



Elevated risk of asthma after hospitalization for respiratory syncytial virus infection in infancy

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SUMMARY

Severe respiratory syncytial virus (RSV) infection in infancy is associated with substantial morbidity worldwide; whether it is a risk factor for childhood asthma is contentious. A systematic review of 28 articles was conducted, summarizing estimates of asthma risk after RSV hospitalization during infancy. Prevalence estimates of asthma, among those hospitalized for RSV in infancy, were from 8% to 63%, 10% to 92%, and 37%, at ages <5, 5 to 11, and ≥12 years, respectively. These rates were higher than those among non-hospitalized comparisons. The attributable risk of asthma due to RSV ranged from 13% to 22% and from 11% to 27% among children aged ≤5 and aged 5 to 11, respectively, and was 32% among children ≥12 years of age. Overall, 59% of asthma prevalence estimates from those previously hospitalized for RSV exceeded 20%, compared to only 6% of non-hospitalized comparison estimates. Despite variability in asthma prevalence estimates after RSV-related hospitalization, available data suggest a link between severe RSV infection in infancy and childhood asthma.

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Introduction

Severe respiratory syncytial virus (RSV) infection is a leading cause of hospitalization for bronchiolitis among infants in both industrialized and developing nations.¹ Many investigators have shown that the risk of developing childhood chronic respiratory conditions, including asthma, is elevated among those hospitalized for RSV disease in infancy,^{2–6} and that the increased risk may persist into adulthood.^{3,7} Rates of asthma among those previously hospitalized for RSV disease appear higher than asthma rates from the general population of North America and Europe.⁸

There is substantial variability in published asthma prevalence estimates among those hospitalized for RSV disease in infancy, however.^{2–4,6,7,9–31} Summarizing the evidence on asthma risk is challenging, as estimates are derived from studies with heterogeneity in study design, duration, and outcome definition; and many studies included small samples underpowered to detect significant differences in outcomes, particularly over lengthy follow-up. Only one recent systematic review has evaluated asthma risk among those with severe RSV disease,³² and reported an association based on twelve studies (which did not require that individuals be hospitalized). As effective prophylactic strategies against severe RSV disease exist,

particularly for babies in high-risk subgroups such as those born premature,³³ accurate estimates of the association between severe RSV and asthma are critical to understanding whether the upfront investment in prophylaxis is offset by cost savings over the long term. Updated estimates are also important, given recent reports of elevated asthma risk among cohorts hospitalized for RSV in infancy, followed for 20 to 30 years.^{3,7} However, a thorough and recent synthesis of age-specific estimates of asthma risk after hospitalization for RSV disease in infancy is lacking.

The objective of this study was to summarize estimates of asthma risk among those hospitalized for severe RSV disease during infancy, from the published literature. The synthesis provides ranges of asthma prevalence among those hospitalized for RSV disease during infancy, and considers the impact of heterogeneity in disease definitions and sources of report on those estimates of risk. These estimates are useful for quantifying increased asthma risk after hospitalization for severe RSV disease in infancy, and target populations with increased susceptibility.

Methods

A systematic review was conducted, synthesizing asthma prevalence and increased risk estimates, among those hospitalized for severe RSV disease in infancy, according to age and the period over which asthma was measured.

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Study selection

During search strategy development, chronic respiratory morbidity was broadly defined to include asthma or recurrent wheezing, to ensure all relevant articles were identified. References from 1950 onwards listed in the MEDLINE, EMBASE, and the Cochrane Library databases were searched through July 2010. Reference lists of retrieved articles were hand-searched to identify additional relevant articles.

Study selection involved a preliminary review of identified abstracts, followed by an in-depth review of full-text articles meeting the inclusion criteria. These were: (1) original article, in English; (2) hospitalization for confirmed RSV disease during the first two years of life; (3) reporting on recurrent wheezing, chronic bronchitis, or asthma, by physicians, parents, or self; and (4) at least 18 months of follow-up after RSV-related hospitalization. Consensus on study eligibility was reached by two independent reviewers.

The focus was on studies evaluating the association between hospitalization for RSV disease and subsequent asthma, from representative North American or European samples. To maximize generalizability and minimize the opportunity for selection bias to affect synthesized estimates, articles focusing on highly specific target populations (e.g., Alaskan First Nations) or with objectives other than measuring the association between RSV hospitalization and asthma, were excluded. No studies were excluded based on design or sample size.

Data extraction

Double data extraction was conducted by two independent reviewers. Asthma was classified according to the definition used by the investigators from the original publication. Prevalence was considered according to three age categories, based on guidelines for the diagnosis and management of asthma: (i) <5; (ii) 5 to 11; and (iii) ≥ 12 years of age.³⁴ Asthma prevalence estimates were grouped according to whether they were calculated cumulatively over the period, or described current symptoms (over the preceding 12 months). Study groups could contribute multiple prevalence estimates within the same age category from separate publications, provided the estimates were measured after differing lengths of follow-up. For studies reporting multiple outcome measures, diaries were prioritized over questionnaires. Studies reporting risks of asthma that spanned age categories were assigned to the oldest age category.²³

Three additional potential covariates were evaluated: (i) age at RSV-related hospitalization (<12 or <24 months), (ii) inclusion of infants at high risk of severe RSV disease,³³ and (iii) source of report (parent/self or physician).

