

Association Between Respiratory Syncytial Virus-Associated Acute Lower Respiratory Infection in Early Life and Recurrent Wheeze and Asthma in Later Childhood

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Background. Recurrent wheeze and asthma in childhood are common causes of chronic respiratory morbidity globally. We aimed to explore the association between respiratory syncytial virus (RSV) infection in early life and subsequent respiratory sequelae up to age 12 years.

Methods. We estimated the strength of association by 3 control groups and 3 follow-up age groups, with data from studies published between January 1995 and May 2018. We also estimated associations by diagnostic criteria, age at infection, and high-risk population.

Results. Overall, we included 41 studies. A statistically significant association was observed between early life RSV infection and subsequent childhood recurrent wheeze, in comparison to those who were healthy or those without respiratory symptoms: OR 3.05 (95% confidence interval [CI], 2.50–3.71) for 0 to <36 months follow-up age; OR 2.60 (95% CI, 1.67–4.04) for 36–72 months; and OR 2.14 (95% CI, 1.33–3.45) for 73–144 months. For the subsequent development of asthma, a statistically significant association was observed only in relation to those aged 73–144 months at follow-up: OR 2.95 (95% CI, 1.96–4.46).

Conclusions. Further studies using standardized definitions and from diverse settings are needed to elucidate the role of confounders and provide more robust estimates.

Keywords. respiratory syncytial virus; recurrent wheeze; asthma; children.

Respiratory syncytial virus (RSV)-associated acute lower respiratory infection (ALRI) is a major cause of hospital admissions in young children, resulting in a substantial burden on health care services. About 45% of hospitalization and in-hospital deaths due to RSV-ALRI occur in children during the first 6 months of life [1]. The development of a safe and effective vaccine to protect young children against RSV infection could have a substantial effect on disease burden in this age group. A monoclonal antibody is available for RSV prophylaxis for at-risk infants; a novel monoclonal antibody and pediatric and maternal candidate vaccines are in the late stages of development [2]. These prophylaxis or vaccination strategies may protect the infants against acute RSV illness during their first months of life. Meanwhile, early childhood RSV-ALRI has been reported to have an association with subsequent development

of wheeze-associated disorders in childhood [3, 4]. Recurrent wheeze and asthma in childhood are a common cause of morbidity globally, that lead to decreased quality of life, frequent health care utilization with high health economic costs, and financial burden to families [5, 6]. Whilst some recurrent wheezing may resolve spontaneously, others persist into adulthood. The public health and economic value of RSV prophylaxis and vaccines would be greater if they also decreased the prevalence and severity of wheeze-associated disorders.

The aim of this review is to explore whether there is an association between RSV infection in early life and subsequent respiratory sequelae (recurrent wheeze or asthma) up to age 12 years.

METHODS

Search Strategy and Selection Criteria

We conducted a systematic review across 9 databases (including 3 Chinese databases) following the approach detailed in the PRISMA guidelines [7]. Tailored search strategies were developed and applied to search Medline, Embase, Global Health, Web of Science, Cumulative Index to Nursing and Allied Health Literature, Global Index Medicus, China National Knowledge Infrastructure (CNKI), Wanfang Data, and Chongqing VIP

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databases ([Supplementary Material Strategy](#)). All searches were limited to between January 1995 and May 2018. No publication status criteria or language restrictions were applied. We included studies that fulfilled the selection criteria described in [Supplementary Panel 1](#).

Three investigators (T. S., Y. O., and E. M. Z.) conducted independent literature searches and extracted data using standardized data extraction templates. One investigator (T. S.) whose first language is Chinese performed the search and data extraction from Chinese language databases (CNKI, Wanfang, and Chongqing VIP). Any uncertainties regarding relevance or inclusion were discussed with and adjudicated by T. S.

The protocol of this review was published in the PROSPERO database (No. CRD42018095112).

Definitions

The population under investigation consists of children up to 12 years old because the literature suggests that lung function is lost early in life and this age cutoff should allow exploration of the association with early life respiratory virus infection [8]. This statement assumes that respiratory morbidity varies by age from infancy to adolescence and the impact of early life RSV infection appears to diminish in later childhood. The exposure group was defined as RSV infection with laboratory confirmation in the first year of life (including those younger than 2/3 years). The control group was defined as infants without respiratory symptoms (RSV/noRS); or respiratory infection associated with other pathogens including rhinovirus (RSV/other); or only rhinovirus infection (RSV/RV) ([Supplementary Panel 2](#)). Outcomes were recurrent wheeze and asthma. The follow-up age group (up to 12 years old) were categorized into 3 subgroups (0 to <36 months, 36–72 months, and 73–144 months) in order to evaluate the association by age.

Statistical Analysis

We standardized the results of all the included studies as odds ratios (ORs) of detecting the occurrence of the outcome in infants with RSV infection compared to the control group with accompanying 95% confidence intervals (95% CIs) to facilitate interpretation and comparison. We applied a continuity correction of 0.0005 if the outcome was detected in 1 group but not the other [9]. This allowed calculation of an OR for these instances and enabled inclusion in subsequent metaanalyses. Furthermore, adjusted odds ratios (aORs) were also extracted, where possible. These were used preferentially in subsequent calculations and analyses.

Using STATA (version 13.0), we performed a metaanalysis of outcome-specific ORs and reported pooled estimates with corresponding 95% CIs using the random effects model (DerSimonian-Laird method) because the included studies are heterogeneous in various aspects and thus are assumed

to have different effect sizes [10]. Each outcome was assessed separately in comparison to 3 control groups. This led to 6 groups of results in total. Within each group, the result was reported as per the above predefined age subgroups. Subgroup analysis stratified by outcome diagnosis (physician diagnosed or parent reported) and age at RSV infection (0–11 months and 0–23 months) were carried out to explore the effect of possible confounders. Similarly, sensitivity analyses in high-risk populations (those with prematurity or atopy) were also conducted.

Quality Assessment

Quality assessment at the individual study level was carried out using the adapted Downs and Black checklist [11]. Items that were not applicable (adverse effects, blinding of subjects, compliance, randomization, concealment) were removed. The power criteria have been defined as having score 1 for providing power calculation and 0 if not. This resulted in evaluation of 22 variables with a maximum score of 22. A score of less than 12 (out of 22) was defined as a low-quality study.

RESULTS

We identified 4520 records and only 41 studies, including about 234 000 children, fulfilled our inclusion criteria ([Supplementary Figure 1](#)). Although the search was carried out for articles published from 1995, most (37/41) included studies published since 2000. Four studies were conducted within developing countries while 37 were from industrialized countries. One study was from a rural setting, 37 from urban areas, and 3 from a mix of urban and rural areas. There was considerable variation in the design of included studies. Ten studies were from retrospective cohorts while 31 were prospective cohort studies. The majority of RSV cases were identified from inpatients (31 studies) while the remaining recruited cases from outpatients, emergency departments, clinic visits, or community. Twenty-eight studies reported the outcome of recurrent wheeze. Among them, 17 studies used infants without respiratory symptoms or healthy infants as controls, 14 studies reported outcome data for infants with other pathogen-associated respiratory infection, and 3 studies had data on infants with rhinovirus as the control group. Twenty-six studies reported the outcome of asthma. Among them, 12, 16, and 3 studies were available, respectively, reporting data for the 3 control groups. A table describing features of the studies is available in [Supplementary Table 1](#). [Supplementary Tables 2–7](#) summarize the key characteristics and result of each included study under each category (6 categories under the combination of 2 outcomes and 3 control groups). The metaanalyses results for both outcomes are available in [Table 1](#). Forest plots are available in [Supplementary Figure 2](#).

RSV Infection and Recurrent Childhood Wheeze

In the RSV/noRS group there were 10, 7, and 6 studies, respectively, for the 3 follow-up age groups, 0 to <36 months, 36–72 months, and 73–144 months. The pooled metaanalysis ORs were 3.05 (CI, 2.50–3.71), 2.60 (95% CI, 1.67–4.04), and 2.14 (95% CI, 1.33–3.45), respectively. In the RSV/other group there were 7, 7, and 2 studies for the 3 follow-up age groups. The OR metaestimates were 0.79 (95% CI, 0.32–1.95) for 0 to <36 months and 0.81 (95% CI, 0.39–1.71) for 36–72 months, respectively. For the RSV/RV group there were only 3 studies, all of which had follow-up of 36–72 months, which resulted in the OR metaestimate of 0.41 (95% CI, 0.20–0.83).

We observed that the OR metaestimates for physician-diagnosed recurrent wheeze and parent-reported recurrent wheeze in the RSV/noRS group for children aged 0 to <36 months were 3.40 (95% CI, 2.60–4.46) and 2.48 (95% CI, 1.60–3.85), respectively. We also estimated that the OR metaestimates for recurrent wheeze in the RSV/other group stratified by age at RSV infection (0–11 months and 0–23 months) were 2.11 (95% CI, 1.42–3.12) and 0.30 (95% CI, 0.10–0.97), respectively (Supplementary Table 8 reports results for 0–11 months). In the RSV/noRS group (age 0 to <36 months), sensitivity analysis in premature infants indicated an OR metaestimate of 3.20 (95% CI, 1.82–5.61) compared to 3.06 (95% CI, 2.63–3.55) in the full-term infants.

RSV Infection and Asthma

In the RSV/noRS group, there were 2, 2, and 9 studies, respectively, for the 3 follow-up age groups, 0 to <36 months, 36–72 months, and 73–144 months. The OR metaestimate for the follow-up age group of 73–144 months was 2.95 (95% CI, 1.96–4.46). In the RSV/other group there were 2, 7, and 7 studies for the 3 follow-up age groups. The OR metaestimates for the 36–72 months and 73–144 months follow-up age groups

were 1.28 (95% CI, 0.84–1.95) and 0.54 (95% CI, 0.28–1.06), respectively. For the RSV/RV group, there were only 3 studies and each study had a different follow-up age group, which precluded any metaanalyses.

