

BMJ Open Association between early bronchiolitis and the development of childhood asthma: a meta-analysis

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ABSTRACT

Objective Early life bronchiolitis has been hypothesised to be associated with the subsequent risk of persistent wheezing or asthma. However, the link remains controversial. The objective of our study was to evaluate the association between bronchiolitis before 2 years of age and the late-onset wheezing/asthma.

Design Systematic review and meta-analysis.

Methods PubMed, Embase and Web of Science databases were systematically searched for studies published between 1955 and January 2020. Meanwhile, we also checked through the reference lists of relevant articles to see whether these references included reports of other studies that might be eligible for the review. Cohort and case-control studies assessing the association between early-life bronchiolitis and late-onset wheezing/asthma were included in this meta-analysis. Data were extracted by two independent reviewers. Results were pooled using a random-effects model or fixed-effects model according to the heterogeneity among studies.

Results 32 original articles with 292 844 participants, which met the criteria, were included in this meta-analysis. Bronchiolitis before 2 years of age was associated with an increased risk of subsequent wheezing/asthma (relative risk=2.46, 95% CI 2.14 to 2.82, $p<0.001$). After categorising studies into different groups based on age at the end of follow-up, geographical region and study quality, the association still remained significant.

Conclusions The meta-analysis indicates an association between bronchiolitis before 2 years of age and the wheezing/asthma in later life. Well-designed and highly standardised prospective studies that better address bias due to potential confounding factors are needed to validate the risk identified in our meta-analysis.

PROSPERO registration number
CRD42018089453.

INTRODUCTION

Asthma is one of the most common chronic, noncommunicable respiratory diseases and its prevalence has increased in the world, leading to high-cost emergency care and hospitalisations,¹ with a substantial negative impact on quality of life among children and adults.² The aetiology of asthma is complex, involving the interactions of multiple environmental and genetic stimuli.³ There have

Strengths and limitations of this study

- This meta-analysis aimed to examine whether early bronchiolitis increased the risk of childhood wheezing/asthma is of great significance.
- All the studies included had moderate to high qualities according to the Newcastle-Ottawa Scale.
- There was substantial heterogeneity in the pooled data even after subgroup analyses.
- Only published studies with sufficient data were included, so the possibility of publication bias cannot be completely ruled out.

been many meta-analyses trying to identify risk factors for asthma. Exposure to smoke,⁴ male gender, atopic dermatitis, family history of asthma, history of wheezing and serum IgE level ≥ 60 kU/L or having specific IgE are found to be positively associated with developing asthma.⁵ Breastfeeding⁶ and exposure to cats and dogs⁷ seem to play protective roles in the development of asthma. However, the associations between high adherence of the Mediterranean diet during pregnancy and childhood⁸ and swing attendance during childhood⁹ with asthma are still unclear.

Bronchiolitis is a lower respiratory tract infection in children younger than 2 years old characterised by respiratory distress, wheezing and crackles.¹⁰ It is primarily caused by viral infections, particularly respiratory syncytial virus (RSV), which is responsible for 70% of episodes of bronchiolitis.¹¹ Other viruses, such as rhinovirus, human metapneumovirus, influenza A and B viruses, parainfluenza virus, adenovirus, papillomavirus and bocavirus, have also been implicated.¹² Bronchiolitis is a major public health problem worldwide, the prevalence of bronchiolitis is 20%–30% in the first year and 10%–20% in the second year of life.¹³ It is also the leading cause of hospitalisation in infants and young children. Approximately, 1%–3% of infants

need hospitalisation for bronchiolitis—most commonly those aged <6 months.¹⁴

Although numerous clinical studies have been conducted since the 1950s to investigate the relationship between bronchiolitis and subsequent persistent wheezing or asthma, the link remains controversial.^{15–18}

The demonstration of a relation between bronchiolitis and the subsequent wheezing/asthma, and a better understanding of the association may be important for the prevention and treatment of asthma. A previous meta-analysis has shown an association between infant RSV hospitalisation and asthma/wheezing sequelae,¹⁹ but it did not consider other viruses causing bronchiolitis. Therefore, we have conducted a systematic review and meta-analysis of the existing available evidence.

METHODS

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The protocol was registered in PROSPERO.

Search strategy

We systematically searched the PubMed, Embase and Web of Science to identify available English language articles published between 1955 and January 2020. Using the following search terms: (infant OR child OR children) AND bronchiolitis AND (wheezing OR asthma). The research strategy for each database was established with the help of a research librarian (see online supplemental table S1). Meanwhile, we also checked through the reference lists of relevant articles to see if these references included reports of other studies that might be eligible for the review.

Inclusion and exclusion criteria

Articles were selected for inclusion only if they meet all the following criteria: (1) cohort study or case–control study type, (2) the diagnosis of bronchiolitis was made by a physician and the maximum age when diagnosed was ≤ 2 years, (3) outcome of interest was wheezing/asthma (diagnosed by a physician or reported by the parents or retrieved from medical insurance databases), (4) measures of association (OR, HR or relative risk (RR)) and their 95% CI or data allowing for computation of summary measures are provided. Results at multiple follow-up times from a same study will be correlated, which will result in SEs (corresponding 95% CIs) that do not reflect the true variability. Therefore, if a study had several periods of follow-up, we used the values from the longest follow-up. Studies were excluded if they did not meet these inclusion criteria. Unpublished or grey literature data (eg, in terms of conference abstracts, dissertations or editorials) were not considered. The selection of the studies was by two reviewers independently and discussion was needed to resolve the discrepancies, if needed, by adjudication from a third reviewer.

Data extraction and quality assessment

Data were extracted by two independent reviewers and, in the case of discrepancies, the final decision was made by a third investigator. From each eligible article, we recorded: first author, publication year, original country where the study was conducted, study type, number of participants, age when diagnosed of bronchiolitis, bronchiolitis infection virus, outcome, age at the end of follow-up and the effect estimate (95% CI). We selected the outcome based on the following criteria if a study reported several potential outcomes of interest (eg, asthma, wheezing and recurrent wheezing): (1) diagnosis by a physician was selected over parental assessment, (2) current respiratory status or respiratory status in the past 12 months was selected over cumulative outcome, (3) asthma was selected over wheezing.²⁰ The quality of each study was independently assessed by two reviewers according to the Newcastle-Ottawa Scale (NOS).²¹ A study awarded a score of 0–3, 4–6 or 7–9 was considered as a low, moderate or high-quality study, respectively. If there are discrepancies, they will be resolved by consensus and discussion.