Analysis

Risk estimates from those previously hospitalized for RSV disease, and from non-hospitalized comparison samples from the same studies, were graphed and visually compared. Prevalence estimates in each age category were summarized by ranges and scatterplots to explore between-study variability. The differences in the frequency of estimates above commonly observed asthma prevalences from the general population (>10%, >20%)⁸ were compared between those hospitalized and those not hospitalized for RSV disease using histograms. Among the studies with non-hospitalized comparison groups, estimates of the increased risk of asthma in those previously hospitalized for RSV disease were summarized using published relative risks or odds ratios, and calculated risk differences (i.e., attributable risks).³⁵

As a sensitivity analysis, articles describing severe recurrent wheezing, that could potentially be misclassified asthma,³⁶ were

also included. The outcome measures employed to classify recurrent wheezing by the original investigators were reviewed by two physicians experienced in the diagnosis and management of pediatric asthma. Those articles reporting recurrent wheezing considered sufficiently severe to potentially be indicative of asthma (usually physician-confirmed or multiple episodes of documented wheezing) were included in a second stage of (sensitivity) analysis.

Results

The search identified 2,544 potentially eligible abstracts; 28 of those were eligible (Figure 1). Prevalence estimates from those 28 studies evaluating the association between hospitalization for RSV disease in infancy and asthma, according to age at follow-up, are summarized below.^{2–4,6,7,9–31} No major trend was seen according to age at RSV-related hospitalization, the inclusion of high-risk infants, or source of report (*data not shown*).

Younger than 5 years of age

Cumulative estimates of asthma prevalence (Figure 2; $n = 6$) among those 2 to 4 years of age hospitalized for RSV disease during infancy ranged from 8% to 63%.^{9,10,12,17,18,31} Five estimates (83%) were >10% prevalence, and three (50%) were >20%. The 8% prevalence estimate was from a study measuring asthma by prescription reimbursement, and lacked a healthy comparison group.¹⁸ The 63% prevalence estimate came from a study that also reported a 13% asthma prevalence among a comparison group hospitalized for rotavirus, where only 52% of the sample completed the assessment.³¹ The remaining four estimates of cumulative asthma prevalence ranged from 10%¹⁷ to 32%⁹ for those <5 years of age hospitalized for RSV during infancy.

Two studies compared RSV-related asthma risk to non-hospitalized groups. Both cumulative prevalence estimates among non-hospitalized comparison groups were 1% (vs. 15%¹² and 23%¹⁰ for RSV). The attributable risk (Table 1) of asthma due to RSV disease among those <5 years of age ranged from 13%¹² to 22%.¹⁰

Two studies without non-hospitalized comparison groups estimated current asthma prevalence among those 3 or 4 years of age (Figure 2). One study reported two estimates; 78% for 'symptoms suggestive of asthma', and 43% for physician-diagnosed asthma.¹⁵ The other reported a lower prevalence (22%) based on >3 episodes of physician-diagnosed wheezing, with pre-existing wheezing or medications.²⁰

5 to 11 years of age

Cumulative estimates of asthma prevalence (Figure 2; $n = 7$) among individuals 5 to 11 years of age hospitalized for RSV disease during infancy ranged from 10% to 92%.^{4,11,12,14,15,17,19} All estimates were >10%, and six (86%) were >20%. The study reporting the 92% prevalence estimate classified asthma using an incomparable definition (any symptoms over a series of follow-up visits).¹⁵ The remaining six estimates of cumulative asthma prevalence ranged from 10%¹⁷ to 57%¹⁴ for those 5 to 11 years of age hospitalized for RSV disease during infancy.

Three studies compared cumulative prevalence estimates to those from non-hospitalized groups. Asthma estimates among those not hospitalized for RSV disease during infancy ranged from 3%¹¹ to 20%,⁴ compared to 26% to 38% among those hospitalized for RSV, from the same studies. The attributable risk (Table 1) of cumulative asthma due to RSV disease among those in the 5 to 11 years of age category ranged from 11%¹² to 27%.¹¹

Current asthma prevalence estimates (Figure 2; $n = 11$) among those 5 to 11 years of age hospitalized for RSV disease during infancy

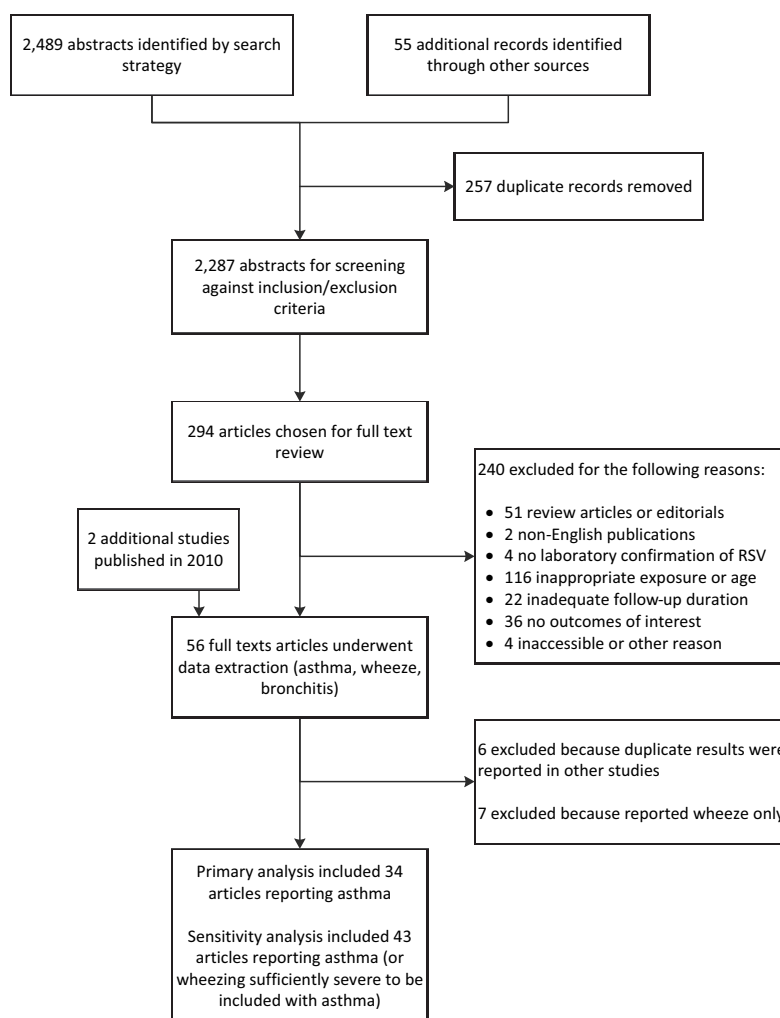


Figure 1. Schematic of study selection for the systematic review.