Our subgroup analysis stratified by age at RSV infection (0–11 months and 0–23 months) for the follow-up age of 73–144 months demonstrated OR metaestimates of 3.68 (95% CI, 1.92–7.04) and 2.28 (95% CI, 1.44–3.60), respectively, for the RSV/noRS group (Supplementary Table 8). Similarly, the OR metaestimates were 0.52 (95% CI, 0.17–1.63) for age at RSV infection 0–11 months and 0.41 (95% CI, 0.17–1.01) for age 0–23 months, for the RSV/other group. Sensitivity analysis focusing on atopic infants indicated that the OR metaestimate was 1.73 (95% CI, 1.13–2.64) in the RSV/other group for the 36–72 months follow-up age group.

The score from the quality assessment varied from 11 to 19 after taking into consideration 22 items. There were 4 studies with low quality (score <12 out of a maximum score of 22). Excluding these studies did not change the results substantially, perhaps due to the limited number of studies deemed to be of low quality.

DISCUSSION

This is the first systematic review to evaluate and summarize the literature on the association between RSV infection in early life and childhood recurrent wheeze and asthma, stratified by 3 control groups and 3 follow-up age groups. Our aim was to best synthesize evidence on this association taking into consideration a list of confounders as completely as possible. A previous publication combined all studies and outcome measures, making it difficult to translate findings into public health policy making [12]. This review also identified a number of new studies. Our review summarized data from 41 studies. We demonstrated consistent evidence in support of an association

Table 1. Metaanalyses Results for Association Between RSV Infection During Infancy and Childhood Recurrent Wheeze and Asthma, Stratified by Control Group and Follow-up Age

Follow-up Age, mo	Recurrent Wheeze		Asthma	
	No. of Studies	OR (95% CI)	No. of Studies	OR (95% CI)
RSV vs no respiratory symptoms				
<36	10	3.05 (2.50–3.71)	2	...
36–72	7	2.60 (1.67–4.04)	2	...
>72	6	2.14 (1.33–3.45)	9	2.95 (1.96–4.46)
RSV vs other pathogens				
<36	7	0.79 (0.32–1.95)	2	...
36–72	7	0.81 (0.39–1.71)	7	1.28 (0.84–1.95)
>72	2	...	7	0.54 (0.28–1.06)
RSV vs rhinovirus				
<36	0	...	1	...
36–72	3	0.41 (0.20–0.83)	1	...
>72	0	...	1	...

Abbreviations: CI, confidence interval; OR, odds ratio; RSV, respiratory syncytial virus.

between early life RSV infection and subsequent childhood recurrent wheeze in the RSV/noRS group: OR 3.05 (95% CI, 2.50–3.71) for 0 to <36 months follow-up age, OR 2.60 (95% CI, 1.67–4.04) for 36–72 months, and OR 2.14 (95% CI, 1.33–3.45) for 73–144 months. Although the strength of the association decreased with age, it remained statistically significant. A similar statistically significant association was observed for subsequent asthma episodes in the RSV/noRS group: OR 2.95 (95% CI, 1.96–4.46) for 73–144 months follow-up age (data not available in other follow-up age groups). However, the association was not significant for either outcome in the RSV/other group. In the RSV/RV group, the association was negatively significant for recurrent wheeze (OR, 0.41 [95% CI, 0.20–0.83]) and uncertain for asthma due to a limited number of studies, which might indicate that rhinovirus could play a comparable or even more important role in childhood recurrent wheeze.

Several subgroup analyses and sensitivity analyses were available from this study. The association between RSV infection during infancy and childhood recurrent wheeze was slightly higher in the physician-diagnosed strata (OR, 3.40 [95% CI, 2.60–4.46]) compared to parent reported (OR, 2.48 [95% CI, 1.60–3.85]) with overlapping 95% CIs (only data in the RSV/noRS group with 0 to <36 months follow-up age). This might demonstrate the difference in the ability of physicians and parents to accurately diagnose recurrent wheeze. In the high-risk premature cohort population, a slightly stronger association (with overlapping CIs) was observed with recurrent wheeze (RSV/noRS group with 0 to <36 months follow-up age). The definition of prematurity varied across studies from <37 weeks to 32–35 weeks of gestational age. In another high-risk cohort population (atopy), a stronger association was observed with asthma (RSV/other group with 36–72 months follow-up age). Children at high risk of atopy were defined as having at least 1 parent with respiratory allergies and/or a history of physician-diagnosed asthma. All these subgroup analyses and sensitivity analyses were based on a limited number of studies and the results were usually only available under specific subgroups. Consistent and more robust results would require more studies.

Although a thorough search was carried out across 9 databases, including 3 Chinese language databases, only 41 studies from the published literature were identified meeting our eligibility criteria. The number of studies was even smaller when metaanalyses were carried out stratified by outcome, control group, and follow-up age group. Limited studies were available for subgroup or sensitivity analyses to explore the heterogeneity by diagnostic criteria (physician diagnosed or parents reported), age at RSV infection, and high-risk cohort population (prematurity, atopy). Most studies (37/41) were from industrialized countries and from urban areas, thus evaluating the influence of region or setting on the association of interest was not possible. Also, there were insufficient studies to evaluate the impact of severity of RSV infection in early life on the association

because RSV cases in most studies (31/41) were identified from inpatients. Similarly, 31 of the 41 studies were prospective cohort studies. Moreover, the sample size in the RSV exposure group varied from 20 to 1266 and from 9 to 138 326 in the control group. The small sample size undoubtedly contributed to the imprecise 95% CIs calculation of some ORs. Therefore, more studies with larger sample sizes are required to produce more robust estimates for the above variables.

Apart from the variables discussed above, there were many other confounders that should be considered in order to evaluate the true association. Only 9 studies recruited a control group matched on date of birth, gender, residence, or ethnicity. Most studies (30/41) reported crude OR without taking into consideration other confounders. The remaining studies (11/41) reported adjusted OR, adjusting for 1 or several of the following: age, gender, prematurity, birth weight, seasonality, duration of breastfeeding, maternal age, maternal education, maternal smoking during pregnancy, maternal history of asthma, ethnicity, care-seeking behavior, day care attendance, or siblings. Coinfection detection was not considered in most studies. For those studies that did consider this, 1 study excluded coinfection while 8 included coinfection. Some studies (24/41) compared the characteristics between exposure group and the control group and others did not. Due to the nature of the study design (retrospective or prospective cohort studies), some participants were lost to follow-up during the study period. Only a few studies (8/41) discussed the characteristics of participants who were lost to follow-up and their possible impact on the result.

The definitions for recurrent wheeze and asthma varied substantially. For recurrent wheeze, ≥ 3 episodes of wheezing in the last 12 months was a commonly used definition in the majority of studies (13/28). However, ≥ 1 episode per year (11/28) and any wheeze during the follow-up (4/28) were also used. For asthma, some studies used current medication for asthma, or physician diagnosed asthma, or required symptoms of asthma within last 12 months, while others also accepted asthma diagnosis at any point during follow-up. There was no standardized asthma definition. Only 4 studies utilized the validated International Study of Asthma and Allergies in Childhood questionnaire. Research on respiratory morbidity suffers from a lack of adherence to international definitions. Four studies with a follow-up age group <5 years old also reported asthma outcome; however, this may pose diagnostic difficulty as objective testing such as spirometry is more challenging in young children [13].

Six studies evaluated the association between RSV prophylaxis (palivizumab or motavizumab) in infancy and childhood recurrent wheeze or asthma [14–19]. These were excluded from the analysis as they were designed (usually randomized controlled trials) to answer a slightly different research question that would be more appropriate to assess in a future analysis, in order to provide more complete evidence on the association

between RSV prophylaxis (or vaccine) strategy in early life and childhood respiratory sequelae. Similarly, among these studies, many variations existed: they recruited cases (receiving RSV prophylaxis) and controls (not receiving RSV prophylaxis) from different settings, used different case/control ascertainment, applied different definitions for the controls, investigated different outcomes, used different definitions and diagnosis methods for outcome, and reported varied follow-up age groups. In these studies, the association between RSV prophylaxis during infancy and childhood recurrent wheeze varied from OR 0.25 (95% CI, 0.09–0.72) to 1.10 (95% CI, 0.60–2.00). For asthma, there was only 1 study reporting the association (OR, 0.52 [95% CI, 0.31–0.87]) [19]. More studies to assess the effects of RSV prevention on these childhood respiratory outcomes are required.

The association between RSV infection during infancy and subsequent childhood recurrent wheeze and asthma may not necessarily indicate causation. Other criteria should be taken into consideration first before causality can be concluded. On applying Bradford Hill criteria [20], we observed that the strength of association varied across the control groups and follow-up age groups. The association was not specific but did have a temporal sequence between exposure and outcome. The remaining criteria were uncertain due to either a lack of evidence or there being inconsistent evidence available. However, the absence of these Bradford Hill criteria does not rule out a possible causal relationship. There are many methodological issues that should be taken into consideration to define causality [21]. Therefore, the association between RSV infection during infancy and childhood respiratory sequelae should be interpreted carefully.

There is considerable international attention on RSV infection in young children at this time when novel vaccine and antiviral strategies are being evaluated and prioritized [2, 22] and more accurate estimate on the long-term effect of RSV on childhood recurrent wheeze and asthma would help to plan for maternal RSV vaccines as well as future policies and interventions.

In conclusion, this review provides some evidence supporting an association between RSV infection in early life and childhood recurrent wheeze and asthma. However, this is only when comparing to infants without respiratory symptoms. Further studies using standard definitions are needed to elucidate the surrounding confounders and provide more robust estimates regarding the association between viral respiratory disease in early life and childhood respiratory sequelae.

