageable, only studies conducted in Western countries, which we defined as the United States, Canada, and Europe (including Turkey and the Russian Federation), were included.

In this systematic literature review, we sought to answer the following question: What is the nature, incidence and impact on long-term respiratory morbidity after RSV LTRI in early life in Western countries, specifically early and late wheeze? The search for this systematic review included studies published between January 1, 1995 and December 31, 2015 indexed in PubMed, EMBASE, the Cochrane Library, and clinicaltrials.gov. The target population was children who were hospitalized for RSV LRTI in early childhood (first 2–3 years of life) and subsequently developed recurrent wheezing/asthma in later life. RSVH was defined as hospital admission for lower respiratory tract symptoms (deep or wet chest cough, wheezing, hoarseness, stridor, shortness of breath) and either a positive enzyme immunoassay or a positive direct immunofluorescence assay for RSV infection of epithelial cells in nasopharyngeal secretions, a positive polymerase chain reaction test or a positive viral culture for RSV.

The following general terms and limits were used in the literature search: "RSV" OR "respiratory syncytial virus" AND "hospital" OR "admission" OR "admitted" AND "respiratory morbidity" OR "respiratory sequelae" OR "complication" OR "manifestation" OR "consequence" OR "long-term" OR "long term" OR "outcome" OR "wheezing" OR "wheeze" OR "asthma AND "limits: human, child (birth-18 years)". ''Bronchiolitis'' and ''pneumonia'' were captured as part of the Medical Subject Headings (MeSH) terms. We recognize that, while some relevant articles might have been missed by the searches, the combined Boolean operators ''AND'' and ''OR'' of the key text words and index terms should have precisely captured the vast majority of relevant citations which were pertinent for this evidence-based review. The search results were supplemented by a review of the bibliographies of key articles for additional studies and inclusion of relevant abstracts presented at key meetings. Other significant studies of the target population, published during the drafting of the manuscript, were also included in the review, as identified by the authors.

Definition of Asthma and Recurrent Wheezing

A variety of definitions of wheezing and asthma have been used in studies of RSV. A formal diagnosis of asthma is outlined in the International Statistical Classification of Diseases and Related Health Problems (ICD) 10 code of J45 or an International Classification of Primary Care (ICPC) code of R96 [21, 22]. The ICPC also provides a specific code for wheezing: R03. For completeness, we have included all relevant studies in the review and provided the definitions used within the summary tables. For future studies, we would recommend that 'current asthma' be defined as a history of asthma diagnosed by a physician, plus asthma symptoms or medication (beta-mimetics or inhaled corticosteroids) use in the last 12 months [23]. For this review, recurrent wheezing was defined as 3 or more wheezing episodes within 12 months, reported by either a physician (preferably) or a patient [14].

Outcomes of Interest

The outcomes of interest for this review included:

(i) asthma, recurrent wheezing and allergic sensitization rates after RSV LRTI in early life,
(ii) lung function after RSV LRTI in early life,
(iii) the relationship between RSV LRTI and subsequent development of clinical allergy or allergic sensitization, and
(iv) factors associated with the development of recurrent wheezing/asthma after RSV LRTI in early life.

Evaluation of Data

Included publications were graded according to the Oxford Centre for Evidence-Based Medicine Levels of Evidence [24, 25] (Supplementary Material 1—REGAL Protocol). For each study, we conducted a risk of bias assessment using the RTI Item Bank (score of 1 = very high risk of bias; score of 12 = very low risk of bias) for observational studies [26]. No quantitative data synthesis was conducted due to heterogeneity between studies in terms of design, patient populations, RSV testing, recording and availability of outcomes, and differences in clinical practice between countries and over time.

Compliance with Ethics Guidelines

The analysis in this article is based on previously published studies and does not involve any new studies of human subjects performed by any of the authors.

RESULTS

Articles Selected

From a total of 2337 publications, 74 studies were included in the final review: 58 identified from the database searches and a further 16 from reference lists/other sources (Fig. 1). Data extraction tables for all 74 studies, including evidence grades and risk of bias assessments can be found in the online supplement.

RSV LRTI in Early Life and the Risk of Developing Recurrent Wheezing/Asthma

Evidence from an increasing number of studies suggests a strong association between severe RSV LRTI in children aged <3 years and the subsequent development of recurrent wheezing/asthma in later life [10–14, 23, 27–44]. Due to differences in study design and methodology,

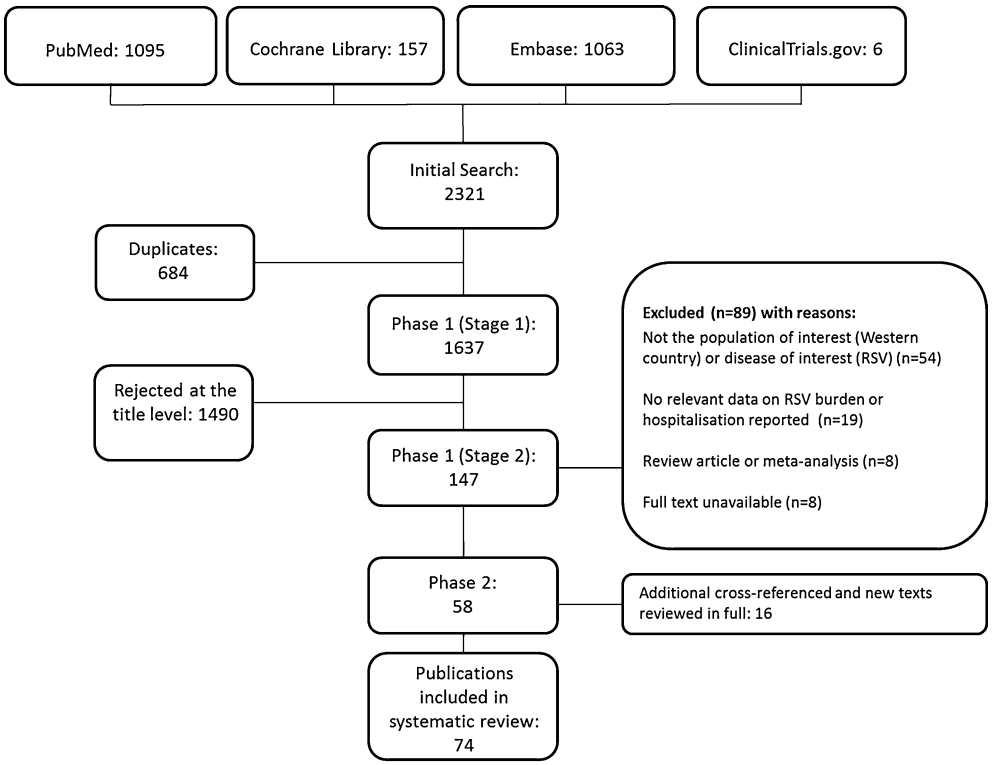

Fig. 1 PRISMA flow diagram: Incidence and impact of long-term respiratory morbidity associated with RSV LRTI in early life