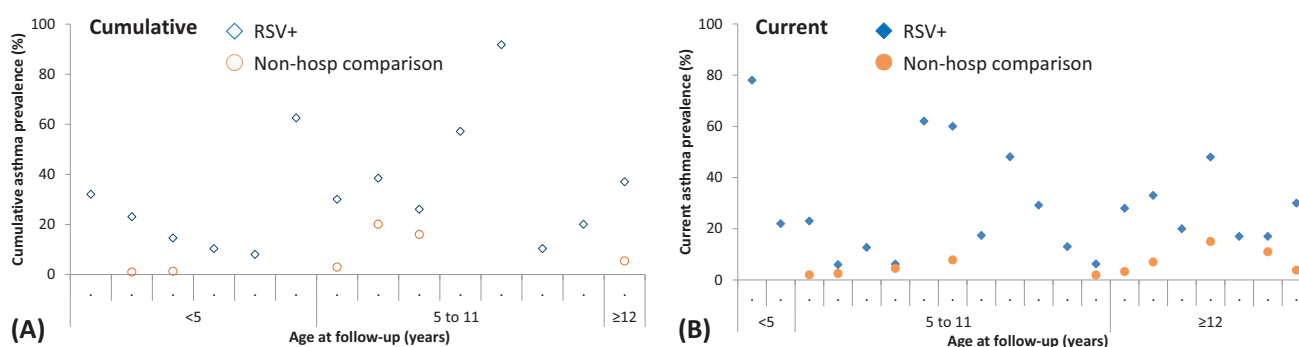


Figure 2. Prevalence estimates (%) from studies reporting on (A) the cumulative risk and (B) the current risk of asthma among those previously hospitalized for RSV disease, and non-hospitalized comparison groups, in the <5 years, 5 to 11 years, and ≥12 years age categories.

ranged from 6% to 62%.^{6,11,13–16,21,23,24,26,27} Eight estimates (73%) were >10%, and five (45%) were >20%. Three studies provided estimates of current asthma prevalence of 6%,^{6,13,27} which were higher (although not significantly so) than estimates from non-hospitalized comparison groups from the same studies (3%,¹³ 5%,⁶ and 2%²⁷). Two studies provided estimates >60%, without non-hospitalized comparisons,^{15,16} and both employed two asthma definitions, with the prevalences associated with the more restrictive definition being lower.^{15,16} The remaining six estimates of current asthma prevalence

ranged from 10% to 23% for those 5 to 11 years of age hospitalized for RSV disease during infancy.^{11,14,21,23,23,26}

Five studies compared current prevalence estimates to those from non-hospitalized groups.^{6,11,13,16,27} Current prevalence estimates ranged from 2%¹¹ to 8%¹⁶ among those not previously hospitalized for RSV disease (compared to 11% and 60% among those hospitalized for RSV during infancy from the same studies, $p < 0.01$). The attributable risk (Table 1) of current asthma due to RSV disease among those in the 5 to 11 years of age category ranged from 2%⁶ to 52%.¹⁶

Table 1

Prevalence, relative, and attributable risk of asthma due to severe RSV disease during infancy from 12 studies including groups of individuals previously hospitalized for RSV disease, and non-hospitalized comparisons

Study	RSV		Non-hospitalized comparison		Odds ratio (95% CI)	Relative risk (95% CI)	Risk difference [Attributable risk ^a] (%)	p-value ^b
	Number	Prevalence (%)	Number	Prevalence (%)				
<5 years								
<i>Cumulative measure</i>								
Sigurs et al. 1995 ¹⁰	47	23.4	93	1.1	–	21.8 (2.9–163.6)	22.3	<0.001
Juntti et al. 2003 ¹²	76	14.5	76	1.3	–	11.0 (1.5–83.1) ^c	13.2	nr
<i>Current measure</i>								
(No study available)								
5 to 11 years								
<i>Cumulative measure</i>								
Sigurs et al. 2000 ¹¹	47	29.8	93	3.2	–	9.2 (2.8–30.6)	26.6	<0.0001
Henderson et al. 2005 ⁴	73	38.4	8039	20.1	2.5 (1.4–4.3)	–	18.3	0.002
Juntti 2003 ¹²	76	26.3	76	15.8	1.9 (0.9–4.2)	–	10.5	0.11
<i>Current measure</i>								
Sigurs et al. 2000 ¹¹	47	23.4	93	2.2	–	10.9 (2.5–47.1)	21.2	<0.001
Mok and Simpson 1982 ¹³	100	6.0	200	2.5	–	2.4 (0.8–7.7) ^c	3.5	nr
Pullan and Hey 1982 ⁶	130	6.2	111	4.5	–	1.4 (0.5–4.1) ^c	1.7	ns
Fjaerli et al. 2005 ¹⁶	35	60.0 ^d	64	7.8 ^d	–	7.7 (3.2–18.6) ^c	52.2	nr
Korppi et al. 1994 ²⁷	32	6.3	52	1.9	–	3.3 (0.3–34.4) ^c	4.4	ns
≥12 years								
<i>Cumulative measure</i>								
Sigurs et al. 2005 ²	46	37.0	92	5.4	–	6.8 (2.7–17.3)	31.6	<0.001
<i>Current measure</i>								
Sigurs et al. 2005 ²	46	28.3	92	3.3	–	8.7 (2.6–28.9)	25.0	<0.001
Sigurs et al. 2010 ³	46	32.6	92	6.5	–	5.0 (2.1–12.0) ^c	26.1	<0.001
Goksor et al. 2006 ²⁵	25	48.0	294	15.0	1.3 (0.5–3.4)	–	33.0	nr
Korppi et al. 2004 ²⁹	36	16.7	45	11.1	1.6 (0.4–5.7)	–	5.6	ns
Ruotsalainen et al. 2010 ⁷	40	30.0	80	3.8	11.4 (3.0–44.1)	–	26.2	significant ^e

95% CI, 95% confidence interval.