SUPPLEMENTARY DATA

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not

copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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1 Supplementary material for “The
2 association between respiratory
3 syncytial virus associated acute lower
4 respiratory infection in early life and
5 subsequent recurrent wheeze and
6 asthma in later childhood”

Search strategy

Medline

1. human respiratory syncytial virus/ or human respiratory syncytial virus a/
2. respiratory syncytial virus infection/
3. RSV.ti,ab.
4. "respiratory syncytial vir*".ti,ab.
5. abnormal respiratory sound/ or breathing disorder/ or wheezing/
6. asthma/ or respiratory tract allergy/ or asthmatic state/
7. wheez*.ti,ab.
8. "recurrent wheez*".ti,ab.
9. asthma.ti,ab.
10. 1 or 2 or 3 or 4
11. 5 or 6 or 7 or 8 or 9
12. 10 and 11
13. limit 12 to child
14. limit 13 to yr="1995 -Current"

Embase

1. human respiratory syncytial virus/ or human respiratory syncytial virus a/
2. respiratory syncytial virus infection/
3. RSV.ti,ab.
4. "respiratory syncytial vir*".ti,ab.
5. abnormal respiratory sound/ or breathing disorder/ or wheezing/
6. asthma/ or respiratory tract allergy/ or asthmatic state/
7. wheez*.ti,ab.
8. "recurrent wheez*".ti,ab.
9. asthma.ti,ab.
10. 1 or 2 or 3 or 4
11. 5 or 6 or 7 or 8 or 9
12. 10 and 11
13. limit 12 to child
14. limit 13 to yr="1995 -Current"

Global Health

1. RSV.ti,ab.
2. "respiratory syncytial vir*".ti,ab.
3. wheez*.ti,ab.
4. "recurrent wheez*".ti,ab.
5. asthma.ti,ab.
6. "child*".ti,ab.
7. "infant*".ti,ab.
8. "adolescent*".ti,ab.
9. 1 or 2
10. 3 or 4 or 5
11. 6 or 7 or 8
12. 9 AND 10 AND 11
13. limit 11 to yr="1995 -Current"

Global Index Medicus

1. RSV.ti,ab.
2. "respiratory syncytial vir*".ti,ab.
3. wheez*.ti,ab.
4. "recurrent wheez*".ti,ab.
5. asthma.ti,ab.
6. "child*".ti,ab.
7. "infant*".ti,ab.
8. "adolescent*".ti,ab.
9. 1 or 2
10. 3 or 4 or 5
11. 6 or 7 or 8

68 12. 9 AND 10 AND 11
 69 13. limit 11 to yr="1995 -Current"
 70
 71 ((tw:(rsv)) OR (tw:(respiratory syncytial vir*))) AND ((tw:(wheez*)) OR (tw:(recurrent wheez*)) OR
 72 (tw:(asthma))) AND ((tw:(child*)) OR (tw:(infant*)) OR (tw:(adolescent*)))
 73

74 **CINAHL**

75 S20 S19 Limiters - Publication Year: 1995-current
 76 S19 S18 Limiters - Age Groups: All Child, All Infant
 77 S18 S16 AND S17
 78 S17 S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15
 79 S16 S1 OR S2 OR S3 OR S4 OR S5 OR S6
 80 S15 AB asthma
 81 S14 TI asthma
 82 S13 AB "recurrent wheez*"
 83 S12 TI "recurrent wheez*"
 84 S11 AB wheez*
 85 S10 TI wheez*
 86 S9 (MH "Asthma")
 87 S8 (MH "Respiratory Hypersensitivity")
 88 S7 (MH "Respiratory Sounds")
 89 S6 AB "respiratory syncytial vir*"
 90 S5 TI "respiratory syncytial vir*"
 91 S4 AB RSV
 92 S3 TI RSV
 93 S2 (MH "Respiratory Syncytial Viruses")
 94 S1 (MH "Respiratory Syncytial Virus Infections")
 95

96 **Web of Science**

97 1. TS=Wheez* or asthma
 98 2. TS=Respiratory syncytial virus* or RSV
 99 3. TS=Child* or adolescent* or infant*
 100

101 **CNKI**

102 Topic: respiratory syncytial virus (vague)
 103 And Topic: wheeze or asthma (vague)
 104 And Topic: children (vague)
 105 Publication time: 1st Jan 1995 – 20th May 2018
 106

107 **Wanfang Data**

108 All (vague): wheeze or
 109 All (vague): asthma or
 110 All (vague): respiratory syncytial virus and
 111 All (vague): children
 112 Time: 1995 – 2018
 113

114 **Chongqing VIP**

115 Title/key word: wheeze
 116 Or Title/key word: asthma
 117 And Title/key word: respiratory syncytial virus
 118 And Title/key word: children
 119 Time: 1995 – 2018
 120
 121

Supplementary Panel 1: Selection criteria

Studies published between January 1st 1995 – May 20th 2018;

Studies with prospective/retrospective cohort study designs;

Studies in children with age up to 12;

At least one control group (listed in Panel 2) is reported;

Studies where RSV infection is confirmed during the first few years of life using valid laboratory tests;

Definition of the outcome (recurrent wheeze or asthma) is clearly defined;

Studies investigating the association between RSV infection during infancy and childhood recurrent wheeze and asthma.

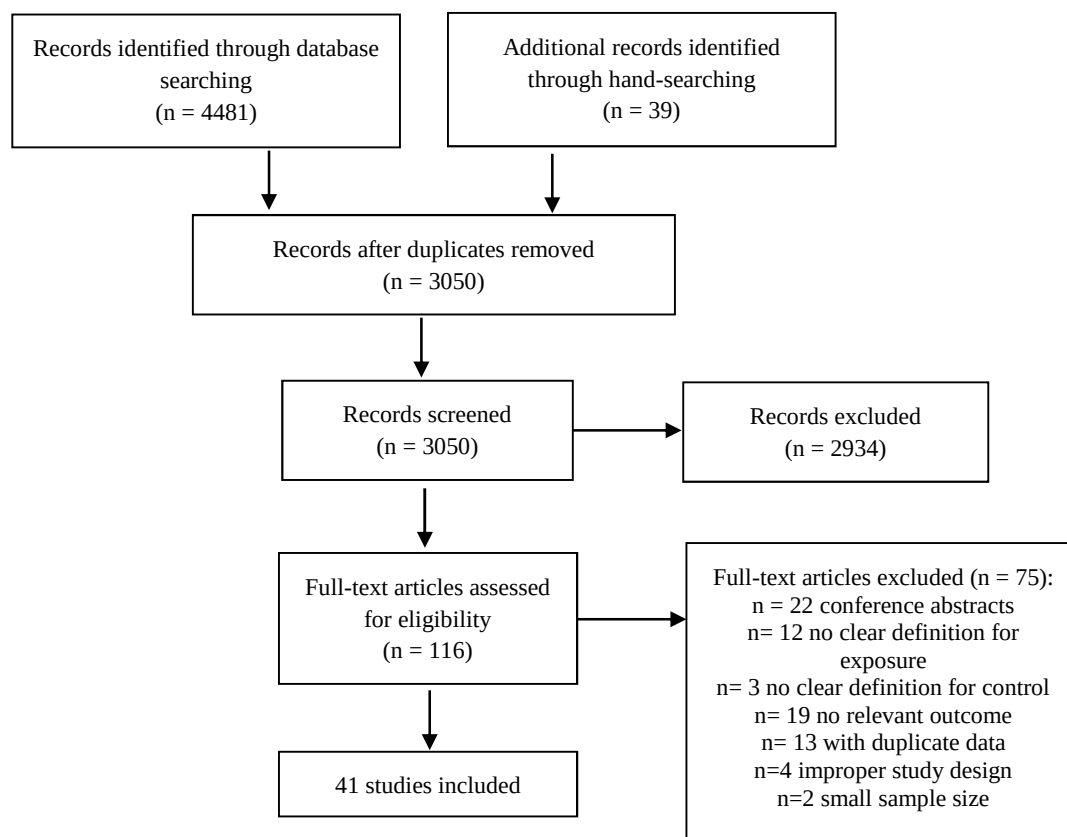
Supplementary Panel 2: Definition of the three control groups

1. 1st control group: Infants without RSV infection and respiratory symptoms (RS) or healthy infants (referred to as **RSV/noRS**) -

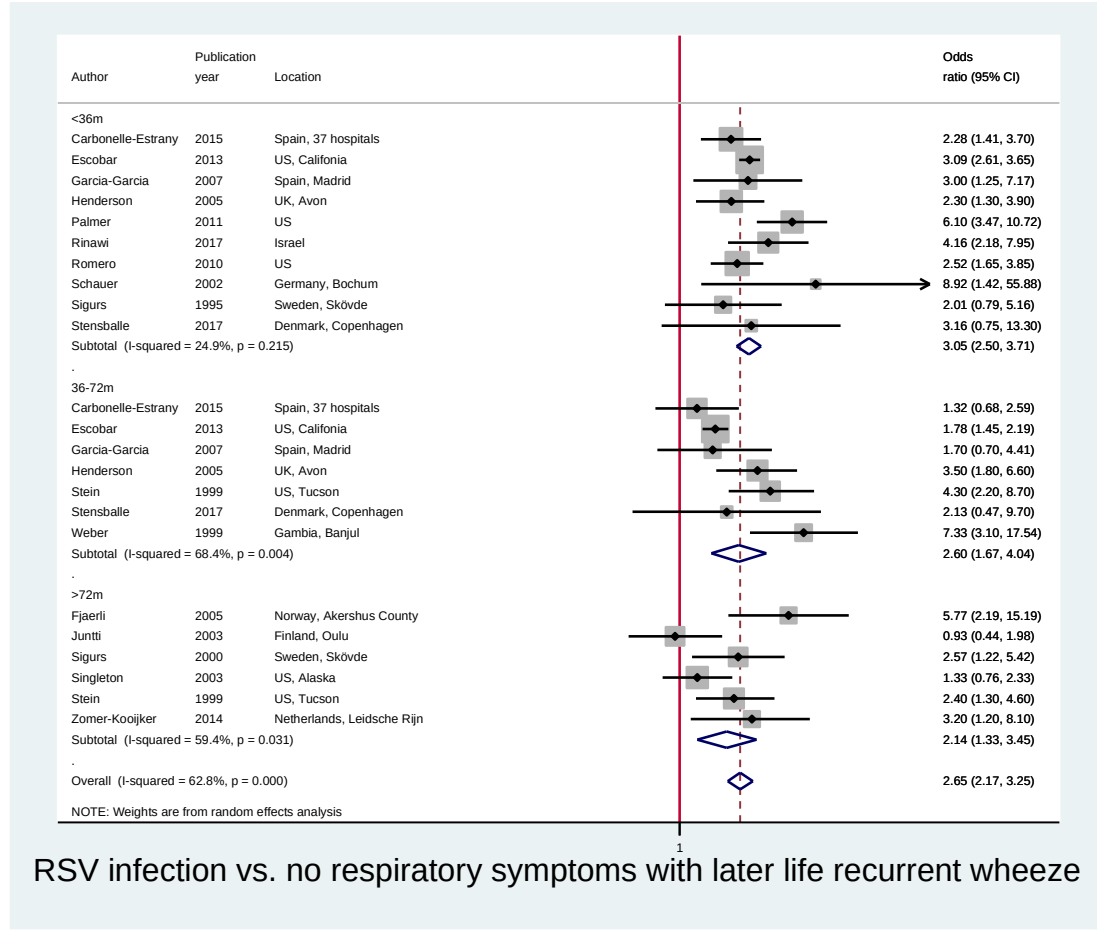
2. 2nd control group: Other pathogens (apart from RSV) associated respiratory infection in infancy (referred to as **RSV/other**)