definitions of wheezing/asthma used (including whether asthma is current/active), patient populations and length of follow-up, the reported rates of recurrent wheezing and asthma vary considerably across studies (Table 1). Following RSV LRTI in early childhood (≤3 years old), recurrent wheezing rates of 4–47% and asthma rates of 8–76% have been reported in studies with up to 25 years follow-up (average follow-up 6–8 years) [14, 28, 33, 42].

Several studies have indicated that, for many children, RSV-associated wheezing might be a transient event, diminishing over time, and may be even disappearing to background levels in early adolescence [10, 11, 28, 30, 31, 45]. In the Tucson Children's Respiratory Study, carried out in the United States, an increased risk of subsequent wheeze in children aged <3 years with RSV LRTI (most of whom were not hospitalized) was observed until the age of 11 years, but, by the time these children were 13 years of age, the association between wheeze and RSV LRTI was no longer significant [30]. Sigurs et al. followed a cohort of 47 Swedish infants aged <12 months hospitalized for severe RSV infections and 93 matched controls at ages 3, 7, 13 and 18 years [10, 11, 28, 29]. Up to age 7, recurrent wheezing was significantly more frequent in the RSVH group compared with control subjects (13.0% vs. 0%, respectively; $P < 0.001$) [10], though the difference, albeit still higher in the RSVH group, was not significant by age 13 (30% vs. 16.3%; $P = 0.093$) [11]. At 18 years, results specifically for recurrent wheezing were not presented, but when recurrent wheezing was combined with asthma, rates were significantly higher for those with a history of RSVH than with controls (39% vs. 9%, respectively; $P = 0.001$) [29]. Another long-term study reported RSV-associated wheezing to persist at >25 years of age [35% vs. 16.3% of controls; odds ratio (OR) 2.79, 95% confidence interval (95% CI) 1.15–6.75] [13]. Hence, whilst there is evidence that RSV-associated wheezing tends to diminish with time, it can persist into adulthood in some patients.

A number of prospective studies have demonstrated that RSV LRTI in childhood is an important risk factor for asthma in early adulthood [10, 12, 13, 29, 32]. In the study by Sigurs et al. [10], multivariate analysis at the 7-year follow-up showed that RSV bronchiolitis had the highest independent risk ratio for asthma (OR, 12.7; 95% CI, 3.4–47.1). This was reconfirmed in the 18-year analysis, where RSVH was an independent risk factor for current asthma/recurrent wheeze (OR, 6.2; 95% CI, 2.0–19.2; $P < 0.001$) and current asthma alone (OR, 7.2; 95% CI, 2.1–23.9; $P < 0.001$) [29]. Current asthma was reported in 33% of RSVH subjects and 7% of controls at up to 18 years of age ($P < 0.001$) [29]. The RSV Bronchiolitis in Early Life study (REBEL) also supports the link between RSV LRTI in childhood and physician-diagnosed asthma by school age [40]. In this prospective cohort study, nearly half (48%) of the children who developed severe RSV LRTI in the first year of life were diagnosed with childhood asthma by 7 years of age. The authors identified that greater levels of nasal epithelial expression of the chemokine CCL5 at the time of bronchiolitis were strongly predictive of physician-diagnosed asthma by the 7th birthday [40]. Other studies have demonstrated that RSVH at <2 years of age is a significant risk factor for adulthood asthma at 18–20 years [12] and >25 years [13]. Based on the findings of a retrospective study analyzing cohort data from 264,010 infants born in the United States between 1995 and 2003, it was proposed that 13% of asthma cases could be prevented by eliminating infant bronchiolitis during the RSV season [37].

Whilst it can be seen from the above that RSVH in early infancy is associated with an increased risk of long-term respiratory morbidity, other respiratory viruses, particularly rhinovirus, might be associated with a comparatively greater risk of wheezing/asthma [33, 46–49]. In a study from Finland, Koponen et al. [33] reported that the risk of asthma was lower after RSV bronchiolitis than after bronchiolitis caused by other viruses (rhinovirus, influenza A virus, parainfluenza type 3 virus, adenovirus, human metapneumovirus, and unknown etiology) in infants hospitalized within the first 6 months of age (8.2% vs. 24% in non-RSV patients; $P = 0.01$) [33]. Other studies from Finland undertaken in the early

Table 1 RSVH in the first 3 years of life and the association with wheezing/asthma in later life

Study	Country	Study design	RSVH status	Study definition of wheezing, asthma or chronic respiratory morbidity	Years of follow-up	Asthma/wheezing RSV vs. control
Schauer 2002 [34]	Germany	Prospective study of 42 infants with RSV without concomitant chronic respiratory, cardiac, or other disease and 84 controls	<12 months old	Asthma and wheezing not defined	1	Recurrent wheezing: 15.5% vs. 3.6%
Sigurs 1995 [28]	Sweden	Prospective cohort study of 47 infants with RSV and 93 age- and gender-matched controls	<12 months old	Asthma: ≥3 episodes of bronchial obstruction verified by a physician. Recurrent wheezing: ≥3 episodes of bronchial obstruction not verified by a physician	1 and 3	At 1 year: Asthma (mean: 11% vs. 0% ($P = 0.004$) Recurrent wheezing (mean: 4% vs. 8% (NS)) At 3 years: Asthma (mean: 23% vs. 1% ($P < 0.001$) Recurrent wheezing (mean: 21% vs. 12% (NS))
Karaman 2011 [44]	Turkey	Prospective study of 70 children, 40 with RSV and 30 with non-RSV bronchiolitis	0–36 months old	Wheezing not defined	1–3	Recurrent wheezing: 35% vs. 53.3% ($P = 0.064$; NS)
Escobar 2010 [39]	US	Retrospective cohort study of 71,102 children born ≥32 wGA	1.7% with medically attended RSV <12 months old	Recurrent wheezing: combination of encounter events, patient diagnoses using ICD codes, and prescription patterns	3	Recurrent wheezing: 16.2% vs. 6.2%[a]