^a Attributable risk was calculated as % prevalence RSV-hospitalized group – % prevalence non-hospitalized comparison.

^b ns, not significant; nr, not reported.

^c Calculated by review authors.

^d Two outcomes presented, currently under supervision for asthma (rather than use of asthma medication) was included here.

^e Reported $p < 0.05$ comparing hospitalized group (with and without RSV disease) vs. non-hospitalized group.

Note: only one additional estimate (by Henderson 2005 et al, for the <5 years of age category) was added in sensitivity analysis, reporting a current asthma prevalence of 18.9% (RSV-hospitalized group) vs. 6.8% (non-hospitalized comparison).

12 years of age or older

Only one study estimated the cumulative prevalence of asthma among those 12 years of age or older, at 37% among those 13 years of age hospitalized for RSV disease during infancy (compared to 5% among those not hospitalized; **Figure 2**).² The attributable risk of asthma due to RSV was 32%.

Current asthma prevalence estimates (**Figure 2**, $n = 7$) among those ≥12 years of age hospitalized for RSV disease during infancy ranged from 17% to 48%.^{2,3,7,22,25,28,29} One study used two definitions,²⁸ and one measured asthma over two periods (preceding 12 or 24 months).⁷ Two study groups contributed estimates at different ages within this category: the first, at 13 and 18 years;^{2,3} and the second, at 13–16, 18–20, and 26–29 years of age.^{2,7,28} All estimates were >10%, and four (57%) were >20%. There was one notably high estimate (48% for previous RSV hospitalization vs. 15% in the non-hospitalized comparison) from a follow-up study at 17–20 years where the outcome was wheezing or asthma and/or the need for anti-asthmatic treatment during the preceding 12 months.²⁵ The remaining six estimates of current asthma prevalence ranged from 17% to 33% for those ≥12 years of age hospitalized for RSV disease during infancy.^{2,3,7,22,28,29}

Five studies estimated current asthma prevalence among non-hospitalized samples, at 3% to 15% (compared to 17% to 48% among those previously hospitalized for RSV, from the same studies). The

attributable risk (**Table 1**) of current asthma due to RSV disease among those in the ≥12 years of age category ranged from 6% to 33%.^{2,3,7,25,29}

Asthma, overall

Figure 3 shows the frequency of asthma prevalence estimates above each 10%-increment prevalence threshold for those hospitalized for RSV disease during infancy and the non-hospitalized comparisons. While 88% of asthma estimates from those hospitalized for RSV disease during infancy were in excess of 10%, only 25% of estimates from non-hospitalized comparison groups exceeded that threshold. Similarly, 59% of asthma prevalence estimates from those hospitalized for RSV disease during infancy were over 20%; only 6% of estimates from non-hospitalized comparisons exceeded that threshold. This trend was consistent when stratified by age (*data not shown*).

Figure 4 presents current asthma prevalence estimates from three longitudinal studies.^{2,3,7,10,11,20–22,27–29} In the first series, prevalence increased from 23% (3 years) to 33% (18 years) in those hospitalized for RSV disease during infancy – vs. from 1% to 7% in the non-hospitalized comparison over the same period.^{2,3,10,11} The second series reported increasing prevalences from 6% (8 to 9 years) to 30% (26 to 29 years), vs. 2% to 4% in the non-hospitalized comparison group.^{7,27–29} The third series reported current asthma prevalence to be stable among children previously hospitalized for RSV disease

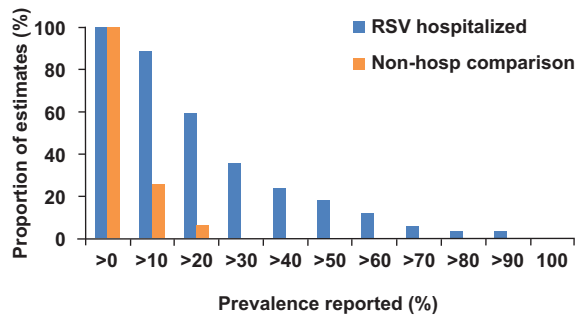


Figure 3. Frequency of prevalence estimates of asthma, over each 10% threshold, for those previously hospitalized for RSV disease, and non-hospitalized comparison groups.

(22% at 3 years to 20% at 11 years); no non-hospitalized comparison was included.^{20–22}

Sensitivity analysis

All articles reporting recurrent wheezing (but not asthma) were reviewed. An additional four articles wherein wheezing was sufficiently severe to potentially indicate asthma,^{37–40} as well as one already reviewed for asthma that estimated recurrent wheezing among younger children,⁴ were included.

Two additional estimates (one cumulative³⁸ and one current⁴) of asthma prevalence in the <5 years of age category and three cumulative^{37,39,40} and two current estimates^{37,40} in the 5 to 11 years category were included. Inclusion of the prevalence estimates

from these additional studies did not change the results; and upper and lower limits of the calculated estimates remained the same (Figure 5).