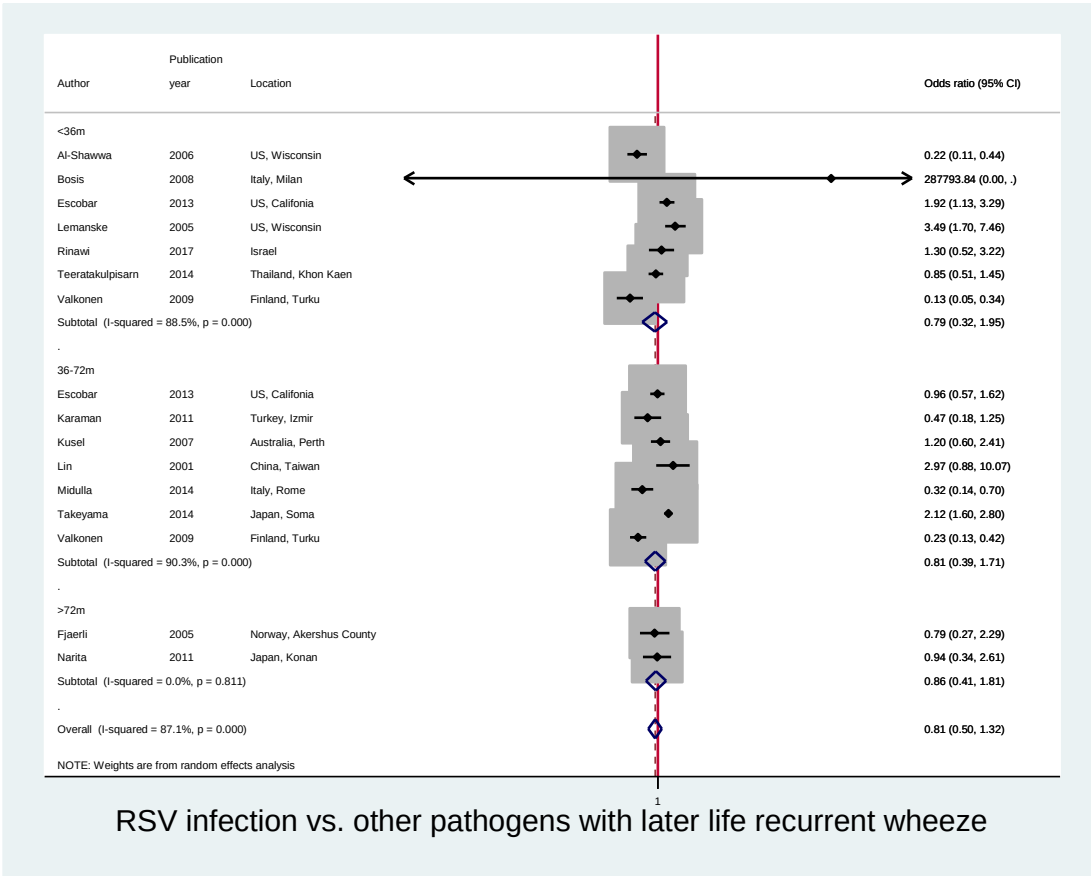
3. 3rd control group: Rhinovirus associated respiratory infection in infancy (referred to as **RSV/RV**)

Supplementary Figure 1: PRISMA flow diagram of the literature search

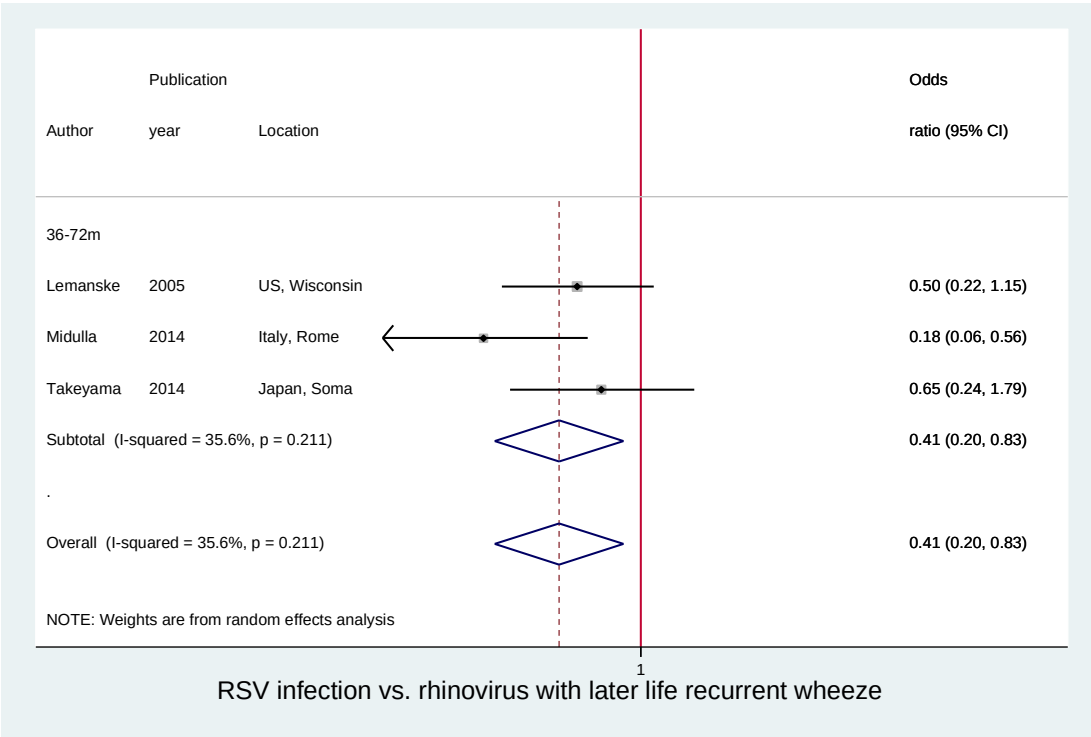


Supplementary Figure 2: Forest plots of meta analyses results for the association between RSV infection during infancy and childhood recurrent wheeze and asthma