Table 1 continued

Study	Country	Study design	RSVH status	Study definition of wheezing, asthma or chronic respiratory morbidity	Years of follow-up	Asthma/ wheezingRSV vs. control
Bont 2004 [35]	Netherlands	Prospective cohort study of 140 infants with RSV (29% born 25–36 wGA; 3% cardiac disease, 2% CLD)	≤12 months old	Respiratory symptoms and wheezing episodes: parent-reported (daily log). Disease episode: presence of respiratory symptoms for ≥2 consecutive days	3	Wheezing: >50% decrease in first year of follow-up ($P < 0.001$)
Escobar 2013 [38]	US	Retrospective cohort study of 72,602 children born ≥32 wGA	1.74% with medically attended RSV < 12 months old [0.69% hospitalized and 1.05% treated as outpatient)	Recurrent wheezing: as in Escobar 2010 [39], using a combination of encounter events, patient diagnoses, and prescription patterns	5	Recurrent wheezing year 5: 12.5% vs. 4.6%[a] Recurrent wheezing year 3-5: 40.0% vs. 12.3%[a]
Carbonell-Estrany 2015 [14]	Spain	Multicenter, observational, nested, case-control study of preterm (32-35 wGA) infants with RSV ($n = 125$) and controls ($n = 362$)	<12 months old	Recurrent wheezing: ≥3 wheezing episodes within 12 months. Severe recurrent wheezing: recurrent wheezing associated with at least one episode of hospitalization, or ≥3 medical attendances or ≥1 courses of systemic steroids, or asthma medication for ≥3 consecutive months or 5 cumulative months in a year	6	At 6 years of age: Recurrent wheezing: 46.7% vs. 27.4% ($P = 0.001$) Severe wheezing: 37.7% vs. 23.7% ($P = 0.010$) Total wheezing: 71.4% vs. 54.4% ($P = 0.006$)

Table 1 continued

Study	Country	Study design	RSVH status	Study definition of wheezing, asthma or chronic respiratory morbidity	Years of follow-up	Asthma/ wheezingRSV vs. control
Zomer-Kooijer 2014 [23]	Netherlands	Prospective, population-based study of 155 previously healthy term infants with RSV and 553 unselected term infants	<12 months old (0.7% hospitalized with RSV)	Asthma: recorded asthma diagnosis (ICPC coded); for 'current asthma' included diagnosis plus asthma symptoms or medication use during preceding 12 months. Wheezing episodes: parent-reported	6	Current wheeze: 21.3% vs. 8.1% Current asthma: 21.4% vs. 5.3%
James 2013 [37]	US	Retrospective study of 264 010 infant births from 2 cohorts (1996–2003 and 1995–2003) (15% with bronchiolitis during RSV season)	History of bronchiolitis <12 months of age during the RSV season	Asthma identified using ICD-9 codes	6	Asthma: 16–23% vs. 8–12%[b]
Bacharier 2012 [40]	US	Prospective cohort study of 206 infants with RSV	≤12 months old hospitalized or seen in emergency department	Asthma and wheezing: physician-diagnosed. Active asthma: physician-diagnosed asthma at any time along with parent-reported wheezing during the last year of follow-up between the child's 3rd and 7th birthdays	6	Recurrent wheezing: 92% ≥1 additional wheezing episode before 3 years Asthma by 7 years: 48% Active asthma by 7 years: 35%

Table 1 continued

Study	Country	Study design	RSVH status	Study definition of wheezing, asthma or chronic respiratory morbidity	Years of follow-up	Asthma/ wheezingRSV vs. control
Jackson 2008 [42]	US	Prospective study of 259 children with wheezing viral infections in first 3 years of life (21% RSV LRTI)	≤36 months old medically attended (majority seen in outpatients)	Asthma: combination of physician diagnosis and prescription patterns	6	Asthma (RSV before age 1): 38% Asthma (RSV before age 2): 43% Asthma (RSV before age 3): 76%
Koponen 2012 [33]	Finland	Prospective study of 166 healthy, full-term infants with bronchiolitis (70.5% RSV)	<6 months old	Asthma: physician-diagnosed or parent-reported wheezing episodes and episodes of other asthma-like symptoms	6.5 (mean)	Current asthma: 8.2% if RSV vs. 24% if non-RSV (P = 0.01)[c]
Henderson 2005 [31]	UK	Prospective population-based study of 14,062 live births [284 infants with bronchiolitis enrolled (1.1% total study cohort had RSV)]	<12 months old	Asthma: physician-diagnosed and wheezing as parent-reported	7	Asthma (at 91 months): 38.4% vs. 20.1% (P = 0.002) Wheezing (30-42 months): 28.1% vs. 13.1% (P = 0.002) Wheezing (69-81 months): 22.6% vs. 9.6% (P = 0.0001)
Fjaerli 2005 [36]	Norway	Follow-up study of 57 infants with RSV and 64 age-matched controls	<12 months old	Asthma: physician-diagnosed Wheezing: episodes of difficult breathing accompanied by a whistling noise in the chest during expiration (by authors)	7	Asthma: 54% vs. 8% ($P < 0.001$) Wheezing ≥3 episodes during follow-up period: 51% vs. 14% ($P < 0.001$)