Discussion

Chronic respiratory conditions in children and adolescents contribute a substantial clinical and economic burden globally,⁴¹ and hospitalization for RSV disease during infancy may be an important risk factor.^{2–4,6,7,9–31} This systematic review demonstrated that asthma prevalence among individuals hospitalized for RSV disease during infancy were higher – frequently, significantly and clinically meaningfully so – than among non-hospitalized comparison groups. While 60% of asthma prevalence estimates after RSV hospitalization in infancy were in excess of 20%, only 5% of estimates from non-hospitalized comparison groups exceeded that threshold.⁸ Unlike other reviews,^{1,32} we did not find that asthma risk after RSV-hospitalization dissipated with time; indeed, follow-up to almost 30 years of age demonstrated continued substantial increased risks.^{3,7} The most recent studies conclude that RSV hospitalization in infancy is a significant independent risk factor for adult asthma.⁷

To assess excess risk, asthma prevalence among those hospitalized and those not hospitalized for RSV disease in infancy was compared. While many studies did not include non-hospitalized comparisons, asthma prevalence estimates from those that did^{2–4,6,7,10–13,16,25,27,29} were consistent with other asthma estimates from the general population. The majority of asthma prevalence estimates from non-hospitalized groups were <20%; only 5% of estimates exceeded this

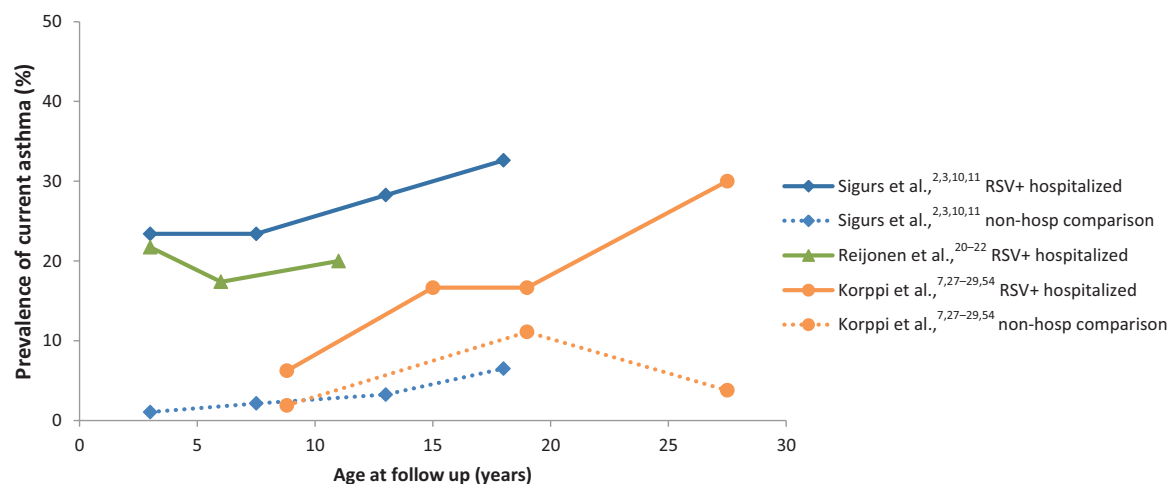


Figure 4. Prevalence estimates of current asthma, from three longitudinal studies. *Only longitudinal studies that defined asthma consistently were plotted. For the Korppi et al. series, data from Kuikka 1994²⁶ were not plotted as a different asthma definition was used compared with the other three publications from that series.^{7,27–29}

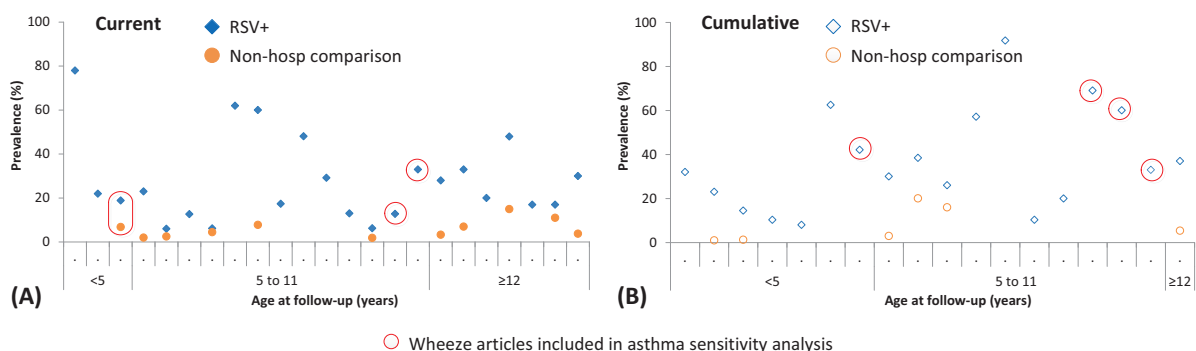


Figure 5. Prevalence estimates (%) from studies reporting on (A) the current risk and (B) the cumulative risk of asthma among those previously hospitalized for RSV disease, and non-hospitalized comparison groups, in the <5 years, 5 to 11 years, and ≥12 years age categories; estimates from articles with recurrent wheezing sufficiently severe to potentially indicate asthma are circled.

threshold. This was consistent with findings from the International Study of Asthma and Allergy in Childhood, which measured cumulative asthma prevalences of 22.5% and 16.3% among 13–14-year-olds in North America and Europe.⁸ Differential estimates of risk among non-hospitalized comparisons may be due to the known geographic variability in underlying asthma risk.⁸