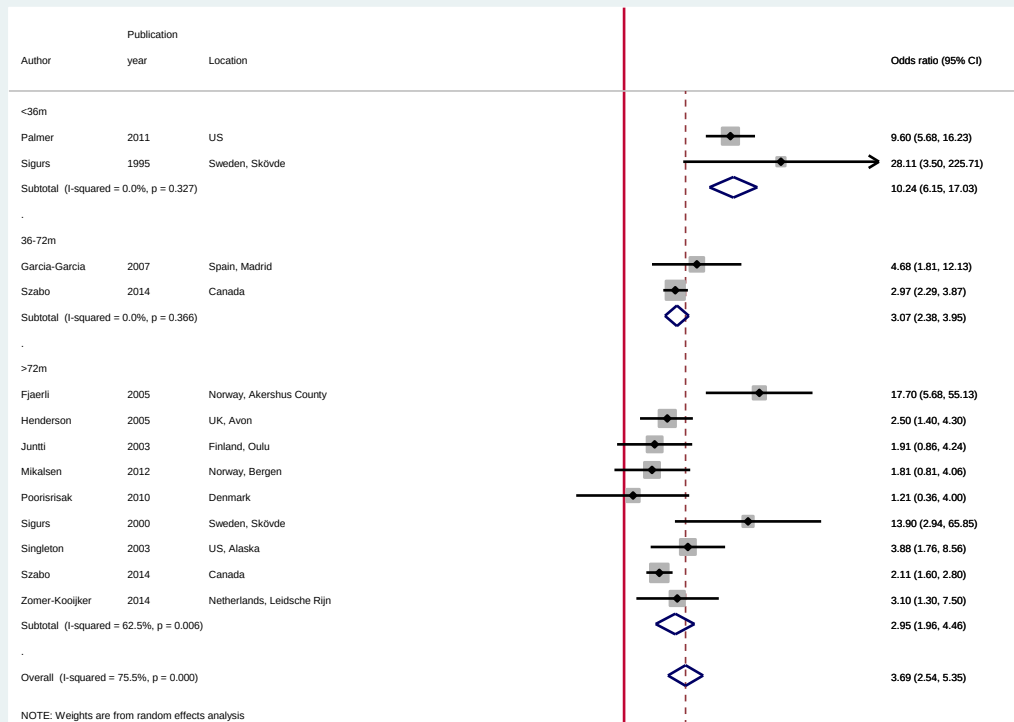




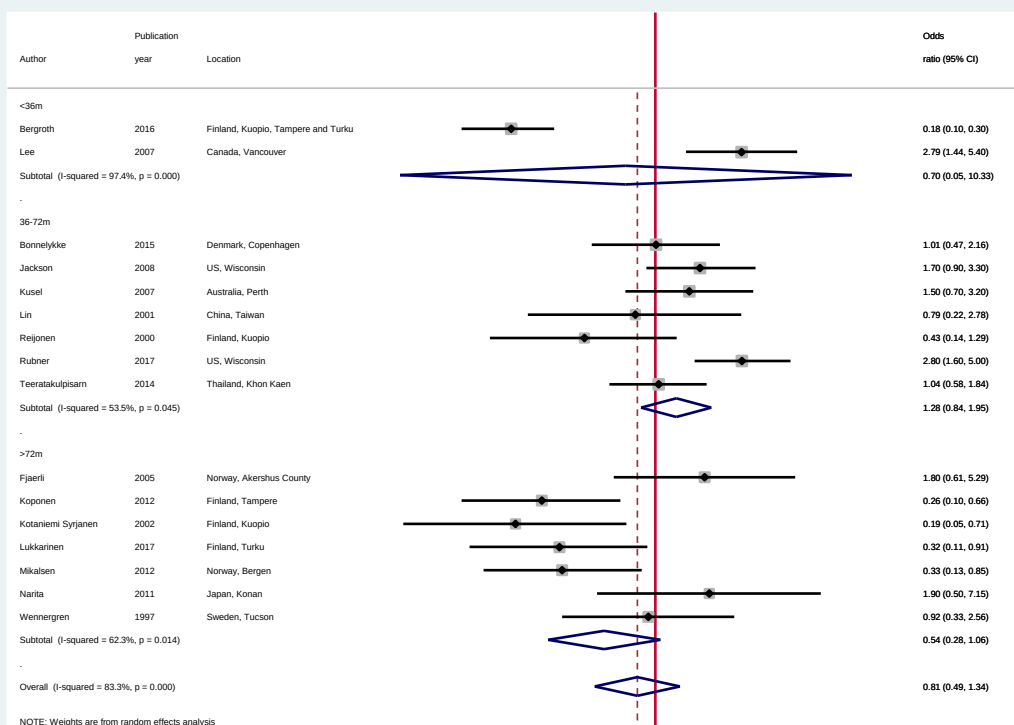
158



159



RSV infection vs. no respiratory symptoms with later life asthma



RSV infection vs. other pathogens with later life asthma

Supplementary Table 1: Characteristics of included studies

Author (year)	Location (setting)	Study design	Exposed	Control	Age infection (months)	RSV diagnosis	Outcomes	Follow-up age (m)	OR (crude, adjusted)	OR (LCI-HCI)	High risk cohort
Al-Shawwa (2006) [1]	US, Wisconsin	P cohort	RSV bronchiolitis, OP/IP	Other pathogens bronchiolitis, OP/IP	≤24	NPA; ELISA	RW	12-36	crude	0.22 (0.11-0.45)	NA
Bergroth (2016) [2]	Finland, Kuopio, Tampere and Turku	P cohort	RSV bronchiolitis, IP	Other pathogens bronchiolitis, IP	<12	NPA; PCR	asthma	12-24	crude	0.18 (0.10-0.30)	NA
				RV bronchiolitis, IP	<12	NPA; PCR	asthma	12-24	crude	0.12 (0.05-0.31)	NA
Bonnelykke (2015) [3]	Denmark, Copenhagen	P cohort	RSV RI, community	Other pathogens RI, community	<36	NPA; PCR	asthma	72	adjusted	1.01 (0.47-2.16)	Atopy
Bosis (2008) [4]	Italy, Milan	P cohort	RSV infection, wheezing, IP	Other pathogens, wheezing, IP	≤12	NPS; real time PCR	RW	18	crude	-*	No
Carbonelle-Estrany (2015) [5]	Spain, 37 hospitals	P cohort	RSV RI, IP	No RI, community	≤12	NA; IF, culture, ELISA	RW	24 36 48 60 72	adjusted	4.40 (2.82-6.86) 2.28 (1.41-3.70) 1.58 (0.91-2.75) 1.72 (0.92-3.20) 1.32 (0.68, 2.59)	Prematurity
Escobar (2013) [6]	US, California	R cohort	RSV, IP/OP/ED	No RSV, community	≤12	NA; DFA, culture	RW	24 36 48 60	crude	4.60 (4.00-5.29) 3.09 (2.61-3.65) 2.84 (2.40-3.38) 1.78 (1.45-2.19)	partly, prematurity ≥32 weeks, BPD, congenital anomaly
				Other pathogens, IP/OP/ED	≤12	NA; DFA, culture	RW	24 36 48 60	crude	1.38 (0.94-2.03) 1.92 (1.13-3.28) 1.65 (0.98-2.79) 0.96 (0.57-1.62)	partly, prematurity ≥32 weeks, BPD, congenital anomaly
Fjaerli (2005) [7]	Norway, Akershus County	R cohort	RSV bronchiolitis, IP	No bronchiolitis, community	≤12	NPA; IF, ELISA	RW	84	crude	5.77 (2.19-15.19)	NA
				Other viruses bronchiolitis, IP	≤12	NPA; IF, ELISA	asthma	84	crude	17.70 (5.68-55.13)	NA
							RW	84	crude	0.79 (0.27-2.29)	NA
							asthma	84	crude	1.80 (0.61-5.29)	NA
Garcia-Garcia (2007) [8]	Spain, Madrid	R cohort	RSV bronchiolitis, no concurrent wheeze or asthma, IP	Rotavirus gastroenteritis, no LRI, no concurrent wheeze or asthma, IP	≤24	NPA; PCR, IF	RW	36	crude	3.00 (1.25-7.17)	Partly, prematurity
								60	crude	1.70 (0.70-4.41)	Partly, prematurity
							asthma	60	crude	4.68 (1.81-12.13)	Partly, prematurity
Henderson (2005) [9]	UK, Avon	Pbirth cohort	RSV bronchiolitis, IP	No bronchiolitis, community	≤12	NPA; IF, culture	wheeze	30-42	adjusted	2.30 (1.30-3.90)	Partly, prematurity, atopy
								69-81	adjusted	3.50 (1.80-6.60)	Partly,

												prematurity, atopy
							asthma	91	adjusted	2.50 (1.40-4.30)		Partly, prematurity, atopy
Jackson (2008) [10]	US, Wisconsin	P cohort	RSV RI, wheezing, OP	Other viruses RI, wheezing, OP	≤12	NPW; PCR	asthma	72	crude	1.70 (0.90-3.30)		Atopy
				RV RI, wheezing, OP	≤12	NPW; PCR	asthma	72	crude	0.69 (0.30-1.57)		Atopy
Juntti (2003) [11]	Finland, Oulu	R cohort	RSV, IP	No RSV, matched on birth date and sex, community	≤12	NPA; ELISA, latex agglutination	RW	72-120	crude	0.93 (0.44-1.98)		No
					≤12	NPA; ELISA, latex agglutination	asthma	72-120	crude	1.91 (0.86-4.24)		No
Karaman (2011) [12]	Turkey, Izmir	P cohort	RSV bronchiolitis, IP	Other pathogens bronchiolitis, IP	<36	NPA; RT-PCR	RW	48-72	crude	0.47 (0.18-1.24)		No
Koponen (2012) [13]	Finland, Tampere	P cohort	RSV bronchiolitis, IP	Other pathogens bronchiolitis, IP	≤6	NPA; IF, PCR	asthma	78	crude	0.26 (0.10-0.66)		NA
Kotaniemi-Syrjanen (2002) [14]	Finland, Kuopio	P cohort	RSV, wheezing, IP	Other pathogens, wheezing, IP	≤24	NPA; ELISA	asthma	86.4 (67.2-105.6)	crude	0.19 (0.05-0.71)		No
Kusel (2007) [15]	Australia, Perth	P cohort	RSV LRI community	Other pathogens LRI community	≤12	NPA; PCR	wheeze	60	adjusted	1.20 (0.60-2.40)		Atopy
							asthma	60	adjusted	1.50 (0.70-3.20)		Atopy
Lee (2007) [16]	Canada, Vancouver	P cohort	RSV infection, community	Other viruses RI, community	≤12	NPA; PCR	asthma	24	adjusted	2.79 (1.44-5.40)		Atopy
Lemanske (2005) [17]	US, Wisconsin	P cohort	RSV RI, wheezing, OP	Other viruses RI, wheezing, OP	≤12	NPA; PCR	wheeze	36	adjusted	3.50 (1.70-7.50)		Atopy
			RSV RI “mod-severe”, OP	RV RI “mod-severe”, OP	≤12	NPA; PCR	wheeze	36	crude	0.50 (0.22-1.15)		Atopy
Lin (2001) [18]	China, Taiwan	P/R cohort	RSV LRI, IP	Other pathogens LRI, IP	≤24	NPA; NA	RW	60	crude	2.97 (0.88-10.06)		No
							asthma	60	crude	0.79 (0.22-2.78)		No
Lukkarinen (2017) [19]	Finland, Turku	P cohort	RSV wheezing, IP	Other pathogens, wheezing, IP	≤24	NPA; PCR, culture, ELISA, radioimmunoassay	asthma	96	crude	0.32 (0.11-0.91)		No
				RV, wheezing, IP	≤24	NPA; PCR, culture, ELISA, radioimmunoassay	asthma	96	crude	0.33 (0.11-0.96)		No
Midulla (2014) [20]	Italy, Rome	P cohort	RSV bronchiolitis, IP	Other viruses bronchiolitis, IP	≤12	NPA; PCR	RW	36-48	crude	0.18 (0.06-0.56)		No
				RV bronchiolitis, IP	≤12	NPA; PCR	RW	36-48	crude	0.32 (0.14-0.71)		No
Mikalsen (2012) [21]	Norway, Bergen	P cohort	RSV bronchiolitis, IP	No RSV, community	≤12	NPA; DFA	asthma	121.2-157.2	crude	1.81 (0.81-4.06)		No
				Other viruses bronchiolitis, IP	≤12	NPA; DFA	asthma	121.2-157.2	crude	0.33 (0.13-0.85)		No
Narita (2011) [22]	Japan, Konan	P cohort	RSV LRI, IP	Other pathogens LRI, IP	<36	NPW; RSV rapid diagnostic kit	wheeze	mean 91	crude	0.94 (0.34-2.61)		NA
							asthma	mean 91	crude	1.90 (0.50, 7.15)		NA