Statistical methods

We extracted the association (OR or RR or HR) and their 95% CI or derived by using data from the original studies (unadjusted $RR = P_1/P_0$, P_1 indicates the incidence of the outcome of interest in the exposed group and P_0 in the nonexposed group).²² It is not recommended to combine HRs with RRs and ORs in a meta-analysis, as HRs represent instantaneous risk over the study time period, whereas RRs and ORs estimate risk/odds at a fixed time point.²³ The ORs were transformed into RRs using the formula $RR = OR / ((1 - P_0) (P_0 \times OR))$.²² HRs and RRs (or RRs derived from ORs) should be presented in separate meta-analyses. Additionally, the transformation from ORs to RRs has some limitations and may underestimate the variance of the RRs derived from the ORs.^{24 25} Therefore, we conducted a sensitivity analysis that excluded the studies where outcome was transformed. We also compared the results applying the Miettinen test-based approach for calculating the variance of the natural logarithm of the RR ($\ln RR$; variance $\ln RR = \text{variance } \ln OR \times (\ln RR / \ln OR)$).²⁶

The statistical analysis was done with Stata V.12.0 (Stata Corp, College Station, Texas, USA). We used the 'metan' command in Stata to pool the $\ln RR / \ln HR$. Forest plots were used to visually assess the individual and pooled estimates with the corresponding 95% CIs. In meta-analysis, the usual way of assessing whether a set of single studies is homogeneous is by means of the Q statistics. However, the Q statistic only informs meta-analysis about the presence versus the absence of heterogeneity, but does not report on the extent of such heterogeneity. Moreover, it has poor power to detect true heterogeneity among studies when the meta-analysis includes a small number of studies. I^2 index is proposed to quantify the degree

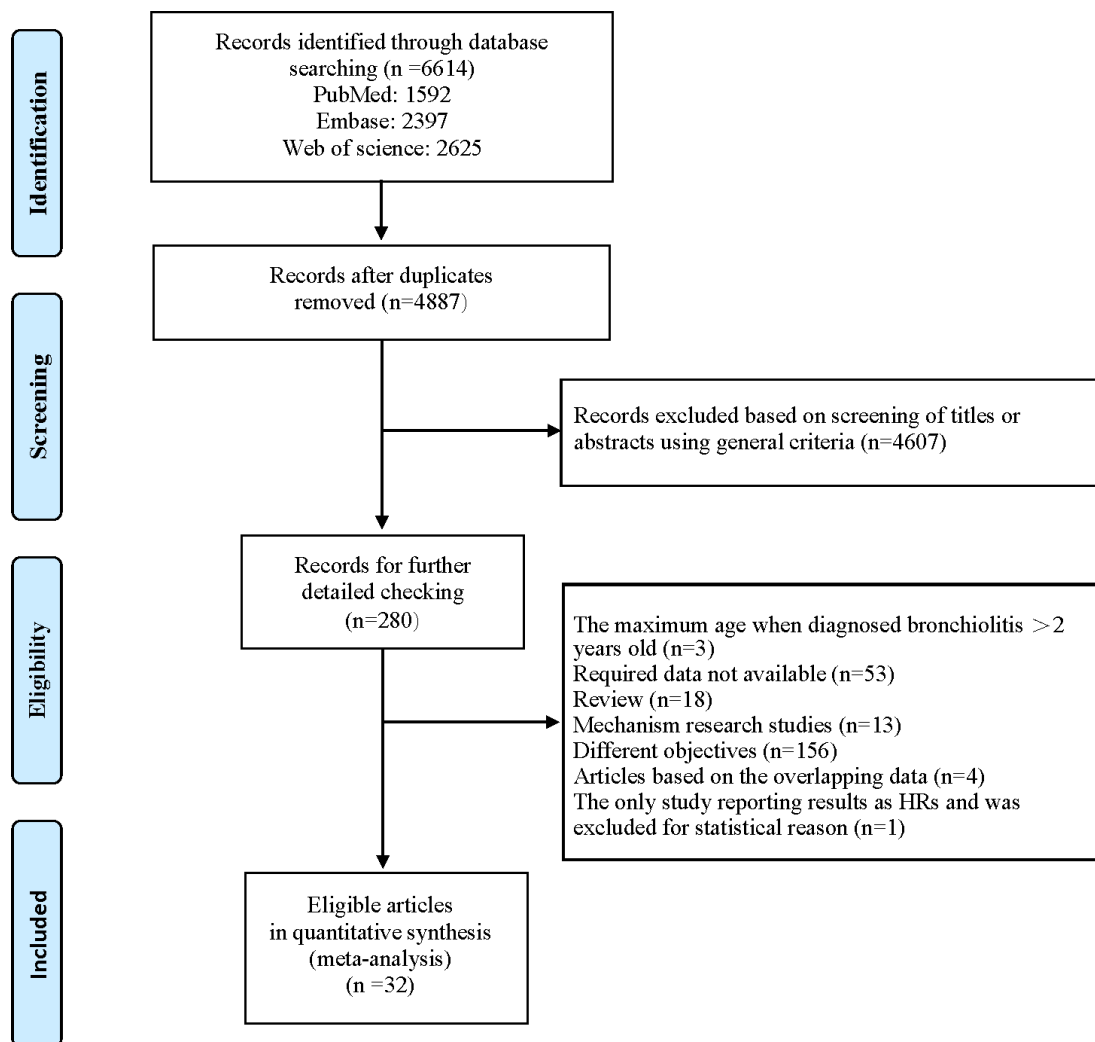


Figure 1 The flow diagram of identifying relevant studies.

of heterogeneity and considered as a complement to the Q statistic, although it has the same problems of power with a small number of studies.²⁷ Therefore, we used the Q statistics (significance level of $p < 0.10$) and I^2 statistics ($> 50\%$ was usually judged to significant inconsistency) to comprehensively evaluate between-study heterogeneity.²⁸ A fixed-effects model was used when heterogeneity between studies was not significant, while a random-effects model was adopted. Analyses were stratified by age at the end of follow-up (< 10 years and ≥ 10 years), geographical region (Europe, North America, South America and Asia) and study quality (NOS score 4–6, moderate quality and NOS score 7–9, high quality). We chose 10 years old as the cut-off in the age stratification analysis for the following reasons: Sears *et al*²⁹ and McGeachie *et al*³⁰ indicate that children presenting with abnormal lung function after the age of 10 years have lower lung function in adulthood; Sousa *et al*³¹ show that onset of fixed airflow obstruction (FAO) starts at 10 years of age. After 10 years of age, the FEV1/FVC ratio is lower in the FAO group than in the non-FAO group. Potential publication bias was assessed by using funnel plot

and Begg's and Egger's tests, and $p < 0.05$ was considered significant.^{32 33}

Patient and public involvement

Patients and the public were not involved in this review.