Table 1 continued

Study	Country	Study design	RSVH status	Study definition of wheezing, asthma or chronic respiratory morbidity	Years of follow-up	Asthma/ wheezingRSV vs. control
Sigurs 2000 [10]	Sweden	Prospective cohort study of 47 infants with RSV and 93 age- and gender-matched controls (follow-up of Sigurs 1995 [28])	<12 months old	Asthma: ≥3 episodes of physician-verified wheeze Recurrent wheezing: ≥3 episodes of parent-reported wheeze	7.5	Asthma: 23% vs. 2% (P < 0.001) Recurrent wheezing: 13% vs. 0% (*P* <0.001)
Szabo 2014 [27]	Canada	Retrospective, population-based study of 145,430 children born 1996–1997 (birth cohort): LRTI cohort: 7,104 (4.9%) RSV cohort: 230 (0.2% of birth cohort and 3.2% of the LRTI cohort) Comparison cohort: 138,326 infants	<2 years old	Chronic respiratory morbidity[d]: identified by physician using ICD-9 codes – included asthma, chronic wheezing, chronic bronchitis, CLD	10	Chronic respiratory morbidity[d]: 2 to <10 years: 50.4% vs. 27.9%[e] 2 to <5 years: 41.7% vs.19.4%[e] 5 to <10 years: 31.7% vs. 18.1%[e]

Table 1 continued

Study	Country	Study design	RSVH status	Study definition of wheezing, asthma or chronic respiratory morbidity	Years of follow-up	Asthma/ wheezingRSV vs. control
Sigurs 2005 [11]	Sweden	Prospective cohort study of 46/47 infants with RSV and 92/93 age- and gender-matched controls (follow-up of Sigurs 1995 [28] and 2000 [10])	<12 months old	Asthma: ≥3 episodes of physician-verified wheezing Recurrent wheezing: ≥3 episodes of wheezing not verified by a physician	13	Asthma/recurrent wheezing during year prior to follow-up: 43% vs. 8% ($P < 0.001$) Asthma (current): 28% vs. 3.3% ($P < 0.001$) Asthma (cumulative): 37% vs. 5.4% ($P < .0001$) Recurrent wheezing (current): 15% vs. 4.3% ($P = 0.065$; NS) Recurrent wheezing (cumulative): 30% vs. 16.3% ($P = 0.093$)
Stein 1999 [30]	US	Prospective study of 888 children with LRTI in first 3 years of life	472 (90.2%) had recorded virus test; of these, 207 (43.9%) had RSV but were not hospitalized	Current wheeze: infrequent wheeze (up to 3 episodes in preceding 12 months) or frequent wheeze (>3 episodes in preceding 12 months)	13	Frequent wheezing: 4.3 times more likely at year 6 compared to children with no LRTI
Ruotsalainen 2013 [32]	Finland	Prospective study of 67 children with RV or RSV bronchiolitis and 155 matched controls	<2 years old	Asthma: physician-diagnosed or self-reported	15.6 (median)	Wheezing symptoms: 32.8% vs. 12.9%

Table 1 continued

Study	Country	Study design	RSVH status	Study definition of wheezing, asthma or chronic respiratory morbidity	Years of follow-up	Asthma/ wheezingRSV vs. control
Sigurs 2010 [29]	Sweden	Prospective cohort study of 46/47 infants with RSV and 92/93 age- and gender-matched controls (follow-up of Sigurs [28], [10] and [11]	<12 months old	Asthma: ≥3 episodes of physician-verified wheeze Recurrent wheezing: ≥3 episodes of parent-reported wheeze	18	Asthma/recurrent wheezing: 39% vs. 9% ($P = 0.001$) Asthma alone: 33% vs. 7% ($P < 0.001$)
Korppi 2014 [12]	Finland	Prospective study of 36 children with RSV and 45 age-matched controls	<2 years old	Asthma: physician-diagnosed or self-reported wheezing or prolonged cough during the preceding 12 months	18–20	Asthma: 17–22%[ef] vs. 11%
Ruotsalainen 2010 [13]	Finland	Prospective study of 40 children with RSV and 80 matched controls	<2 years old	Asthma: physician-diagnosed or self-reported	>25	Asthma: 13–30% vs. 1.3–3.8%[e] Wheezing: 35% vs. 16.3%
Backman 2014 [41]	Finland	Prospective follow-up study of 43 adults with RSV (24 confirmed and 19 probable RSV) and 86 population-based controls	<2 years old	Asthma: physician-diagnosed or self-reported	30	Asthma: 23–28% vs. 13–17%[e]

Summary

Number of studies	Number of countries	Years of follow-up	Recurrent wheezing (%)	Asthma (%)
2	2	1	4–15.5	11
4	4	1–3	16.2–35	23
1	1	3–5	12.5–40.0	–
9	7	6–8	13–46.7	8.2–76

Table 1 continued

Summary				
Number of studies	**Number of countries**	**Years of follow-up**	**Recurrent wheezing (%)**	**Asthma (%)**
4	2	13–30	15–35	13–37

CI confidence interval, *CLD* chronic lung disease, *ICD* International Classification of Diseases, Clinical Modification codes, *ICPC* International Classification of Primary Care, *LRTI* lower respiratory tract infection, *NR* not recorded, *NS* not statistically significant, *OR* odds ratio, *RR* risk ratio, *RSV* respiratory syncytial virus, *RSVH* respiratory syncytial virus hospitalization, *RV* rhinovirus, *SPT* skin prick test, *wGA* weeks' gestational age

[a] Versus children without RSVH

[b] Data for the 2 cohorts versus children without a history of infant bronchiolitis during RSV season

[c] Current asthma

[d] Defined as asthma, chronic wheezing, chronic bronchiolitis or chronic lung disease

[e] Depending on asthma definition

[f] Current and previous asthma and wheezing or prolonged cough during preceding 12 months

2000s [50, 51] suggest that the risk of early school-age asthma following RSVH might be of a similar order or slightly lower than that seen in children hospitalized with wheezing with no evidence of RSV (8–50% vs. 45–57%, respectively, depending on age at admission) [51]. Valkonen et al. [47] reported that Turkish children hospitalized with bronchiolitis caused by viruses other than RSV develop recurrent wheezing at substantially higher rates than do children with RSV-associated bronchiolitis. The risk of developing recurrent wheezing was significantly increased in the non-RSV group within the first 2 years [relative risk (RR), 2.9; 95% CI, 1.7–5.1] and 3 years (RR, 3.4; 95% CI, 2.0–5.7) after hospitalization [47]. A more recent study from Spain found that children aged ≥4 years with a history of rhinovirus, metapneumovirus or bocavirus associated bronchiolitis had more hospital admissions for respiratory conditions than RSV-positive children for respiratory conditions (30% vs. 17%, respectively; $P = 0.075$), persistent asthmatic symptoms (25% vs. 7%; $P = 0.003$), and asthmatic exacerbations in the last year (40% vs. 22%; $P = 0.023$) [48]. Studies have indicated that the differences in risk of wheezing/asthma following RSV versus non-RSV bronchiolitis is not associated with differences in age, seasonal factors, prematurity, day-care attendance, atopic dermatitis, allergic sensitization, pulmonary function, smoke exposure, sex, or family history of asthma/allergic rhinitis [47–49].