Palmer (2011) [23]	US	R cohort	RSV LRI, IP	No RSV, no LRI, hospital	≤12	NA	wheeze	mean ages 16.21-18.35	crude	6.10 (3.47-10.72)	Prematurity
							asthma	mean ages 16.21-18.35	crude	9.60 (5.68-16.23)	Prematurity
Pooririsak (2010) [24]	Denmark	R cohort	RSV infection, IP	No RSV, twin, community	≤24	NA; IF, ELISA	asthma	mean 91.2, IQR 70.8-110.4	crude	1.21 (0.36-4.00)	NA
Reijonen (2000) [25]	Finland, Kuopio	P cohort	RSV, wheezing, IP	Other pathogens, wheezing, IP	≤24	NPA; IF, radioimmunoassay	asthma	48 (38.4-61.2)	crude	0.43 (0.14-1.29)	No
Rinawi (2017) [26]	Israel	R cohort	RSV bronchiolitis, IP	No bronchiolitis, no RSV, matched for age, sex and residence, community	<6	Sputum; PCR, ELISA	RW	36	crude	4.16 (2.18-7.95)	No
				Other pathogens bronchiolitis, IP	<6	Sputum; PCR, ELISA	RW	36	crude	1.30 (0.52-3.23)	No
Romero (2010) [27]	US	R cohort	RSV infection, hospital	No RSV, matched (unknown), hospital	≤6	NA; NA	Wheeze	24-36	adjusted	2.52 (1.65-3.85)	prematurity or low birth weight (<2500g)
Rubner (2017) [28]	US, Wisconsin	P cohort	RSV RI, wheezing, OP	Other viruses RI, wheezing, OP	<36	NPW; PCR	asthma	72	crude	2.80 (1.60-5.00)	Atopy
								96	crude	2.60 (1.40-4.60)	Atopy
								132	crude	2.90 (1.60-5.40)	Atopy
Schauer (2002) [29]	Germany, Bochum	P cohort	RSV bronchiolitis, IP	No bronchiolitis, matched on date of birth and sex, community	≤12	NPA; ELISA	RW	8.4-19.2	adjusted	8.92 (1.42-55.88)	No
Sigurs (1995) [30]	Sweden, Skövde	P cohort	RSV bronchiolitis, IP	No RSV, no respiratory symptoms. matched on DOB, sex and residence, community	≤12	NPA; ELISA	RW	8.4-18	crude	0.55 (0.11-2.74)	No
								32.4-42	crude	2.01 (0.79-5.16)	No
							asthma	8.4-18	crude	-*	No
								32.4-42	crude	28.11 (3.50-225.71)	No
Sigurs (2000) [31]	Sweden, Skövde	P cohort	RSV bronchiolitis, IP	No RSV, no respiratory symptoms. matched on DOB, sex and residence, community	≤12	NPA; ELISA	RW	85.44-96.96	crude	2.57 (1.22-5.42)	No
							asthma	85.44-96.96	crude	13.90 (2.94-65.85)	No
Singleton (2003) [32]	US, Alaska	P cohort	RSV infection, IP	No LRI, no IP, age and village matched, community	≤24	NA; rapid antigen, culture	wheeze	60-96	crude	1.33 (0.76-2.33)	Partly
							asthma	60-96	crude	3.88 (1.76-8.56)	Partly

Stein (1999) [33]	US, Tucson	P cohort	RSV LRI, OP	No LRI, OP	<36	NPS; IF	RW	72	crude	4.30 (2.20-8.70)	NA
								96	crude	1.90 (0.90-4.20)	NA
								142	crude	2.40 (1.30-4.60)	NA
Stensballe (2017) [34]	Denmark, Copenhagen	P cohort	RSV infection, IP	Non-airway disease, IP	≤24	NPA; PCR, IF	wheeze	18m after inclusion	adjusted	3.16 (0.75-13.30)	Partly
								18-60m after inclusion	adjusted	2.13 (0.47-9.70)	Partly
Szabo (2014) [35]	Canada	R cohort	RSV LRI, IP	No LRI, community	≤24	NA; NA	asthma	24-60	crude	2.97 (2.29-3.87)	Partly
								60-120	crude	2.11 (1.60-2.80)	Partly
Takeyama (2014) [36]	Japan, Soma	P cohort	RSV LRI, IP	Other pathogens LRI, IP	<36	NPA; RT PCR	wheeze	72	crude	2.11 (1.60-2.80)	Partly
				RV LRI, IP	<36	NPA; RT PCR	wheeze	72	crude	0.65 (0.24-1.79)	Partly
Teeratakulpisarn (2014) [37]	Thailand, Khon Kaen	P cohort	RSV bronchiolitis, IP	Other pathogens bronchiolitis, IP	≤24	NPA; RT PCR	RW	36	crude	0.85 (0.50-1.44)	No
							asthma	72	crude	1.04 (0.58-1.84)	No
Valkonen (2009) [38]	Finland, Turku	R cohort	RSV bronchiolitis, IP	Other pathogens bronchiolitis, IP	≤24	NPA; PCR, IF	RW	36	crude	0.13 (0.05-0.34)	No
								48	crude	0.29 (0.15-0.53)	No
								60	crude	0.23 (0.13-0.42)	No
Weber (1999) [39]	Gambia, Banjul	P cohort	RSV LRI, IP	No LRI, matched for age and residence, community	≤12	NA; NA	wheeze	median cases 40 (IQR 34-42) controls 39 (34-41)	adjusted	7.33 (3.10-17.54)	Partly
Wennergren (1997) [40]	Sweden, Tucson	P cohort	RSV, wheezing bronchitis/bronchial asthma, IP	Other pathogens, wheezing bronchitis/bronchial asthma, IP	≤24	NPA; ELISA, latex agglutination, radioimmunoassay	asthma	120	crude	0.92 (0.33-2.56)	NA
Zomer-Kooijker (2014) [41]	Netherlands, Leidsche Rijn	P cohort	RSV bronchiolitis, IP	No RSV, community	<13	NPA; PCR, IF	wheeze	60-96	adjusted	3.20 (1.20-8.10)	NA
							asthma	60-96	adjusted	3.10 (1.30-7.50)	NA

OR=odds ratio. LCI=lower confidence interval. HCI=higher confidence interval. P cohort=Prospective cohort. R-cohort=Retrospective cohort. RSV=respiratory syncytial virus. RI=respiratory infection. LRI=lower respiratory infection. IP=inpatient. OP= outpatient. ED=emergency department. ISAAC=International Study of Asthma and Allergies in Childhood. m=months. DOB=date of birth. RV=rhinovirus. NPA=nasopharyngeal aspirate. NPS=nasopharyngeal swab. NPW=nasopharyngeal wash. PCR= polymerase chain reaction. RT-PCR=reverse transcriptase polymerase chain reaction. IF=immunofluorescent antibody test. DFA=direct immunofluorescent antibody test. ELISA=enzyme-linked immunosorbent assay. NA=not available. *The outcome was only identified in the exposure group which led to an enormous OR which is thus not shown. Data from each study is under the Edinburgh DataShare platform (<https://datashare.is.ed.ac.uk/handle/10283/3295>).

Supplementary Table 2: Characteristics of included studies stratified by outcome and control group - RSV vs. no respiratory symptoms, outcome recurrent wheeze

Author (year)	Location (setting)	Study period	Exposed definition, source	Control definition, source	Outcome definition	Physician or parent	Follow-up age (months)	OR (LCI-HCI)
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						diagnosis		
Carbonelle-Estrany (2015) [5]	Spain, 27 hospitals (urban)	2005-2007	RSV RI, IP	No RI, community	≥3 wheezing or bronchiolitis episodes within a year	Both	24	4.40 (2.82-6.86)
							36	2.28 (1.41-3.70)
							48	1.58 (0.91-2.75)
							60	1.72 (0.92-3.20)
							72	1.32 (0.68-2.59)
Escobar (2013) [6]	US, California (urban)	1996-2004	RSV, IP/OP/ED	No RSV, community	a combination of encounter events, patient diagnoses, and prescription patterns	Physician	24	4.60 (4.00-5.29)
							36	3.09 (2.61-3.65)
							48	2.84 (2.40-3.38)
							60	1.78 (1.45-2.19)
Fjaerli (2005) [7]	Norway, Akershus County (urban)	1993-2001	RSV bronchiolitis, IP	No bronchiolitis, community	≥3 wheezing episodes ever in 6-7 years follow up	Parent	84	5.77 (2.19-15.19)
Garcia-Garcia (2007) [8]	Spain, Madrid (urban)	2000-2008	RSV bronchiolitis no concurrent wheeze or asthma, IP	Rotavirus gastroenteritis, no LRI, no concurrent wheeze or asthma, IP	Asthma OR up to 2 episodes of wheezing verified by a physician in 1 year	Physician	36	3.00 (1.25-7.17)
							60	1.70 (0.70-4.41)
Henderson (2005) [9]	UK, Avon (urban)	1991-1997	RSV bronchiolitis, IP	No bronchiolitis, community	Any wheeze in 1 year reported from parents	Parent	30-42	2.30 (1.30-3.90)
							69-81	3.50 (1.80-6.60)
Juntti (2003) [11]	Finland, Oulu (urban)	1991-2001	RSV, IP	No RSV, matched on birth date and sex, community	Wheeze in last year, ISAAC questionnaire	Both	72-120	0.93 (0.44-1.98)
Palmer (2011) [23]	US (mixed)	2003-2008	RV LRI, IP	No RSV, no LRI, hospital	Any wheeze in 1 year	Physician	Mean ages 16.21-18.35	6.10 (3.47-10.72)
Rinawi (2017) [26]	Israel (mixed)	2005-2010	RSV bronchiolitis, IP	No bronchiolitis, no RSV, match for age, sex and residence, community	≥2 wheezing episodes between 6m and 3 years of age	Physician	36	4.16 (2.18-7.95)
Romero (2010) [27]	US (urban)	2001-2007	RSV infection, hospital	No RSV, matched (unknown), hospital	≥3 office, OP or ED visits with asthma or wheezing; ≥1 visit plus corticosteroids within 7 days; IP stay with asthma/wheezing or ≥150 days asthma medication	Physician	24-36	2.52 (1.65-3.85)
Schauer (2002) [29]	Germany, Bochum (urban)	1999-2002	RSV bronchiolitis, IP	No bronchiolitis, matched on DOB and gender, community	≥3 episodes of bronchial obstruction	Parent	8.4-19.2	8.92 (1.42-55.88)
Sigurs (1995) [30]	Sweden, Skövde (urban)	1989-1992	RSV bronchiolitis, IP	No RSV, no respiratory symptoms, matched on DOB, sex and residence, community	≥3 episodes of bronchial obstruction in 1 year, but not verified by a physician	Parent	8.4-18	0.55 (0.11-2.74)
							32.4-42	2.01 (0.79-5.16)
Sigurs (2000) [31]	Sweden, Skövde (urban)	1989-1992	RSV bronchiolitis, IP	No RSV, no respiratory symptoms, matched on DOB, sex and residence, community	RW cumulative; ≥3 episodes of bronchial obstruction in 1 year, but not verified by a physician	Parent	Between 85.44-96.96	2.57 (1.22-5.42)
Singleton (2003) [32]	US, Alaska (rural)	1993-2001	RSV infection, IP	No LRI, age and village matched, community	Any wheeze in 1 year determined by interview with parent, review of OP visits in the medical record, or wheezing on study examination	Both	60-96	1.33 (0.76-2.35)