RESULTS

Study characteristics

A total of 6614 citations were identified: 1592 from PubMed, 2397 from Embase and 2625 from Web of Science. Of these, 1727 were excluded for duplicates and 4607 were excluded after the first screening based on abstracts or titles, leaving 280 articles for full-text review. The study by Lin H-W and Lin S-C³⁴ has shown that the acute bronchiolitis in young children younger than 2 years old is correlated with the later development of asthma. It was the only study reporting results as HRs after full-text review. However, one study should not result in any model tests of significance and allow us to perform a separate meta-analysis. So, we did not include it in the pooled analyses and excluded it. Two articles were published by the same author in the

Table 1 Characteristics of studies included in meta-analysis (n=33)

First author	Publication year	Country	Study type	Number of participants	Age at time of bronchiolitis (months)	Virus	Outcome	Age at the end of follow-up (years)	Effect estimate (95% CI)	NOS
Sims DG <i>et al</i> ¹⁶	1978	UK	Cohort study	70	<12	RSV	Wheezing	8	RR 1.00 (0.63 to 1.58)	5
Sherman CB <i>et al</i> ¹⁵	1990	USA	Cohort study	770	<12	Not reported	Asthma	5–9	RR 0.94 (0.15 to 6.02)	5
Murray M <i>et al</i> ¹⁷	1992	UK	Cohort study	202	<12	Mixed	Wheezing	6	RR 2.82 (1.54 to 5.17)	6
Korppi M <i>et al</i> ⁴²	1994	Finland	Cohort study	179	<24	Mixed	Asthma	8	RR 7.55 (0.99 to 57.64)	6
Sigurs N <i>et al</i> ³⁷	2010	Sweden	Cohort study	140	3.5	RSV	Asthma	18	OR 7.2 (2.1 to 23.9)	7
Olivetti JF <i>et al</i> ⁴³	1996	USA	Case-control	262	<24	Not reported	Asthma	4–9	OR 4.71 (2.18 to 10.20)	6
Noble V ⁶¹	1997	UK	Cohort study	108	<12	Mixed	Asthma	9–10	OR 4.43 (1.63 to 12.0)	7
Gold DR <i>et al</i> ⁴⁴	1999	USA	Cohort study	505	<12	Not reported	wheezing	1	RR 3.10 (2.03 to 4.70)	6
Larouch V <i>et al</i> ⁴⁶	2000	Canada	Cohort study	84	<18	Not reported	Asthma	17–35	RR 3.20 (1.29 to 7.94)	6
Schauer U <i>et al</i> ⁴⁷	2002	Germany	Cohort study	126	<12	RSV	Recurrent wheezing	0.7–1.5	OR 8.92 (1.42 to 55.88)	6
Chatkin MN <i>et al</i> ⁶³	2003	Brazil	Cohort study	981	<12	Not reported	Asthma	4–5	aRR 1.46 (1.05 to 2.03)	7
Pliippo-Savolainen E <i>et al</i> ⁴⁸	2004	Finland	Cohort study	199	<24	Not reported	Asthma	18–21	aOR 2.97 (0.96 to 9.18)	7
Henderson J <i>et al</i> ⁴⁹	2005	UK	Cohort study	14 062	<12	RSV	Asthma	7–8	OR 2.5 (1.4 to 4.3)	8
Fjaerli HO <i>et al</i> ⁵⁰	2005	Norway	Cohort study	121	<24	RSV	Asthma	7	RR 6.96 (2.90 to 16.69)	7
Ramsey CD <i>et al</i> ⁴⁵	2007	USA	Cohort study	505	<12	Not reported	Asthma	7	OR 2.77 (1.23 to 6.22)	8
Pereira MU <i>et al</i> ⁶⁴	2007	Brazil	Cohort study	1011	<24	Not reported	Asthma	10	OR 11.9 (7.5 to 19.0)	6
García-García ML <i>et al</i> ⁵¹	2007	Spain	Cohort study	83	<24	Mixed	Asthma	5	RR 4.90 (1.93 to 12.47)	6
Carroll KN <i>et al</i> ⁶⁶	2009	USA	Cohort Study	90 341	<12	Not reported	Asthma	3.5–5.5	RR 2.04 (1.92 to 2.22)	8

Continued

Table 1 Continued

First author	Publication year	Country	Study type	Number of participants	Age at time of bronchiolitis (months)	Virus	Outcome	Age at the end of follow-up (years)	Effect estimate (95% CI)	NOS
Mikalsen IB ⁵²	2012	Norway	Cohort study	272	<12	Mixed	Asthma	11	RR 2.24 (1.20 to 4.19)	7
Midulla F <i>et al</i> ⁵³	2012	Italy	Cohort study	352	<12	Mixed	Recurrent wheezing	<2	RR 5.14 (2.02 to 13.09)	5
Kim BJ <i>et al</i> ⁵⁴	2013	Korea	Cohort study	1743	<24	Not reported	Asthma	8–10	OR 2.80 (1.43 to 5.52)	6
Ruotsalainen M <i>et al</i> ⁵⁵	2013	Finland	Cohort study	255	<24	Mixed	Asthma	16.5	OR 10.65 (3.83 to 29.67)	7
Lee E <i>et al</i> ⁶⁵	2014	Korea	Cohort study	7389	<24	Not reported	Asthma	13–15	aOR 3.27 (2.32 to 4.60)	7
Zomer-Kooijker K <i>et al</i> ⁶⁶	2014	Netherlands	Cohort study	708	<13	RSV	Asthma	6	OR 3.1 (1.3 to 7.5)	6
Backman K <i>et al</i> ⁶⁵	2014	Finland	Cohort study	208	<24	Not reported	Asthma	28–31	OR 3.8 (1.6 to 8.9)	7
Strickland MJ ⁵⁷	2014	USA	Cohort study	143 258	<12	Not reported	Asthma	5	RR 1.9 (1.7 to 2.1)	7
Jeng MJ <i>et al</i> ⁶⁰	2014	China	Cohort study	21 791	<24	Not reported	Asthma	3–10	aOR 1.633 (1.44 to 1.85)	7
Jung YH <i>et al</i> (elementary school children) ⁴¹	2015	Korea	Cohort study	1341	<24	Not reported	Asthma	7–12	aOR 3.11 (1.84 to 5.24)	7
Jung YH <i>et al</i> (nursery children) ⁴¹	2015	Korea	Cohort study	919	<24	Not reported	Asthma	3–7	aOR 3.94 (2.27 to 6.84)	7
Ardura-Garcia C <i>et al</i> ⁶⁸	2015	Ecuador	Case-control	179	<24	Mixed	Asthma	5–15	OR 38.9 (3.26 to 465)	6
Törmänen S <i>et al</i> ⁵⁹	2017	Finland	Cohort study	830	<6	RSV	Asthma	11–13	RR 1.22 (0.61 to 2.42)	7
Balekian DS <i>et al</i> ¹⁸	2017	USA	Cohort study	3653	<12	Not reported	Asthma	5	OR 2.57 (1.61 to 4.09)	8
Riiikonen R <i>et al</i> ⁶²	2019	Finland	Cohort study	197	<6	Mixed	Asthma	10–13	RR 1.21 (0.57 to 2.57)	7

NOS, Newcastle-Ottawa Scale; RR, relative risk; RSV, respiratory syncytial virus.