Despite mounting evidence of the importance of RSV-related hospitalization as a risk factor for asthma, including from population-based studies such as the Tucson⁴² and ALSPAC⁴ birth cohorts, the long-term impact of severe RSV disease remains unclear.^{1,43,44} Synthesizing evidence from the literature is challenging due to heterogeneity in exposure and outcome measurement, and differences in study design. One recent systematic review of twelve studies confirmed the association between RSV (not necessarily hospitalization) in infancy and asthma risk, although they suspected it dissipated with age.³² This supposition originates from two sets of reports; the first, from older studies by Sigurs et al., which reported declining (but still significantly elevated) increased risks of asthma over time.^{2,10,11} The second set consisted of two small studies reporting lesser asthma prevalences at older ages^{12,29} than other (unrelated) studies reporting asthma risk at earlier time periods using different definitions. Subsequent publications by those investigators have demonstrated increased risk well into adulthood,^{3,7} in part due to the development of late-onset asthma not evident at earlier visits.^{2,3,11} The most recent evidence concludes that asthma risk is significantly elevated among those hospitalized for RSV disease in infancy; that these elevated risks are sustained into adulthood; and that RSV-related hospitalization in infancy is a significant risk factor for adult asthma.^{3,7}

Part of the uncertainty around the magnitude of increased asthma risk after RSV-related hospitalization is due to the small sample sizes of contributing studies, which could cause even large differences in prevalence to be statistically insignificant. Meta-analysis is one approach to synthesizing estimates from underpowered studies. However, unlike randomized trials which provide an unbiased estimate of an association's effect size, estimates from observational studies may deviate due to the effects of confounding, bias, or both.^{45,46} As a result, meta-analysis of observational studies may produce very precise, but spurious results, particularly when great heterogeneity in outcome measures is present, limiting the validity of estimating a combined outcome. Despite the restrictions imposed within the present review, the designs and results of included studies remained sufficiently heterogeneous to question the validity of meta-analysis. The qualitative approach to data synthesis undertaken here, however, can be valid and informative for exploring and understanding drivers of variability, and hypothesis generating.^{45,46}

Another source of uncertainty in synthesizing asthma estimates was due to the lack of consistency in asthma definitions from the original studies; and the high degree of overlap between definitions for asthma and recurrent wheezing. To minimize the effects of differing definitions, we focused only on asthma (which was defined with a higher consistency), and included severe recurrent wheezing as a sensitivity analysis. This approach maximized the sensitivity of the outcome of 'asthma' for detecting chronic and severe respiratory conditions, which is important for studies reporting on younger children where difficulties in measuring pulmonary function would prevent definitive asthma diagnoses. The overlap in definitions questions whether asthma and recurrent wheezing are truly differing constructs; or if varied definitions reflect geographic variability in terminology alongside challenges in accurately diagnosing asthma in young children.^{47,48} Future epidemiologic studies may measure the first age-specific occurrence of asthma or recurrent wheezing, in addition to considering the outcomes separately.

An important consideration for studies examining the link between RSV and asthma relates to the etiology of respiratory symptoms. It is unclear whether RSV hospitalization causes a form of asthma,

or if RSV and asthma are on the same causal pathway from a common distal cause.^{1,43,44,49,50} Distinguishing a causative role for RSV in the pathogenesis of asthma is challenging because 'asthma' represents an umbrella for phenotypically distinct diagnoses,⁵¹ within which an RSV-specific phenotype may be grouped. While impossible to disentangle in the context of this systematic review, the issue of causation highlights two missing pieces of the RSV/asthma puzzle. First, a precise and population-based quantification of the risk of asthma due to RSV is required. Second, an estimate of the effectiveness of RSV prophylaxis for decreasing asthma risk via preventing RSV hospitalizations is lacking.

Overall, the validity of the synthesis was limited by the features of study design employed in the original articles. As the review included mostly observational studies, there was the potential for selection bias, information bias, and confounding to have affected the results of the original studies (and therefore the synthesis).³⁵ Many studies did not include healthy comparison groups. Furthermore, the study samples differed in the distributions of other factors known to be associated with asthma, such as daycare attendance or smoking in the household;⁵² these factors were inconsistently measured and could not be adjusted for between studies.

To our knowledge, this work represents the most thorough systematic review of asthma risk after hospitalization for RSV disease during infancy. Misclassification on exposure was minimized by limiting inclusion to studies where RSV disease was confirmed on laboratory testing, and wherein all subjects were hospitalized.³² To maximize the generalizability, a broad approach was employed that included studies without non-hospitalized samples; recognizing that this limited the ability to make comparisons. Prevalence was considered according to the levels of potentially important covariates, including whether individuals were initially at high risk of, and timing of, RSV-related hospitalization; and according to the source (parent or physician) of report. To minimize the effects of heterogeneity in follow-up periods, estimates of risk were compared within three clinically relevant age categories,³⁴ stratified according to whether the measure was assessed cumulatively, or reflected current asthma symptoms.

This review characterized the prevalence, and increased risk, of asthma among those previously hospitalized for RSV disease, providing age-specific ranges of asthma prevalence. Despite the variability in estimates from the studies reviewed, the evidence continually suggests an increased risk of childhood asthma after hospitalization for RSV disease during infancy, maintained into adulthood. Nonetheless, the literature reporting on this association would benefit from a population-based study employing standardized definitions to provide accurate, robust, and representative estimates of the increased risk of asthma among those hospitalized for RSV disease in infancy, particularly among those at higher risk of severe respiratory infections or morbidity.

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Conflict of interest statement

HW and SMS are employees of Oxford Outcomes. KLG is and PG was an employee of Abbott. ARL is a consultant to Oxford Outcomes.

Contributors' roles

SMS, ARL, KLG, and IM contributed to the conception and design of the study. SMS and HW were responsible for acquisition of data. All authors participated in analysis and interpretation. SMS, ARL, and KLG drafted the article; HW, IM and PB critically revised it. All authors provided final approval of the version to be published.