Stein (1999) [33]	US, Tuscon (urban)	1980-1997	RSV LRI, OP	No LRI, OP	>3 episodes of wheeze in 1 year	Physician	72	4.30 (2.20-8.70)
Stensballe (2017) [34]	Denmark, Copenhagen (urban)	2001-2007	RSV infection, IP	Non-airway disease, IP	Any wheeze, asthmatic bronchitis or asthma at any time during follow-up	Parent	Exposed group median 26.88 Controls median 26.4	3.16 (0.75-13.50)
							Exposed group median 68.88 Controls median 68.4	2.13 (0.47-9.70)
Weber (1999) [39]	Gambia, Banjul (mixed)	1994-1996	RSV LRI, IP	No LRI, age and residence matched, community	Any wheeze in (median 25m) follow up	Yes	Median age exposed group 40 (IQR 34,42) controls 39 (34,41)	7.28 (1.60-33.11)
Zomer-Kooijker (2014) [41]	Netherlands, Leidsche Rijn (urban)	2001-2011	RSV bronchiolitis, IP	No RSV, community	Any wheeze or whistling in 1 year	Parent	60-96	3.20 (1.20-8.10)

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174 **Supplementary Table 3: Characteristics of included studies stratified by outcome and control group - RSV vs. no respiratory symptoms, outcome**
175 **asthma**

Author (year)	Location (setting)	Study period	Exposed definition, source	Control definition, source	Outcome definition	Physician or parent diagnosis	Follow-up age (months)	OR (LCI-HCI)
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Fjaerli (2005) [7]	Norway, Akershus (urban)	1993-2001	RSV bronchiolitis, IP	No bronchiolitis, community	Current follow up for asthma by a medical doctor	Physician	84	17.70 (5.68-55.13)
Garcia-Garcia (2007) [8]	Spain, Madrid (urban)	2000-2008	RSV bronchiolitis, no concurrent wheeze or asthma, IP	Rotavirus gastroenteritis, no LRI, no concurrent wheeze or asthma, IP	≥3 episodes of bronchial obstruction verified by a physician	Physician	60	4.68 (1.81-12.13)
Henderson (2005) [9]	UK, Avon (urban)	1991-1997	RSV bronchiolitis, IP	No bronchiolitis, community	Asthma physician diagnosed ever	Physician	91	2.50 (1.40-4.30)
Juntti (2003) [11]	Finland, Oulu (urban)	1991-2001	RSV, IP	No RSV, matched on birth date and sex, community	Asthma physician diagnosed ever (or paediatric allergologist review based on symptom questionnaire)	Physician	72-120	1.91 (0.86-4.24)
Mikalsen (2012) [21]	Norway, Bergen (urban)	1997-2009	RSV bronchiolitis, IP	No RSV, community	ISAAC, a combination of a history of 'asthma ever' and a positive answer to at least one of the two questions on wheezing/whistling/chest tightness during the preceding 12 months or use of asthma medication during the preceding 12 months	Parent	121.2-157.2	1.81 (0.81-4.06)
Palmer (2011) [23]	US (mixed)	2003-2008	RSV LRI, IP	No RSV, no LRI, hospital	Asthma (any wheeze in 1 year)	Physician	mean ages 4.21-6.35 plus 12m	9.60 (5.68-16.23)
Poorisrisak (2010) [24]	Denmark (urban)	1994-2003	RSV infection, community	No RSV, twin, community	Asthma physician diagnosed (GINA guidelines)	Physician	mean 91.2, IQR 70.8-110.4	1.21 (0.36-4.00)
Sigurs (1995) [30]	Sweden, Skövde (urban)	1989-1992	RSV bronchiolitis, IP	No RSV, no respiratory symptoms, matched on DOB, sex and residence, community	3 episodes of bronchial obstruction verified by a physician	Physician	8.4-18	-*
							32.4-42	28.11 (3.50-225.71)
Sigurs (2000) [31]	Sweden, Skövde (urban)	1989-1992	RSV bronchiolitis, community	No RSV, no respiratory symptoms, matched on DOB, sex and residence, community	3 episodes of bronchial obstruction verified by a physician	Physician	85.44-96.96	13.90 (2.94-65.85)
Singleton (2003) [32]	US, Alaska (rural)	1993-2001	RSV LRI, IP	No LRI, age and village matched, community	Asthma physician diagnosed ever (ISAAC)	Physician	60-96	3.88 (1.76-8.56)
Zomer-Kooijker (2014) [41]	Netherlands, Leidsche Rijn (urban)	2001-2011	RSV bronchiolitis, IP	No RSV, community	Combination of a history of doctor's diagnosed asthma plus asthma symptoms or medication use in the last 12m	Physician	60-96	3.10 (1.30-7.50)

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Supplementary Table 4: Characteristics of included studies stratified by outcome and control group - RSV vs. other pathogens associated respiratory infection, outcome recurrent wheeze

Author (year)	Location (setting)	Study period	Exposed definition, source	Control definition, source	Outcome definition	Physician or parent diagnosis	Follow-up age (months)	OR (LCI-HCI)
Al-Shawwa (2006) [1]	US, Wisconsin (urban)	2001-2003	RSV bronchiolitis, OP/IP	Other pathogens bronchiolitis, OP/IP	≥1 respiratory illness associated with wheezing and documented by a physician within a year from first visit excluding the first 2 weeks after the initial illness	Physician	12-36	0.22 (0.11-0.45)
Bosis (2008) [4]	Italy, Milan (urban)	2005-2006	RSV infection, wheezing, IP	Other pathogens, wheezing, IP	≥1 wheezing episode in last 6m	Parent	18	.*
Escobar (2013) [6]	US, California (urban)	1996-2004	RSV, IP/OP/ED	Other pathogens, IP/OP/ED	a combination of encounter events, patient diagnoses, and prescription patterns	Physician	24	1.38 (0.94-2.03)
							36	1.92 (1.13-3.28)
							48	1.65 (0.98-2.79)
							60	0.96 (0.57-1.62)
Fjaerli (2005) [7]	Norway, Akershus (urban)	1993-2001	RSV bronchiolitis, IP	Other viruses bronchiolitis, IP	≥3 wheezing episodes in 6-7 years	Parent	84	0.79 (0.27-2.29)
Karaman (2011) [12]	Turkey, Izmir (urban)	2006-2010	RSV bronchiolitis, IP	Other pathogens bronchiolitis, IP	Recurrence of wheeze episodes	Physician	48-72	0.47 (0.18-1.24)
Kusel (2007) [15]	Australia, Perth (urban)	NA	RSV LRI, community	Other pathogens LRI, community	Wheeze in the 1 year before the 5-year visit	Parent	60	1.20 (0.60-2.40)
Lemanske (2005) [17]	US, Wisconsin (urban)	1998-2003	RSV RI, wheezing, OP	Other viruses RI, wheezing, OP	Ever wheeze in 1 year	Parent	36	3.50 (1.70-7.50)
Lin (2001) [18]	China, Taiwan (urban)	1994-2000	RSV LRI, IP	Other pathogens LRI, IP	≥2 wheezing episodes in first 5 years of life	Parent	60	2.97 (0.88-10.06)
Midulla (2014) [20]	Italy, Rome (urban)	Oct 2004-May 2010	RSV bronchiolitis, IP	Other viruses bronchiolitis, IP	≥2 physician verified episodes of wheezing a year during 3 consecutive years	Physician	36-48	0.32 (0.14-0.71)
Narita (2011) [22]	Japan, Konan (urban)	2002-2009	RSV LRI, IP	Other pathogens LRI, IP	≥3 episodes of wheezing	Physician	Mean 91	0.94 (0.34-2.61)
Rinawi (2012) [26]	Israel (mixed)	2005-2010	RSV bronchiolitis, IP	Other pathogens bronchiolitis, IP	≥2 wheezing episodes between 6 months and 3 years of age	Physician	36	1.30 (0.52-3.23)
Takeyama (2014) [36]	Japan, Soma (urban)	2008-2012	RSV LRI, IP	Other pathogens LRI, IP	a visit to hospital/clinic with a wheezing episode, and/or requiring long-term therapy for physician-diagnosed asthma, and/or hospitalization with an asthma attack	Physician	72	2.11 (1.60-2.80)
Teeratakulpisarn (2014) [37]	Thailand, Khon Kaen (urban)	2002-2010	RSV, bronchiolitis, wheezing, IP	Other viruses, bronchiolitis, wheezing, IP	history of healthcare visits with wheezing or having receiving beta2 agonist nebulisation to relieve respiratory symptoms	Parent	36	0.85 (0.50-1.44)
Valkonen (2009) [38]	Finland, Turku (urban)	1988-2004	RSV bronchiolitis, IP	Other pathogens bronchiolitis, IP	development of RW (≥3 medically attended wheezing episodes) requiring long-term asthma medication	Physician	36	0.13 (0.05-0.34)
							48	0.29 (0.15-0.53)
							60	0.23 (0.13-0.42)