The risk of asthma after bronchiolitis may be related to the severity of the first episode [49, 52, 53]. In a prospective study by Carroll et al. [52], 18% of children with clinically significant bronchiolitis during infancy accounted for 31% of children with early childhood asthma. In addition, the level of healthcare utilization during the bronchiolitis episode correlated with the risk of subsequent asthma, with the greatest risk of asthma following bronchiolitis hospitalization. Relative to children with no history of infant bronchiolitis, the adjusted ORs for asthma were 1.86 (95% CI, 1.74–1.99), 2.41 (2.21–2.62) and 2.82 (2.61–3.03) in the Outpatient, Emergency Department, and Hospitalization groups, respectively [52]. Al-Shawwa et al. [49]

evaluated the potential effect of severity of RSV LRTI on subsequent wheezing in 155 children <2 years of age. Again, hospitalized patients were more likely to have recurrent wheezing compared with non-hospitalized patients (OR 2.84; 95% CI, 1.24–6.50) [49].

Long-term Respiratory Morbidity in Specific High-risk Groups

Premature Infants

Infants born prematurely are at risk of RSV-related sequelae, including recurrent wheezing [14, 39, 54–57]. Data from a prospective study by Greenough et al. [56] demonstrated that chronic respiratory morbidity occurs in preterm infants born between 32 and 35 weeks' gestational age (wGA), regardless of whether their RSV infection required hospitalization. Escobar et al. [38] retrospectively studied 72,602 infants born at ≥32 wGA. In total, 1.74% had a confirmed RSV infection (0.69% were hospitalized and 1.05% were treated as an outpatient). Across all children, the prevalence of recurrent wheezing decreased over time from 5.6% during the second year of life to 4.7% during the fifth year of life. Three important risk factors (RSV disease in the first year of life, moderate prematurity and exposure to supplemental oxygen in the neonatal period) emerged to be significantly associated with the development of recurrent wheezing during the fifth year of life. The adjusted OR for prolonged RSVH was 2.59 (95% CI, 1.49–4.50) [38]. Similarly, data from the SPRING study [14], a multicenter, observational, nested, case–control study undertaken in Spain, showed a decline in the incidence of wheezing with age. While the incidence of recurrent wheezing was higher in cases than in controls for each individual year of follow-up, the difference remained statistically significant only during the first 3 years of life (Table 2). However, when considering the overall proportion of cases and controls that experienced recurrent wheezing through 6 years of age, this was significantly greater in the former than the latter (46.7% vs. 27.4%, respectively; $P = 0.001$). Multivariate analysis revealed that RSVH was the most important factor for wheezing (recurrent wheezing: OR, 4.40; 95% CI, 2.82–6.86; $P < 0.001$; severe wheezing: OR, 4.31; 95% CI, 2.78–6.68; $P < 0.001$) [14].

A 12-month follow-up of the French CASTOR (Comparison of the rAte of hoSpitalization for RSV bronchioliTis between preterm infants born at 32 weeks' gestational age or less without brOnchopulmonary dysplasia and full-teRm infants) study cohort was undertaken to evaluate the respiratory morbidity of preterm infants <33 wGA without BPD during the subsequent 12-month period [54]. In this study, 242 preterm infants were compared with 201 full-term infants (39–41 wGA). Preterm infants had increased respiratory morbidity during the follow-up period compared with full-term infants; they were more likely to have wheezing (21% vs. 11%, $P = 0.007$) and recurrent wheezing (≥3 episodes of within 12 months; 4% vs. 1%, $P = 0.049$). The 17 infants (14 preterms, 3 full-terms) who had been hospitalized for RSV-confirmed LRTI during their first RSV season had significantly more wheezing episodes during the follow-up period than the infants who had not been hospitalized for RSV confirmed LRTI (OR, 4.72; 95% CI, 1.71–13.08; $P = 0.003$) [54].

Congenital Heart Disease

Whilst it is well established that children with CHD are at risk for severe RSV LRTI, limited data are available on the long-term respiratory morbidity associated with RSVH in early life in this patient population. In a retrospective study of 3223 children with CHD, 19 (0.6%) and 417 (12.9%) were hospitalized for RSV or LRTI, respectively, before the age of 2 years [58]. Fifty-nine percent of children with CHD who were hospitalized for LRTI in infancy were diagnosed with chronic respiratory morbidity at the age of 10 years, as compared with 31.5% of children with CHD not hospitalized for LRTI in infancy [58].

Down Syndrome

Down syndrome is an independent risk factor for RSVH and severe RSV disease [59]. There are limited data, however, on long-term respiratory morbidity associated with RSV LRTI in early life

Table 2 Incidence of recurrent wheezing years 2–6 in the SPRING study[a] [14]

Wheezing	Year 2		Year 3		Year 4		Year 5		Year 6	
	RSV[b]	Control	RSV[b]	Control	RSV[b]	Control	RSV[b]	Control	RSV[b]	Control
Number of children (%)	41.4	12.1	29.3	15.4	18.5	12.6	15.0	9.3	12.4	9.7
P	<0.001		0.001		NS		NS		NS	
OR (95% CI)	5.14 (2.68–9.87)		2.28 (1.41–3.70)		1.58 (0.91–2.75)		1.72 (0.92–3.20)		1.32 (0.68–2.59)	

CI confidence interval, *NS* not statistically significant, *OR* odds ratio, *RSV* respiratory syncytial virus

[a] For each individual year of follow-up, the number (proportion) of children with wheezing is shown, utilizing all available data for that particular year (therefore, the same child may be included in more than 1 year). Recurrent wheezing defined as ≥3 episodes of wheezing within 12 months

[b] RSVH in preterm infants (32–35 weeks' gestational age) in first year of life

in children with Down syndrome. In a combined retrospective/prospective cohort study, Bloemers et al. [60] found that RSV LRTI did not significantly contribute to the risk of recurrent wheeze in children with Down syndrome (RSVH: 36% vs. non-hospitalized: 30%; not statistically significant). Similar non-significant differences were found for parent-reported recurrent wheeze (42% vs. 32%, respectively) and physician-diagnosed asthma (11% vs. 9%, respectively). Physician-diagnosed wheeze, however, was more common in children with Down syndrome hospitalized for RSV LRTI than healthy controls (31% vs. 8%; $P = 0.004$). The authors proposed that abnormal lung function or airway hyper-responsiveness, as well as an abnormal immunologic status, could play a role in the development of long-term airway morbidity in children with Down syndrome, irrespective of RSV status [60].