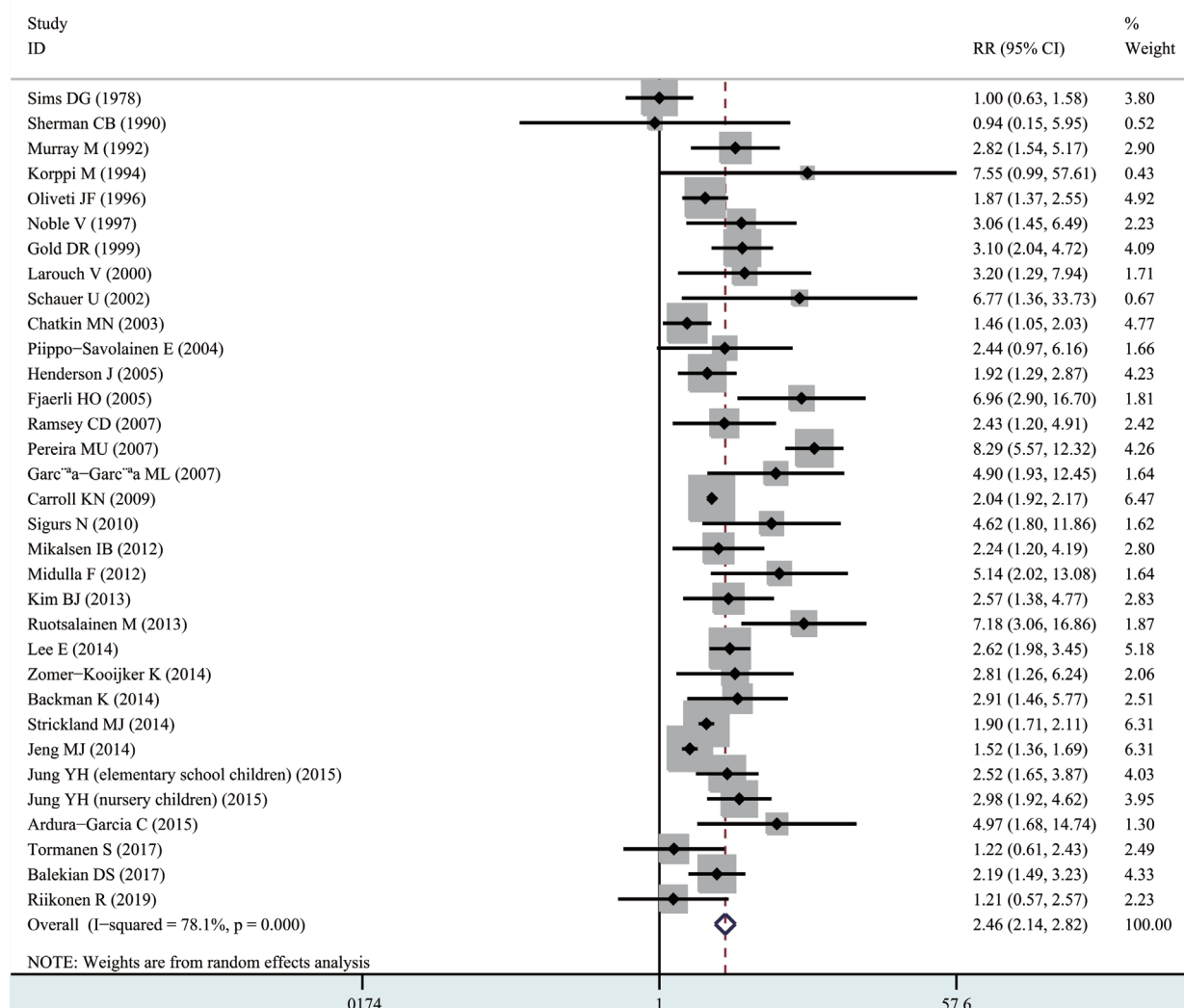


Figure 2 Forest plot of the overall association between bronchiolitis before 2 years of age and the subsequent development of wheezing/asthma.

same year and reported the results of a same cohort study,^{35 36} but with different objectives. We avoided duplicate inclusion of data by selecting only the more complete article.³⁵ Additionally, four articles reported the results of a same longitudinal cohort study (Sigurs *et al*^{37–40}) with different lengths of follow-up period, we only included the one with longest follow-up according to the inclusion criteria. Finally, 32 articles (33 studies, one article included two independent cohort studies)⁴¹ were eligible and included in our meta-analysis^{15–18 34 35 37 41–66} (figure 1). Among these studies, two were case-control studies,^{43 58} 31 were cohort studies.^{15–18 34 35 37 41 42 44–57 59–66} The main characteristics of the included studies are summarised in table 1.

Quality assessment

All included studies were assessed by NOS and their score ranged from 5 to 8, suggesting that the methodological quality was acceptable. The details of NOS assessment for each enrolled study are shown in online supplemental table S2 and S3.

Quantitative synthesis

Significant heterogeneity among studies was present ($I^2=78.1\%$, $p<0.001$), and thus a random-effects model was performed overall analysis. The combined results demonstrated that bronchiolitis before 2 years of age was associated with increased risk of wheezing/asthma (RR=2.46, 95% CI 2.14 to 2.82, $p<0.001$; figure 2). We further evaluate whether the association between bronchiolitis and development of wheezing/asthma would change with age. Significant heterogeneity was identified (<10 years, $I^2=82.5\%$, $p<0.001$; ≥ 10 years, $I^2=49.8\%$, $p=0.043$), and thus a random-effects model was used. The association still remained significant in <10 years (RR=2.40, 95% CI 2.04 to 2.82, $p<0.001$) and ≥ 10 years (RR=2.54, 95% CI 1.84 to 3.50, $p<0.001$, figure 3). When stratified analysis was conducted by geographical region, the association still remained significant in Europe (RR=2.78, 95% CI 2.04 to 3.79, $p<0.001$), North America (RR=2.02, 95% CI 1.89 to 2.16, $p<0.001$), South America (RR=3.85, 95% CI 1.02 to 14.52, $p<0.05$) and Asia (RR=2.31, 95% CI 1.63 to