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Supplementary Table 5: Characteristics of included studies stratified by outcome and control group - RSV vs. other pathogens associated respiratory infection, outcome asthma

Author (year)	Setting	Study period	Exposed definition, source	Control definition, source	Outcome definition	Physician or parent diagnosis	Follow-up age (months)	OR (LCI-HCI)
Bergroth (2016) [2]	Finland, Kuopio, Tampere and Turku (urban)	2008-2011	RSV bronchiolitis, IP	Other pathogens bronchiolitis, IP	Asthma medication use in last year, questionnaire adapted from ISAAC questionnaire	Parent	12-24	0.18 (0.10-0.30)
Bonnelykke (2015) [3]	Denmark, Copenhagen (urban)	1998-2008	RSV RI, community	Other pathogens RI, community	Asthma diagnosis by physician, according to international guidelines	Physician	72	1.01 (0.47-2.16)
Fjaerli (2005) [7]	Norway, Akershus (urban)	1993-2001	RSV bronchiolitis, IP	Other viruses bronchiolitis, IP	Current follow-up for asthma by a medical doctor	Physician	84	1.80 (0.61-5.29)
Jackson (2008) [10]	US, Wisconsin (urban)	1998-2006	RSV RI, wheezing, OP	Other viruses RI, wheezing, OP	Physician diagnosed asthma or asthma medication use in last year	Physician	72	1.70 (0.90-3.30)
Koponen (2012) [13]	Finland, Tampere (urban)	2001-2011	RSV bronchiolitis, IP	Other pathogens bronchiolitis, IP	Child was on continuous maintenance medication for asthma, or if the child had suffered from doctor diagnosed wheezing or prolonged (>4 weeks) cough or night cough, apart from infection, during the preceding 12m	Physician	60	0.79 (0.22-2.78)
Kotaniemi Syrjanen (2002) [14]	Finland, Kuopio (urban)	1992-1999	RSV, wheezing, IP	Other pathogens, wheezing, IP	Continuous maintenance medication for asthma OR she/he had suffered from repeated (>= 2) episodes of wheezing and/or prolonged cough (>=4 weeks) apart from infection during the preceding 12m reported by parents AND the exercise challenge test was regarded as positive	Physician	86.4 (67.2-105.6)	0.19 (0.05-0.71)
Kusel (2007) [15]	Australia, Perth (urban)	NA	RSV LRI, community	Other pathogens LRI, community	asthma and wheeze in the year before the 5-year visit	Physician	12	1.50 (0.70-3.20)
Lee (2007) [16]	Canada, Vancouver (urban)	NA	RSV infection, community	Other viruses RI, community	Combination of allergologist diagnosis, episodes of cough and wheeze and response to treatment	Physician	154	2.79 (0.22-2.78)
Lin (2001) [18]	China, Taiwan	1994-2000	RSV LRI, IP	Other pathogens LRI, IP	Coughing and wheezing at night in the absence of URI, coughing and wheezing on exertion, wheezing or whistling sound in the chest with or without URI, and doctor diagnosed asthma	Physician	60	0.79 (0.22-2.78)
Lukkarinen (2017) [19]	Finland, Turku (urban)	2000-2012	RSV, wheezing, IP	Other pathogens, wheezing, IP	Physician diagnosis, use of asthma med, BD reversibility, exercise testing	Physician	96	0.32 (0.11-0.91)
Mikalsen (2012)	Norway, Bergen (urban)	1997-2009	RSV bronchiolitis, IP	Other viruses bronchiolitis, IP	ISAAC, a combination of a history of 'asthma ever' and a positive answer to at least one of the two questions on wheezing/whistling/chest tightness during the preceding 12 months or use of asthma medication during the preceding 12 months	Parent	121.2-157.2	0.33 (0.13-0.85)
Narita (2011) [22]	Japan, Konan (urban)	2002-2009	RSV LRI, IP	Other pathogens LRI, IP	Under a regular treatment for asthma	Physician	Mean 91	1.90 (0.50-7.15)
Reijonen (2000)	Finland,	1992-	RSV, wheezing, IP	Other pathogens,	≥1 physician-diagnosed episode of wheezing during	Physician	48 (38.4-	0.43 (0.14-1.29)

[25]	Kuopio (urban)	1996		wheezing, IP	the year preceding the 3-year visit, or if he/she still received maintenance therapy for asthma		61.2)	
Rubner (2017) [28]	US, Wisconsin (urban)	1998-2006	RSV RI, wheezing, OP	Other viruses RI, wheezing, OP	Physician diagnosed or asthma medication use in last year	Physician	72	2.80 (1.60-5.00)
							96	2.60 (1.40-4.60)
							132	2.90 (1.60-5.40)
Teeratakulpisarn (2014) [37]	Thailand, Khon Kaen (urban)	2002-2010	RSV, bronchiolitis, wheezing, IP	Other viruses, bronchiolitis, wheezing, IP	GINA guideline in children with RW with predictive factors, a doctor's diagnosis and the child's being prescribed inhaled corticosteroid for control	Physician	72	1.04 (0.58-1.84)
Wennergren (1997) [40]	Sweden, Tucson (urban)	1984-1995	RSV, wheezing bronchitis/bronchial asthma, IP	Other pathogens, wheezing bronchitis/bronchial asthma, IP	International Paediatric Asthma Consensus, classified as mild, moderate or severe, as estimated by the frequency of symptoms and the need for treatment to remain symptom-free	Parent	120	0.92 (0.35-2.56)

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184 **Supplementary Table 6: Characteristics of included studies stratified by outcome and control group - RSV vs. rhinovirus, outcome recurrent**
185 **wheeze**

Author (year)	Location (setting)	Study period	Exposed definition, source	Control definition, source	Outcome definition	Physician diagnosis	Follow-up age	OR (LCI-HCI)
Lemanske (2005) [17]	US, Wisconsin (urban)	1998-2003	RSV RI “mod-severe”, OP	RV RI “mod-severe”, OP	≥1 wheezing episode in 1 year	Parent	36	0.50 (0.22-1.15)
Midulla (2014) [20]	Italy, Rome (urban)	Oct 2004-May 2010	RSV bronchiolitis, IP	RV bronchiolitis, IP	≥2 physician verified episodes of wheezing a year during 3 consecutive years	Physician	36-48	0.18 (0.06-0.56)
Takeyama (2014) [36]	Japan, Soma (urban)	2008-2012	RSV LRI, IP	RV LRI, IP	a visit to hospital/clinic with a wheezing episode, and/or requiring long-term therapy for physician-diagnosed asthma, and/or hospitalization with an asthma attack	Physician	72	0.65 (0.24-1.79)

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187 **Supplementary Table 7: Characteristics of included studies stratified by outcome and control group - RSV vs. rhinovirus, outcome asthma**

Author (year)	Location (setting)	Study period	Exposed definition, source	Control definition, source	Outcome definition	Physician diagnosis	Follow-up age	OR (LCI-HCI)
Bergroth (2016) [2]	Finland, Kuopio, Tampere and Turku (urban)	2008-2011	RSV bronchiolitis, IP	RV bronchiolitis, IP	Asthma medication use, questionnaire adapted from ISAAC questionnaires	Parent	12-24	0.12 (0.05-0.31)
Jackson (2008) [10]	US, Wisconsin (urban)	1998-2006	RSV, wheezing, IP	RV, wheezing, IP	Asthma physician diagnosed or asthma medication use in last year	Physician	72	0.69 (0.30-1.57)
Lukkarinen (2017) [19]	Finland, Turku (urban)	2000-2012	RSV, wheezing, IP	RV, wheezing, IP	Physician diagnosis, use of asthma med, BD reversibility, exercise testing	Physician	96	0.33 (0.11-0.96)

188 OR=odds ratio. LCI=lower confidence interval. HCI=higher confidence interval. RSV=respiratory syncytial virus. RI=respiratory infection. LRI=lower respiratory infection. IP=inpatient. OP= outpatient.
189 ED=emergency department. ISAAC=International Study of Asthma and Allergies in Childhood. m=months. DOB=date of birth. RV=rhinovirus. *The outcome was only identified in the exposure
190 group which led to an enormous OR which is thus not shown.

Supplementary Table 8: Meta analyses results for the association between RSV infection during infancy (focusing on 0-11m) and childhood recurrent wheeze and asthma, stratified by control group and follow-up age

Recurrent wheeze		
RSV vs. no respiratory symptoms		
Follow-up age	No. of studies	OR (LCI-HCI)
<36m	8	3.06 (2.42-3.87)
36-72m	4	2.58 (1.41-4.73)
>72m	4	2.48 (1.16-5.28)
RSV vs. other pathogens		
Follow-up age	No. of studies	OR
<36m	4	2.11 (1.42-3.12)
36-72m	3	0.74 (0.37-1.52)
>72m	1	-
RSV vs. rhinovirus		
Follow-up age	No. of studies	OR
<36m	0	-
36-72m	2	-
>72m	0	-
Asthma		
RSV vs. no respiratory symptoms		
Follow-up age	No. of studies	OR
<36m	2	-
36-72m	0	-
>72m	6	3.68 (1.92-7.04)
RSV vs. other pathogens		
Follow-up age	No. of studies	OR
<36m	2	-
36-72m	2	-
>72m	3	0.52 (0.17-1.63)
RSV vs. rhinovirus		
Follow-up age	No. of studies	OR
<36m	1	-
36-72m	1	-
>72m	0	-

RSV=respiratory syncytial virus. OR=odds ratio. LCI=lower 95% confidence interval. HCI=higher 95% confidence interval

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