Reduced Lung Function

RSV LRTI in early life is associated with reduced lung function and increased airway reactivity at school age [11, 12, 30, 36, 61, 62], potentially extending into adulthood [12]. A prospective cohort study from the UK reported that viral LRTIs, regardless of hospitalization, adversely affect preterm infants' (<36 wGA) lung function at 12-month follow-up [63]. Longer-term data from the UK demonstrated that preterm infants (<32 wGA) who develop bronchopulmonary dysplasia (BPD) and are hospitalized for RSV infection in the first 2 years of life have significantly worse lung function at 8–10 years [62]. Similarly, the Tucson Children's Respiratory Study reported that children who had RSV LRTI before the age of 3 years had decreased lung function at school age [30]. In a prospective, 20-year follow-up study from Finland, at least one abnormal lung function result was observed in 44% of subjects who developed RSV LRTI in the first 2 years of life, compared with 31% of controls ($P < 0.05$) [12]. In addition, RSV LRTI in infancy was an independent risk factor for lung function abnormality [spirometric airway function (FVS; OR, 5.27, 95% CI, 1.60–17.36) and also for decreased forced expiratory volume in 1 s FEV_1/FVC (FEV%) and mid-expiratory flow at 50% of FVC (MEF50), when these were analyzed separately] [12]. At the 18-year follow-up of the study by Sigurs et al. [29], reduced spirometric airway function [1 s FEV_1, ratio of FEV_1 to FVC, and forced expiratory flow at 25–75% FVC ($FEF_{25–75}$)] was observed in the RSV cohort compared with controls. However, in contrast to the previous studies, a Finnish study indicated a potentially more restrictive pattern of lung function abnormality, documented by significantly decreased FVC values concomitantly with normal FEV_1 values and even elevated FEV_1/FVC values [64]. Finally, another recent study from Finland observed that less than 1% of 5- to 7-year-old children, hospitalized for bronchiolitis caused mainly by RSV at age <6 months, had persistent lung function reduction [65].

It is unclear whether the abnormalities in lung function seen at follow-up result from the

RSV infection itself or reflect premorbid abnormal lung function [62]. Studies from the Netherlands indicate that both hypotheses may be involved [66]. The MAKI trial has strongly implicated RSV infection as an important mechanism of recurrent wheeze during the first year of life in such infants [66]. A further study from the same group proposed that lower lung function in school-aged children that were previously hospitalized for RSV LRTI cannot only be attributed to the RSV infection itself, but might be partially pre-existent [67].

Factors Associated with the Development of Recurrent Wheezing/Asthma after RSV LRTI in Early Life

Risk Factors

Several risk factors associated with the development of asthma in children with a history of RSV LRTI in early life have been proposed by Cassimos et al. [68]. In this retrospective study, the development of asthma was independently associated with male gender [adjusted odds ratio (aOR), 5.0; 95% CI, 2.2–11.5], breast-feeding <3 months (aOR, 8.4; 95% CI, 3.1–22.4), living in a home environment with moisture damage (aOR, 2.9; 95% CI, 1.3–6.3) and/or tobacco smoke by two or more residents (aOR, 4.9; 95% CI, 1.8–9.2), and sensitization to at least one aeroallergen (aOR, 7.1; 95% CI, 2.8–18.1). Lung function was significantly lower in children with RSV LRTI compared to a matched control group, even in children with a history of RSV LRTI who were not asthmatic [68].

The mechanisms underlying the interaction between RSV LRTI in infancy and active smoking as determinants of asthma in early adult life are unknown [69]. Further findings from the Tucson Children's Respiratory Study indicate that subjects with RSV LRTI during the first 3 years of life who actively smoke are at increased risk of having current asthma (95% CI, 1.2–2.3; $P = 0.003$) and increased peak flow variability (amplitude % mean: 10.0% vs. 6.4%; $P = 0.02$) in adulthood, as compared with those who do not smoke [69]. The authors suggest that their findings support the potential interactive role of early-life insult by RSV and subsequent active cigarette smoking on the development of obstructive lung diseases, such as asthma and chronic obstructive pulmonary disease (COPD), in later life [69].

Atopy and Allergy

There are limited and conflicting data on the association between RSV LRTI in early life and the subsequent development of clinical allergy and/or allergic sensitization. Sigurs et al. [10, 11] demonstrated that RSV severe enough to cause hospitalization was significantly associated with the development of allergic sensitization up to the age of 13 years. Multivariate analyses of possible risk factors for sensitization showed that RSV LRTI was a significant independent risk factor for allergic sensitization (OR, 2.4; 95% CI, 1.1–5.5) [10]. Similarly, Schauer et al. [34] found RSV LRTI to be the single most important risk factor for sensitization (OR, 20.66; 95% CI, 3.53–120.75). In the study by Korppi et al. [12], the presence of asthma, bronchial reactivity, and lung function abnormalities after RSV infection in infancy were clearly associated with atopy, as defined by skin test responses to common inhaled allergens. Several other studies, however, did not find an association between RSV infection and subsequent atopy [30, 31, 41, 70]. Stein et al. [30] found no link between the incidence of RSV LRTI in early life and the subsequent development of atopic sensitization. Henderson et al. [31] also did not observe a significant association between RSV LRTI in infancy and allergic sensitization to aeroallergens at age 7 years. Finally, Strannegård et al. [71] reported that RSV LRTI may be an important risk factor for later development of atopic disease, but the authors could not exclude that bronchiolitis simply serves as a marker that predicts later development of atopy.