References

- Kneyber MCJ, Steyerberg EW, de Groot R, Moll HA. Long-term effects of respiratory syncytial virus (RSV) bronchiolitis in infants and young children: a quantitative review. *Acta Paediatr* 2000; **89**(6):654–60.
- Sigurs N, Gustafsson PM, Bjarnason R, et al. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. *Am J Respir Crit Care Med* 2005; **171**(2):137–41.
- Sigurs N, Aljassim F, Kjellman B, et al. Asthma and allergy patterns over 18 years after severe RSV bronchiolitis in the first year of life. *Thorax* 2010; **65**(12):1045–52.
- Henderson J, Hilliard TN, Sherriff A, Stalker D, Al Shammari N, Thomas HM. Hospitalization for RSV bronchiolitis before 12 months of age and subsequent asthma, atopy and wheeze: a longitudinal birth cohort study. *Pediatr Allergy Immunol* 2005; **16**(5):386–92.
- Korppi M, Piippo-Savolainen E, Korhonen K, Remes S. Respiratory morbidity 20 years after RSV infection in infancy. *Pediatr Pulmonol* 2004 Aug; **38**(2):155–60.
- Pullan CR, Hey EN. Wheezing, asthma, and pulmonary dysfunction 10 years after infection with respiratory syncytial virus in infancy. *Br Med J (Clin Res Ed)* 1982 Jun 5; **284**(6330):1665–9.
- Ruotsalainen MM, Piippo-Savolainen EMP, Hyvarinen MKM, Korppi MM. Respiratory morbidity in adulthood after respiratory syncytial virus hospitalization in infancy [Report]. *Pediatr Infect Dis J* 2010 Sep; **29**(9):872–4.
- Pearce N, Ait-Khaled N, Beasley R, et al. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax* 2007 Sep 1; **62**:758–66.
- Bont L, Van Aalderen WMC, Versteegh J, Brus F, Draaisma JTM, Pikelharing-Berghuis M, et al. Airflow limitation during respiratory syncytial virus lower respiratory tract infection predicts recurrent wheezing. *Pediatr Infect Dis J* 2001; **20**(3):277–82.
- Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B, Bjorksten B. Asthma and immunoglobulin E antibodies after respiratory syncytial virus bronchiolitis: a prospective cohort study with matched controls. *Pediatrics* 1995; **95**(4):500–5.
- Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. *Am J Respir Crit Care Med* 2000 May; **161**(5):1501–7.
- Juntti H, Kokkonen J, Dunder T, Renko M, Niinimäki A, Uhari M. Association of an early respiratory syncytial virus infection and atopic allergy. *Allergy* 2003 Sep; **58**(9):878–84.
- Mok JY, Simpson H. Outcome of acute lower respiratory tract infection in infants: Preliminary report of seven-year follow-up study. *Br Med J* 1982; **285**(6338):333–7.
- Cassimos DC, Tsalkidis A, Tripsianis GA, et al. Asthma, lung function and sensitization in school children with a history of bronchiolitis. *Pediatr Int* 2008; **50**(1):51–6.
- Sly PD, Hibbert ME. Childhood asthma following hospitalization with acute viral bronchiolitis in infancy. *Pediatr Pulmonol* 1989; **7**(3):153–8.
- Fjaerli HO, Farstad T, Rod G, Ufert GK, Gulbrandsen P, Nakstad B. Acute bronchiolitis in infancy as risk factor for wheezing and reduced pulmonary function by seven years in Akershus County, Norway. *BMC Pediatr* 2005; **5**:31.
- Hall CB, Hall WJ, Gala CL, McGill FB, Leddy JP. Long-term prospective study in children after respiratory syncytial virus infection. *J Pediatr* 1984 Sep; **105**(3):358–64.
- Valkonen H, Waris M, Ruohola A, Ruuskanen O, Heikkinen T. Recurrent wheezing after respiratory syncytial virus or non-respiratory syncytial virus bronchiolitis in infancy: a 3-year follow-up. *Allergy* 2009; **64**(9):1359–65.
- Lin HC, Hwang KC, Yang YH, Lin YT, Chiang BL. Risk factors of wheeze and allergy after lower respiratory tract infections during early childhood. *J Microbiol Immunol Infect* 2001 Dec; **34**(4):259–64.
- Reijonen TM, Kotaniemi-Syrjänen A, Korhonen K, Korppi M. Predictors of asthma three years after hospital admission for wheezing in infancy. *Pediatrics* 2000; **106**(6):1406–12.
- Kotaniemi-Syrjänen A, Laatikainen A, Waris M, Reijonen TM, Vainionpää R, Korppi M. Respiratory syncytial virus infection in children hospitalized for wheezing: virus-specific studies from infancy to preschool years. *Acta Paediatr* 2005; **94**(2):159–65.
- Hyvarinen MK, Kotaniemi-Syrjänen A, Reijonen TM, Korhonen K, Korppi MO. Teenage asthma after severe early childhood wheezing: an 11-year prospective follow-up. *Pediatr Pulmonol* 2005; **40**(4):316–23.
- Wennergren G, Hansson S, Engstrom I, et al. Characteristics and prognosis of hospital-treated obstructive bronchitis in children aged less than two years. *Acta Paediatr* 1992; **81**(1):40–5.
- Wennergren G, Amark M, Amark K, Oskarsdottir S, Sten G, Redfors S. Wheezing bronchitis reinvestigated at the age of 10 years. *Acta Paediatr* 1997 Apr; **86**(4):351–5.
- Gokso E, Amark M, Alm B, Gustafsson PM, Wennergren G. Asthma symptoms in early childhood – what happens then? *Acta Paediatr* 2006 Apr; **95**(4):471–8.