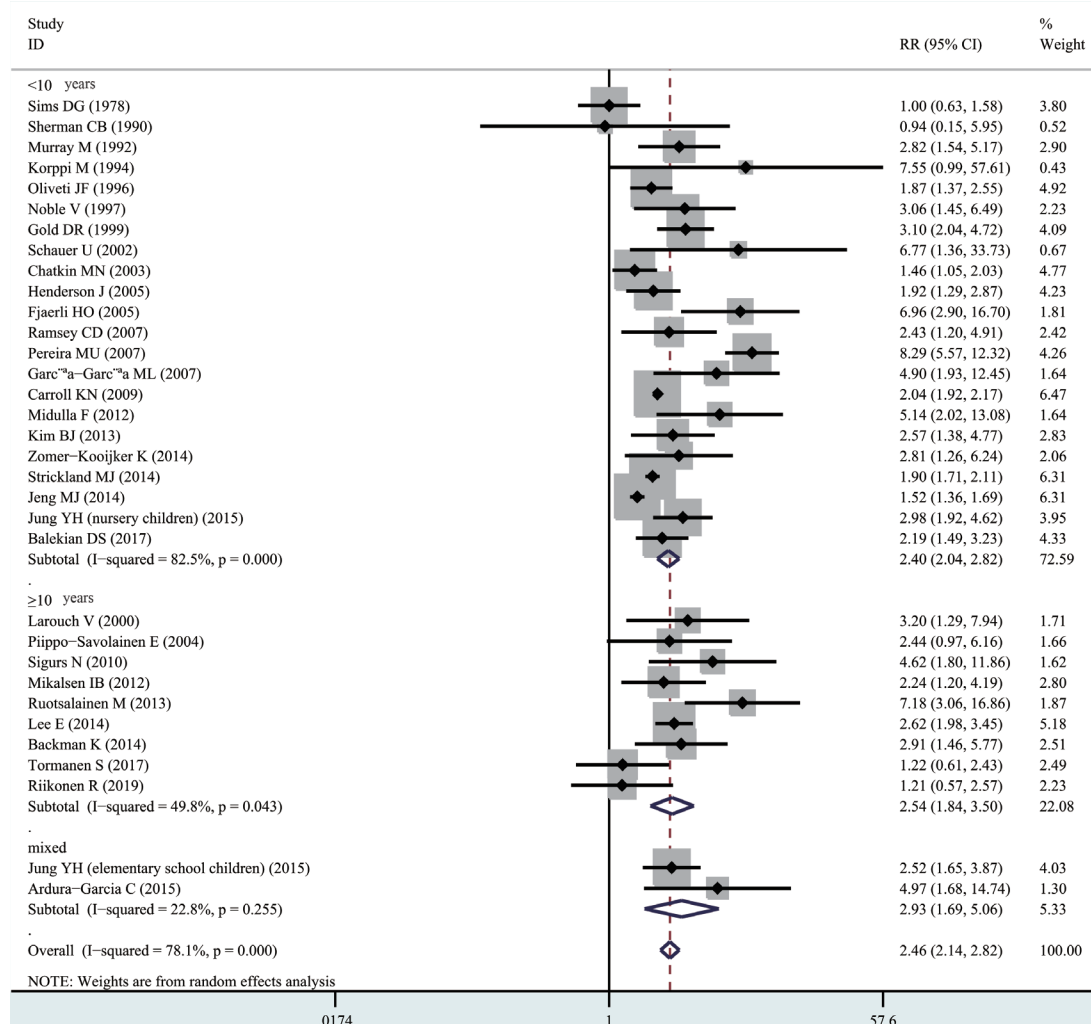


Figure 3 Forest plot of the association between bronchiolitis before 2 years of age and the subsequent development of wheezing/asthma, stratified by age at the end of follow-up.

3.28, $p < 0.001$; [figure 4](#)). In subgroup analysis by study quality, the significant association was identified in both moderate quality (RR=3.16, 95% CI 2.12 to 4.70, $p < 0.001$) and high quality (RR=2.15, 95% CI 1.88 to 2.46, $p < 0.001$) ([figure 5](#)).

Sensitivity and publication bias analysis

The sensitivity analysis that excluded all studies for which the transformation of ORs to RRs was used, which showed a similar result with a pooled RR of 2.07 (95% CI 1.74 to 2.45, $p < 0.001$). We used the funnel plot to assess the publication bias, and the result showed there was no obvious asymmetry ([figure 6](#)). Furthermore, Begg's and Egger's test showed there was no significant publication bias ($p > 0.05$).

DISCUSSION

Principal findings

This meta-analysis on 33 studies provided considerable evidence indicating the positive association between early-life bronchiolitis and the subsequent development of wheezing/asthma. Regnier and Huels¹⁹ have

indicated that the association between RSV hospitalisation in infants and asthma/wheezing decreases with age at the end of follow-up. To assess whether this association between bronchiolitis and later onset of wheezing/asthma would also change with age, we conducted subgroup analysis based on age at the end of follow-up, and the association still remained significant in both <10 years old and ≥ 10 years old. The reason for this difference may be due to the multiple viral respiratory pathogens involved in the enrolled studies.

Mechanisms of bronchiolitis on wheezing/asthma

Bronchiolitis is the most common acute lower respiratory tract infection in infants and the primary cause of hospitalisation in this age group. Recently, a growing number of studies have been conducted to explore the association between bronchiolitis and the development of subsequent wheezing and asthma. However, the results are inconclusive.^{15–18} Therefore, it is crucial to include all eligible studies and to assess the overall association. In this meta-analysis,

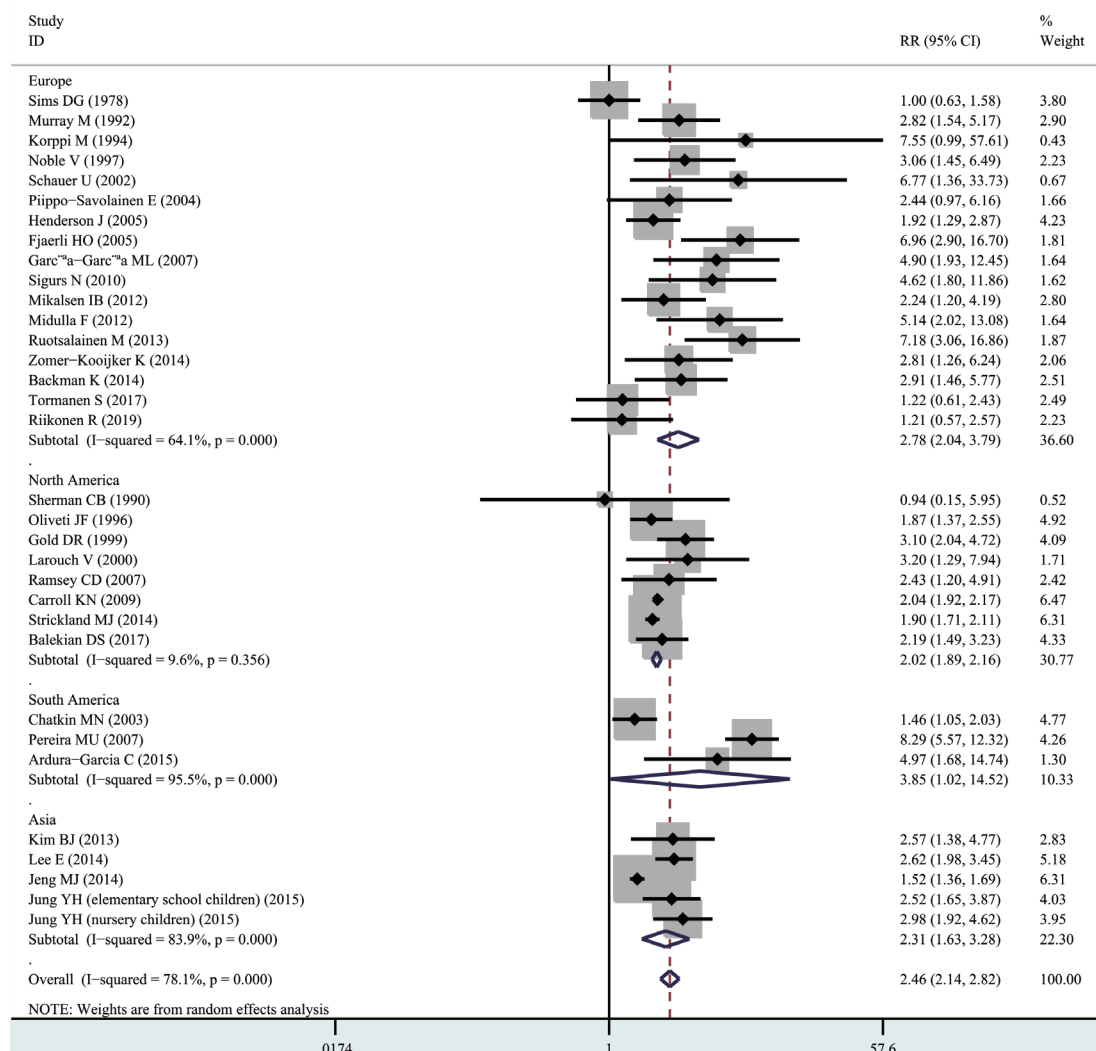


Figure 4 Forest plot of the association between bronchiolitis before 2 years of age and the subsequent development of wheezing/asthma, stratified by geographical region.