Genetic Factors

Not all children exposed to RSV experience subsequent wheezing, suggesting that genetic factors may also play a role in this phenomenon [72]. Several studies have therefore aimed to identify genetic determinants of recurrent wheeze after RSV LRTI [72–77].

Results of a multicenter cohort study by Schuurhof et al. [73] found that the production of IL10 by monocytes after RSV infection is higher in patients with recurrent wheezing than in patients without wheezing [74]. In a 6-year, prospective, follow-up study of 101 children hospitalized for RSV LRTI at ≤12 months of age, the IL-13 Gln allele was found to be associated with late wheezing (OR, 3.27; 95% CI, 1.32–8.06), but not with early wheezing [75]. The IL8 polymorphism was not shown to be related to either early or late wheezing after RSV LRTI in this study [75]; however, it was found to be related to wheezing and RSV LRTI in a study by Goetghebuer et al. [77]. In a subsequent study by Ermers et al. [76], the genetic variation in adaptive immunity genes, and particularly in *IL10* family member genes *IL19* and *IL20* genes, seemed to be associated with recurrent wheeze after RSV LRTI, and perhaps infant wheeze in the general population. This suggests a role for IL19 and IL20 cytokines in airway disease.

A more recent study from the United States demonstrated that rare nonsynonymous variants contribute to the development of asthma following severe RSV LRTI in infancy, notably *ADRB2*. Torgerson et al. [72] performed pooled, anonymous, sequencing of coding exons from 131 asthma candidate genes in 182 individuals (99 European Americans and 83 African Americans) with severe RSV LRTI in infancy from the REBEL study [40] for variant discovery, and then directly genotyped a set of 190 nonsynonymous variants. Four rare, nonsynonymous variants were found to be significantly associated with asthma following severe RSV LRTI, including single variants in *ADRB2*, *FLG* and *NCAM1* in European Americans ($P = 4.6 \times 10^{-4}$, 1.9×10^{-13} and 5.0×10^{-5}, respectively), and *NOS1* in African Americans ($P = 2.3 \times 10^{-11}$) [72]. Additional studies are needed to confirm these associations and determine the functional consequences of these genetic variants.

Three population-based studies of twins, undertaken in Denmark utilizing bronchiolitis information from patient registries, assessed causality between RSV infection in infancy and childhood asthma [16, 78, 79]. Thomsen et al. [78] reported that RSV infection severe enough to require hospitalization did not appear to cause asthma but was an indicator of the genetic predisposition to asthma. Stensballe et al. [79] reported that asthma hospitalization after RSVH was increased as much as six- to eight-fold during the first 2 months after RSVH but not 1 year later. A further study of 37 monozygotic twin pairs discordant for severe RSV bronchiolitis in infancy indicated no differential effect of severity of RSV infection on the development of asthma [16].

Altered Immunology

One of the specific characteristics of asthma is an imbalance in Th1- and Th2-predominant immune responses [80]. Castro et al. [80] hypothesized that severe RSV infection resulting in bronchiolitis may stimulate a persistent Th2 response profile with elevated IL4 and IL13 production at 6 years of age in those children who developed asthma. Two hundred and six previously healthy infants hospitalized for a first episode of RSV LRTI were enrolled into the REBEL cohort study and followed prospectively through 6 years of age. Th1 cytokines tended to decrease over time after initial severe RSV bronchiolitis and Th2 cytokines tended to increase over time, but these patterns were unrelated to asthma and allergy outcomes. No significant difference in Th1 or Th2 cytokine production at the initial RSV infection was observed in those who developed asthma or allergic sensitization by 6 years of age as compared to those who did not. Furthermore, the production of Th2 cytokines relative to Th1 cytokines, represented by the ratio of IL4: IFN-γ, was not different in those who developed asthma compared to those who did not. Th1 cytokines tended to decrease over time after initial severe RSV bronchiolitis and Th2 cytokines tended to increase over time but these patterns were unrelated to asthma and allergy outcomes [80].

Plasmacytoid dendritic cells play a crucial role in antiviral immunity and promoting Th1 polarization, possibly protecting against development of allergic disease [81]. Silver et al. [81] showed that children with a history of severe RSV LRTI in early life and physician-diagnosed asthma by age 6 years appear to have a relative deficiency of plasmacytoid dendritic cells in

peripheral blood compared to those who were not diagnosed with asthma. Further data from a recent prospective study demonstrated that children with recurrent wheezing following severe RSV LRTI had a higher proportion of nasal plasmacytoid dendritic cells, which may reflect a heightened antiviral response in the airway leading to the subsequent development of asthma [82]. Further studies are therefore needed to confirm these findings.

Researchers have also evaluated the relationship between viral load in infants hospitalized for RSV and recurrent wheezing later in childhood. Nenna et al. [83] observed higher RSV-RNA load and significant correlations between RSV-RNA load and higher interferon-λ1/2/3 levels in children previously hospitalized for RSV LRTI and diagnosed with recurrent wheezing at 3 years follow-up.

Eosinophilia

Several studies have shown that eosinophilia at the time of bronchiolitis is associated with a higher risk of developing persistent wheezing in later childhood [84–87]. Calvo Rey et al. [84] reported that eosinophil values of >1% during an episode of acute bronchiolitis in infancy was associated with a higher risk of developing persistent wheezing in the first 5 years of life. Ehlenfield et al. [85] retrospectively studied 43 infants hospitalized with RSV LRTI at ≤18 months old. Of children who had eosinophilia with RSV LRTI, 56% had persistent wheezing at 7 years of age compared with 22% without detectable eosinophilia with RSV LRTI ($P = 0.045$) [84]. In a further study, Pifferi et al. [86] observed significantly higher serum eosinophil cationic protein levels ($P < 0.001$) at enrolment in infants with RSV LRTI who developed persistent wheezing 5 years later compared with subjects who did not develop late wheezing. Similarly, Kristjánsson et al. [87] reported that a high level of urinary eosinophil protein X appeared to increase the risk of future wheezing in children hospitalized for RSV LRTI.

Maternal Antibody

A case–cohort study undertaken in Denmark examined the influence of maternally derived RSV neutralizing antibodies on the risk of RSVH and recurrent wheeze using data from The Danish National Birth Cohort and the RSV Database [88]. Stensballe et al. [88] identified 2562 children with RSVH and 6153 children with recurrent wheeze. One of the main findings of the study was that the titer of maternally derived RSV neutralizing antibodies in cord blood was associated with an increased risk of recurrent wheeze in children both with and without RSVH [88].