- Kuikka L, Reijonen T, Remes K, Korppi M. Bronchial asthma after early childhood wheezing: a follow-up until 4.5–6 years of age. *Acta Paediatr* 1994; **83**(7):744–8.
- Korppi M, Kuikka L, Reijonen T, Remes K, Juntunen-Backman K, Launiala K. Bronchial asthma and hyperreactivity after early childhood bronchiolitis or pneumonia: an 8-year follow-up study. *Arch Pediatr Adolesc Med* 1994 Oct 1; **148**(10):1079–84.
- Hyvarinen MK, Piippo-Savolainen E, Korhonen K, Korppi M. Teenage asthma after severe infantile bronchiolitis or pneumonia. *Acta Paediatr* 2005 Oct; **94**(10):1378–83.
- Korppi M, Piippo-Savolainen E, Korhonen K, Remes S. Respiratory morbidity 20 years after RSV infection in infancy. *Pediatr Pulmonol* 2004; **38**(2):155–60.
- Piippo-Savolainen E, Korppi M, Korhonen K, Remes S. Adult asthma after non-respiratory syncytial virus bronchiolitis in infancy: Subgroup analysis of the 20-year prospective follow-up study. *Pediatr Int* 2007; **49**(2):190–5.
- García-García ML, Calvo C, Casas I, et al. Human metapneumovirus bronchiolitis in infancy is an important risk factor for asthma at age 5. *Pediatr Pulmonol* 2007; **42**(5):458–64.
- Pérez-Yarza EG, Moreno A, Lázaro P, Mejías A, Ramilo O. The association between respiratory syncytial virus infection and the development of childhood asthma: a systematic review of the literature. *Pediatr Infect Dis J* 2007; **26**(8):733–9.
- Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. The IMPact-RSV Study Group. *Pediatrics* 1998 Sep; **102**(3 Pt 1):531–7.
- National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the diagnosis and management of asthma – Summary Report 2007. *J Allergy Clin Immunol* 2007; **120**(5 Suppl):S93–138.
- Szklo M, Nieto FJ. *Epidemiology: Beyond the Basics*. Sudbury, MA: Jones and Bartlett; 2004.
- Sly PD, Kusel M, Holt PG. Do early-life viral infections cause asthma? *J Allergy Clin Immunol* 2010 Jun; **125**(6):1202–5.
- Welliver RC, Duffy L. The relationship of RSV-specific immunoglobulin E antibody responses in infancy, recurrent wheezing, and pulmonary function at age 7–8 years. *Pediatr Pulmonol* 1993 Jan; **15**(1):19–27.
- Welliver RC, Sun M, Rinaldo D, Ogra PL. Predictive value of respiratory syncytial virus-specific IgE responses for recurrent wheezing following bronchiolitis. *J Pediatr* 1986 Nov; **109**(5):776–80.
- Rooney JC, Williams HE. The relationship between proved viral bronchiolitis and subsequent wheezing. *J Pediatr* 1971 Nov; **79**(5):744–7.
- Erners MJ, Hoebee B, Hodemaekers HM, Kimman TG, Kimpen JLL, Bont L. IL-13 genetic polymorphism identifies children with late wheezing after respiratory syncytial virus infection. *J Allergy Clin Immunol* 2007; **119**(5):1086–91.
- Braman SS. The global burden of asthma. *Chest* 2006 Jul 1; **130**(1 suppl):4S–12S.
- Stein RT, Sherrill D, Morgan WJ, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999 Aug 14; **354**(9178):541–5.
- Meissner HC, Long SS. Respiratory syncytial virus infection and recurrent wheezing: a complex relationship. *J Pediatr* 2007; **151**(1):6–7.
- Kuehni CE, Spyker BD, Silverman M. Causal links between RSV infection and asthma: no clear answers to an old question. *Am J Respir Crit Care Med* 2009 Jun 15; **179**(12):1079–80.
- Egger M, Smith GD, Schneider M. Systematic reviews of observational studies. In: Egger M, Smith GD, Altman DG, editors. *Systematic Reviews in Health Care: Meta-analysis in Context*. London: BMJ Publishing Group; 2010. p. 211–27.
- Colditz GA, Burdick E, Mosteller F. Heterogeneity in meta-analysis of data from epidemiologic studies: a commentary. *Am J Epidemiol* 1995 Aug 15; **142**(4):371–82.
- Feher A, Castile R, Kisling J, et al. Flow limitation in normal infants: a new method for forced expiratory maneuvers from raised lung volumes. *J Appl Physiol* 1996 Jun 1; **80**(6):2019–25.
- Castile R, Filburn D, Flucke R, Franklin W, McCoy K. Adult-type pulmonary function tests in infants without respiratory disease. *Pediatr Pulmonol* 2000; **30**(3):215–27.
- Openshaw P, Dean GS, Culley FJ. Links between respiratory syncytial virus bronchiolitis and childhood asthma: clinical and research approaches. *Pediatr Infect Dis J* 2003; **22**(2 Suppl):S58–64. Discussion: S64–5.
- Erners MJ, Rovers MM, van Woensel JB, Kimpen JLL, Bont LJ. RSV Corticosteroid Study Group. The effect of high dose inhaled corticosteroids on wheeze in infants after respiratory syncytial virus infection: randomised double blind placebo controlled trial. *BMJ* 2008 Mar 31; **338**:b897.
- Pekkanen J, Sunyer J, Anto JM, Burney P; on behalf of the European Community Respiratory Health Study (ECRHS). Operational definitions of asthma in studies on its aetiology. *Eur Respir J* 2005 Jul 1; **26**(1):28–35.
- Taussig LM, Wright AL, Holberg CJ, Halonen M, Morgan WJ, Martinez FD. Tucson Children's Respiratory Study: 1980 to present. *J Allergy Clin Immunol* 2003; **111**(4):661–75.