the combined results demonstrated the association between early bronchiolitis and the development of wheezing/asthma. In the first year of life, both the respiratory tract and the immune system mature rapidly, and it seems that postnatal development is affected by viral infection. A variety of potential biological mechanisms might underlie the association of bronchiolitis with wheezing/asthma. (1) Induction of inflammation typical of allergic asthma by T lymphocyte differentiation into Th2⁶⁷, (2) activation of Th17 cells and induction of IL-17 production. Activated Th17 cells regulate the production of other proinflammatory cytokines (IL-6, tumor necrosis factor (TNF)- α , metalloproteinases etc), which may play important roles in the pathogenesis of asthma,⁶⁸ (3) upregulation of IL-4 and downregulation of interferon (IFN)- γ levels,⁶⁹ (4) induction of bronchial hyperactivity by inflammatory cells and sensory C-fibre neuropeptide,⁷⁰ (5) imbalance of respiratory microbial communities.⁷¹

Implications for practice

Effective strategies against bronchiolitis could reduce the consequences of immune response to pathogens, thus reducing the risk of asthma. Unfortunately, despite the large public health burden, no effective treatment shortening the course or hastening the resolution of symptoms are available, other than supportive care in young children with bronchiolitis.^{72–74} It is mainly because of the wide variety of viruses involved in causing bronchiolitis and poor cross-protection between prior heterologous infections. RSV is considered as the main cause of bronchiolitis. There have been some studies exploring the effect of RSV prevention on respiratory morbidity. Scheltema *et al*⁷⁵ indicate that RSV prevention in preterm infants is associated with a decrease in parent-reported wheeze at 6 years of age. Similar results have been reported by Mochizuki *et al*⁷⁶ and Prais *et al*.⁷⁷ However, the study conducted by Scheltema *et al* shows no effect of RSV prevention on current physician-diagnosed asthma at

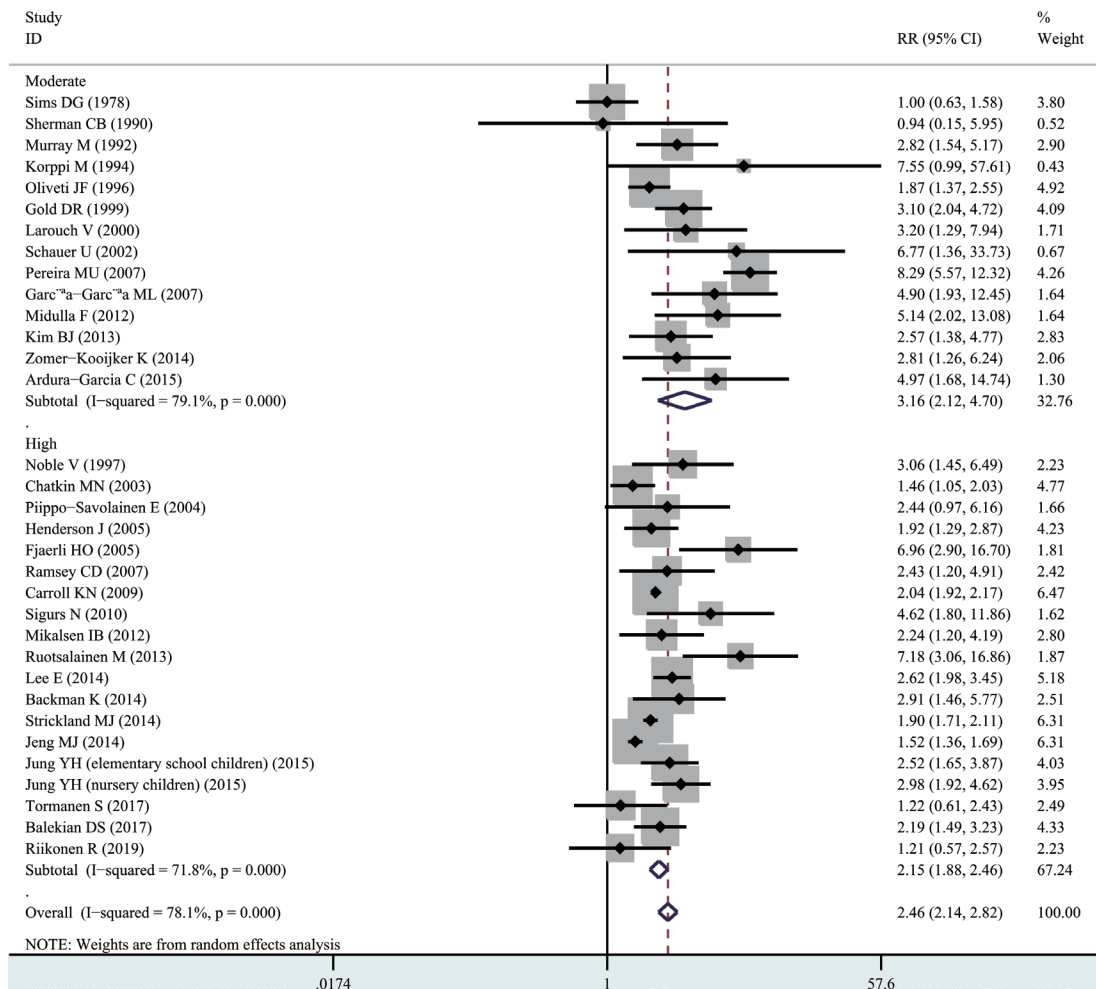


Figure 5 Forest plot of the association between bronchiolitis before 2 years of age and the subsequent development of wheezing/asthma, stratified by study quality.

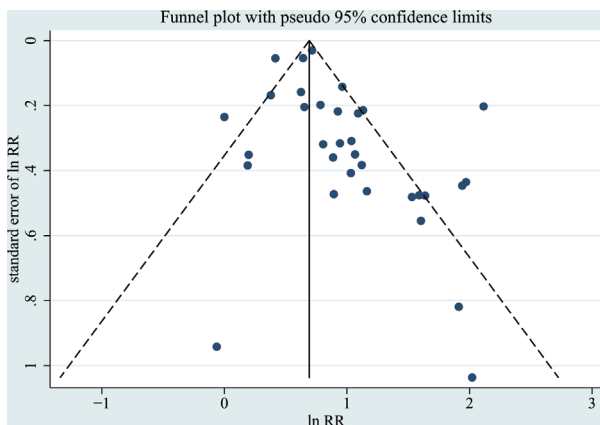


Figure 6 Funnel plot of publication bias for the association between bronchiolitis before 2 years of age and the subsequent development of wheezing/asthma. The horizontal axis represents lnRR and the vertical axis means the SE of lnRR. Vertical line and sloping lines in funnel plot represent summary RR and expected 95% CI for a given SE, respectively. RR, relative risk.

age of 6 years. A randomised controlled trial in term native American infants using motavizumab for RSV prophylaxis also indicates no effect of RSV prevention on medically attended wheeze up to age of 3 years.⁷⁸ Two possible explanations exist for the differences between parent-reported and physician-diagnosed asthma. First, information bias might have occurred. Second, asthma symptoms might have not been severe enough to warrant a doctor’s visit. In further studies, we should consider combining subjective outcomes (such as physician-confirmed asthma symptoms and patient-reported outcomes) with objective lung function measurements to minimise bias or exploring the effect of prevention of other important pathogens of bronchiolitis on asthma.