Long-term Respiratory Morbidity and Impact on Quality of Life and Cost of Care

RSV LRTI is associated with subsequent decreased QoL and increased healthcare costs [14, 15, 41], although data remain limited. In the SPRING study [14], the respiratory subscale QoL of the preschool children Quality of Life questionnaire (TAPQOL) was significantly lower ($P = 0.001$) through 6 years of age in preterm infants born 32–35 wGA hospitalized for RSV infection in the first year of life than in controls. Backman et al. [41] also reported that, on average, former RSV patients had a lower respiratory health-related quality of life (HRQoL) on the St George's Respiratory Questionnaire (components: symptoms, activity, impact), at 28–31 years of age than population-based controls. The difference was mainly seen in the symptoms score ($P = 0.005$) [41]. In an earlier study, Bont et al. [15] reported that HRQoL at 3 years of age was attributed to post-bronchiolitis wheezing, but not to pre-existent risk factors, such as age, gender and premature birth. In addition to these studies, two further studies from Norway demonstrated that being hospitalized for acute bronchiolitis (specific virus not stated) in infancy was significantly associated with later reduced QoL and that disease severity appeared to negatively influence

the QoL of the infants and the parental perception of the child's health 9 months later [89, 90].

Healthcare resource utilization was significantly higher ($P < 0.001$) through 6 years of age in cases than controls in the SPRING study [14]. Greenough et al. [91] reported that preterm infants who had had CLD had a greater number of outpatient attendances for respiratory problems (mean 2.52 vs. 0.85; $P = 0.007$). In addition, the cost of care was significantly greater for outpatient attendances, including those for respiratory problems [91]. A further study by Greenough et al. [62], that enrolled the same cohort of children, found that those who were hospitalized for RSV in the first 2 years after birth had more outpatient attendances and a greater related cost of care between the ages of 5–7 and worse lung function than children not admitted in the first 2 years for a respiratory cause. Healthcare utilization, however, decreased with increasing postnatal age regardless of RSVH status [61].

Limitations

There are several key limitations of this review that should be recognized, most notably the variability in defining wheeze and asthma between studies, which restricts cross-study comparisons. Allied to this are the differences in frequency and length of follow-up between studies and the relatively limited amount of prospective data beyond 7–8 years after the index RSVH. Differences in study populations in terms of the presence of underlying comorbidities and prematurity, for example, also complicate interpretation of the results. The confounding influence of co-infections, which were infrequently documented in studies, might also in part account for discrepancies in findings among studies. Improvements over time in both medical and surgical practice and RSV surveillance may also influence interpretation of the results.

Key statements/findings	Level of evidence[a]
There is increasing evidence that RSV LRTI in early life is a significant risk factor for subsequent recurrent wheezing/asthma, persisting at least through early childhood	Level 1 (Level 1 studies: $n = 21$; Risk of bias[b]: very low)
Recurrent wheezing rates of 4–47% and asthma rates of 8–76% have been reported in studies with up to 25 years follow-up (average follow-up 6–8 years)	
RSV LRTI in early life is associated with reduced lung function and increased airway reactivity	Level 1 (Level 1 studies: $n = 8$; Risk of bias[b]: very low)
Abnormalities reported for spirometric airway function include reduced FEV_1, FEV_1/FVC, and $FEF_{25–75}$	
RSV-related respiratory morbidity may be related to a combination of the viral insult, preexisting abnormal lung function and/or other factors predisposing for wheezing/asthma	Level 1 (Level 1 studies: $n = 17$; Risk of bias[b]: very low)
Other factors include: genetics (e.g. increased production of IL10), altered immunology (e.g., altered plasmacytoid dendritic cell levels), eosinophilia, transfer of maternally derived RSV antibody, and other risk factors (e.g., tobacco smoke exposure)	
There is conflicting evidence on the association between RSV LRTI in early life and the subsequent development of clinical allergy and/or allergic sensitization	Level 1 (Level 1 studies: $n = 7$; Risk of bias[b]: very low)
RSV LRTI is associated with decreased quality of life and increased healthcare costs, although data are limited	Level 1 (Level 1 studies: $n = 6$; Risk of bias[b]: very low)

continued

Key statements/findings	Level of evidence[a]
Key areas for research:	
Further prospective, follow-up studies are needed to clarify the risk factors and long-term respiratory outcome of children hospitalized for severe RSV LRTI (including in specific populations, such as those with CHD, and the potential link with COPD/emphysema)	
Future research should aim to elucidate the pathophysiological mechanisms through which RSV LRTI causes recurrent wheezing/asthma	

CHD congenital heart disease, *CI* confidence interval, FEV_1 forced expiratory volume in one second, FEV_1/FVC percentage of the vital capacity which is expired in the first second of maximal expiration, FEF_{25-75} forced expiratory flow at 25–75% of the pulmonary volume, *LRTI* lower respiratory tract infection, *NS* not statistically significant, *OR* odds ratio, *RSV* respiratory syncytial virus

[a] Level 1 local and current random sample surveys (or censuses); Level 2 systematic review of surveys that allow matching to local circumstances; Level 3 local non-random sample; Level 4 case-series [24, 25]

[b] Average RTI Item Bank Score [26], where ≤2 = very high risk of bias and 10–12 = very low risk of bias

CONCLUSIONS

There is a growing body of evidence to suggest that RSV LRTI, regardless of hospitalization status, is a significant risk factor for on-going respiratory morbidity characterized by transient early wheezing and recurrent wheezing within the first decade of life and possibly into adulthood. These infants are also at increased risk of reduced pulmonary function and a higher risk or predisposition to asthma and allergies. The increased respiratory morbidity may lead to a reduced QoL and increased health care costs. It still remains unclear, however, whether RSV LRTI causes respiratory morbidity and/or serves as a marker for those infants genetically predisposed to develop asthma or wheezing. Further prospective, follow-up studies are needed to clarify the risk factors and long-term respiratory outcome of children hospitalized for severe RSV LRTI. Future research should aim to elucidate the pathophysiological mechanisms through which RSV LRTI causes recurrent wheezing/asthma.

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