Limitations

There are some limitations to note. (1) The children with wheezing in the early stage of life may not necessarily develop into asthma, and some children with early-onset asthma will get better with time.



Therefore, the early prevalence estimates may not accurately reflect the true prevalence of childhood asthma among children with bronchiolitis in infancy. (2) Although some of the studies included in this meta-analysis were adjusted for potential confounding factors, there was still residual confounding affecting the risk estimates in each study and thus pooled estimates in the meta-analysis. Such as tobacco smoke exposure⁷⁹ and genetic determinants,⁸⁰ which have been defined as risk factors for both bronchiolitis and the development of asthma. (3) We used NOS to assess the quality of the enrolled studies. However, it may be controversial because its total scores involve the internal weight of component items. Regardless of whether or not the estimated effect varies with the quality score, investigators can skip the quality score analysis and go directly to the quality component analysis to find out which components are responsible for the variation or avoid the risk of misleading conclusions. Therefore, some researchers consider that the quality score analysis may be redundant.⁸¹ Moreover, since our meta-analysis included both cohort and case-control studies, there is heterogeneity by study design. Therefore, while NOS evaluation within a group with the same study design would be meaningful, subgroup analysis only with the NOS while ignoring differences in study design may compromise the results. (5) Some data are not presented in the articles and cannot be obtained from the original researchers, so we can only use the formula to derive the uncorrected data, which may lead to the deviation of the results. (6) The diagnosis of wheezing/asthma was not always made by a physician, which might lead to bias; even if the diagnosis was provided by a physician, it was not sure whether the physician was blind to the presence or absence of bronchiolitis before 2 years of age. There is the possibility of reverse causality, including the possibility that there may be misdiagnosis of bronchiolitis that was actually asthma, and equally possible that later asthma is also misdiagnosed. (7) The study by Lin H-W and Lin S-C³⁴ has also shown that infants with bronchiolitis are at increased risk for developing asthma. Excluding this study for statistical reason would not change the overall conclusions but would change the pooled risk estimates. (8) Heterogeneity and possible publication bias should be considered. There was substantial heterogeneity in the pooled data even after subgroup analyses. The considerable amount of heterogeneity may be due to differences in study designs, characteristics of subjects, viral respiratory pathogens, effect estimates reported, confounders and adjustment for confounders. As we also included retrospective case-control studies, therefore, heterogeneity may also originate from reporting and recall biases. We just included published studies with sufficient data, so the publication bias might not be completely avoided,

even though no statistically significant publication bias was identified.

CONCLUSIONS

In summary, this meta-analysis indicates that bronchiolitis before 2 years of age may be associated with subsequent development of wheezing/asthma. Assuming the association is causal, early life prevention or treatment of bronchiolitis would be medically important and might play a vital role to decrease the burden of asthma. In view of these limitations, more large-scale prospective studies that fully address potential confounding factors are required to validate the risk identified in the current meta-analysis.

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REFERENCES

- 1 Asher I, Pearce N. Global burden of asthma among children. *Int J Tuberc Lung Dis* 2014;18:1269–78.
- 2 Franco R, Nascimento HF, Cruz AA, et al. The economic impact of severe asthma to low-income families. *Allergy* 2009;64:478–83.
- 3 Meng J-F, Rosenwasser LJ. Unraveling the genetic basis of asthma and allergic diseases. *Allergy Asthma Immunol Res* 2010;2:215–27.
- 4 He Z, Wu H, Zhang S, et al. The association between secondhand smoke and childhood asthma: a systematic review and meta-analysis. *Pediatr Pulmonol* 2020;55:2518–31.
- 5 Bao Y, Chen Z, Liu E, et al. Risk factors in preschool children for predicting asthma during the preschool age and the early school age: a systematic review and meta-analysis. *Curr Allergy Asthma Rep* 2017;17:85.
- 6 Lodge CJ, Tan DJ, Lau MXZ, et al. Breastfeeding and asthma and allergies: a systematic review and meta-analysis. *Acta Paediatr* 2015;104:38–53.

- 7 Gao X, Yin M, Yang P, *et al.* Effect of exposure to cats and dogs on the risk of asthma and allergic rhinitis: a systematic review and meta-analysis. *Am J Rhinol Allergy* 2020;34:703–14.
- 8 Zhang Y, Lin J, Fu W, *et al.* Mediterranean diet during pregnancy and childhood for asthma in children: a systematic review and meta-analysis of observational studies. *Pediatr Pulmonol* 2019;54:949–61.
- 9 Valeriani F, Protano C, Vitali M, *et al.* Swimming attendance during childhood and development of asthma: meta-analysis. *Pediatr Int* 2017;59:614–21.
- 10 Friedman JN, Rieder MJ, Walton JM, *et al.* Bronchiolitis: recommendations for diagnosis, monitoring and management of children one to 24 months of age. *Paediatr Child Health* 2014;19:485–91.
- 11 Brandão HV, Vieira GO, Vieira TO, *et al.* Acute viral bronchiolitis and risk of asthma in schoolchildren: analysis of a Brazilian newborn cohort. *J Pediatr* 2017;93:223–9.
- 12 Lee KK, Hegele RG, Manfreda J, *et al.* Relationship of early childhood viral exposures to respiratory symptoms, onset of possible asthma and atopy in high risk children: the Canadian asthma primary prevention study. *Pediatr Pulmonol* 2007;42:290–7.
- 13 Meissner HC. Viral bronchiolitis in children. *N Engl J Med* 2016;374:62–72.
- 14 Smyth RL, Openshaw PJM. Bronchiolitis. *Lancet* 2006;368:312–22.
- 15 Sherman CB, Tosteson TD, Tager IB, *et al.* Early childhood predictors of asthma. *Am J Epidemiol* 1990;132:83–95.
- 16 Sims DG, Downham MA, Gardner PS, *et al.* Study of 8-year-old children with a history of respiratory syncytial virus bronchiolitis in infancy. *Br Med J* 1978;1:11–14.
- 17 Murray M, Webb MS, O'Callaghan C, *et al.* Respiratory status and allergy after bronchiolitis. *Arch Dis Child* 1992;67:482–7.
- 18 Balekian DS, Linnemann RW, Hasegawa K, *et al.* Cohort study of severe bronchiolitis during infancy and risk of asthma by age 5 years. *J Allergy Clin Immunol Pract* 2017;5:92–6.
- 19 Régnier SA, Huels J. Association between respiratory syncytial virus hospitalizations in infants and respiratory sequelae: systematic review and meta-analysis. *Pediatr Infect Dis J* 2013;32:820–6.
- 20 Liu L, Pan Y, Zhu Y, *et al.* Association between rhinovirus wheezing illness and the development of childhood asthma: a meta-analysis. *BMJ Open* 2017;7:e013034.
- 21 Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25:603–5.
- 22 Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA* 1998;280:1690–1.
- 23 Tierney JF, Stewart LA, Ghersi D, *et al.* Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;8:16.
- 24 McNutt L-A, Wu C, Xue X, *et al.* Estimating the relative risk in cohort studies and clinical trials of common outcomes. *Am J Epidemiol* 2003;157:940–3.
- 25 Greenland S. Model-Based estimation of relative risks and other epidemiologic measures in studies of common outcomes and in case-control studies. *Am J Epidemiol* 2004;160:301–5.
- 26 Miettinen O. Estimability and estimation in case-referent studies. *Am J Epidemiol* 1976;103:226–35.
- 27 Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, *et al.* Assessing heterogeneity in meta-analysis: Q statistic or I² index? *Psychol Methods* 2006;11:193–206.
- 28 J H, S G. *Cochrane Handbook for systematic reviews of interventions*. John Wiley & Sons, Ltd, 2008.
- 29 Sears MR, Greene JM, Willan AR, *et al.* A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med* 2003;349:1414–22.
- 30 McGeachie MJ, Yates KP, Zhou X, *et al.* Patterns of growth and decline in lung function in persistent childhood asthma. *N Engl J Med* 2016;374:1842–52.
- 31 Sousa AW, Barros Cabral AL, Arruda Martins M, *et al.* Risk factors for fixed airflow obstruction in children and adolescents with asthma: 4-year follow-up. *Pediatr Pulmonol* 2020;55:591–8.
- 32 Begg CB, Mazumdar M. Operating characteristics of a RANK correlation test for publication bias. *Biometrics* 1994;50:1088–101.
- 33 Egger M, Davey Smith G, Schneider M, *et al.* Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
- 34 Lin H-W, Lin S-C. Environmental factors association between asthma and acute bronchiolitis in young children—a perspective cohort study. *Eur J Pediatr* 2012;171:1645–50.
- 35 Backman K, Piippo-Savolainen E, Ollikainen H, *et al.* Increased asthma risk and impaired quality of life after bronchiolitis or pneumonia in infancy. *Pediatr Pulmonol* 2014;49:318–25.
- 36 Backman K, Piippo-Savolainen E, Ollikainen H, *et al.* Adults face increased asthma risk after infant RSV bronchiolitis and reduced respiratory health-related quality of life after RSV pneumonia. *Acta Paediatr* 2014;103:850–5.
- 37 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;65:1045–52.
- 38 Sigurs N, Bjarnason R, Sigurbergsson F, *et al.* 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;161:1501–7.
- 39 Sigurs N, Bjarnason R, Sigurbergsson F, *et al.* Asthma and immunoglobulin E antibodies after respiratory syncytial virus bronchiolitis: a prospective cohort study with matched controls. *Pediatrics* 1995;95:500–5.
- 40 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;171:137–41.
- 41 Jung Y-H, Seo J-H, Kim H-Y, *et al.* The relationship between asthma and bronchiolitis is modified by TLR4, CD14, and IL-13 polymorphisms. *Pediatr Pulmonol* 2015;50:8–16.
- 42 Korppi M, Kuikka L, Reijonen T, *et al.* Bronchial asthma and hyperreactivity after early childhood bronchiolitis or pneumonia. An 8-year follow-up study. *Arch Pediatr Adolesc Med* 1994;148:1079–84.
- 43 Oliveti JF, Kercsmar CM, Redline S. Pre- and perinatal risk factors for asthma in inner City African-American children. *Am J Epidemiol* 1996;143:570–7.
- 44 Gold DR, Burge HA, Carey V, *et al.* Predictors of repeated wheeze in the first year of life: the relative roles of cockroach, birth weight, acute lower respiratory illness, and maternal smoking. *Am J Respir Crit Care Med* 1999;160:227–36.
- 45 Ramsey CD, Gold DR, Litonjua AA, *et al.* Respiratory illnesses in early life and asthma and atopy in childhood. *J Allergy Clin Immunol* 2007;119:150–6.
- 46 Larouch V, Rivard G, Deschesnes F, *et al.* Asthma and airway hyper-responsiveness in adults who required hospital admission for bronchiolitis in early childhood. *Respir Med* 2000;94:288–94.
- 47 Schauer U, Hoffjan S, Bittscheidt J, *et al.* Rsv bronchiolitis and risk of wheeze and allergic sensitisation in the first year of life. *Eur Respir J* 2002;20:1277–83.
- 48 Piippo-Savolainen E, Remes S, Kannisto S, *et al.* Asthma and lung function 20 years after wheezing in infancy: results from a prospective follow-up study. *Arch Pediatr Adolesc Med* 2004;158:1070–6.
- 49 Henderson J, Hilliard TN, Sherriff A, *et al.* Hospitalization for RSV bronchiolitis before 12 months of age and subsequent asthma, atopy and wheeze: a longitudinal birth cohort study. *Pediatr Allergy Immunol* 2005;16:386–92.
- 50 Fjaerli H-O, Farstad T, Rød G, *et al.* 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.
- 51 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;42:458–64.
- 52 Mikalsen IB, Halvorsen T, Øymar K. The outcome after severe bronchiolitis is related to gender and virus. *Pediatr Allergy Immunol* 2012;23:391–8.
- 53 Midulla F, Pierangeli A, Cangiano G, *et al.* Rhinovirus bronchiolitis and recurrent wheezing: 1-year follow-up. *Eur Respir J* 2012;39:396–402.
- 54 Kim BJ, Seo JH, Jung YH, *et al.* Air pollution interacts with past episodes of bronchiolitis in the development of asthma. *Allergy* 2013;68:517–23.
- 55 Ruotsalainen M, Hyvärinen MK, Piippo-Savolainen E, *et al.* Adolescent asthma after rhinovirus and respiratory syncytial virus bronchiolitis. *Pediatr Pulmonol* 2013;48:633–9.
- 56 Zomer-Kooijker K, van der Ent CK, Ermers MJJ, *et al.* Increased risk of wheeze and decreased lung function after respiratory syncytial virus infection. *PLoS One* 2014;9:e87162.
- 57 Strickland MJ, Marsh CA, Darrow LA. Gestational age-specific associations between infantile acute bronchiolitis and asthma after age five. *Paediatr Perinat Epidemiol* 2014;28:521–6.
- 58 Ardua-García C, Vaca M, Oviedo G, *et al.* Risk factors for acute asthma in tropical America: a case-control study in the city of Esmeraldas, Ecuador. *Pediatr Allergy Immunol* 2015;26:423–30.
- 59 Törmänen S, Lauhkonen E, Riikonen R, *et al.* Risk factors for asthma after infant bronchiolitis. *Allergy* 2018;73:916–22.
- 60 Jeng M-J, Lee Y-S, Tsao P-C, *et al.* A longitudinal study on early hospitalized airway infections and subsequent childhood asthma. *PLoS One* 2014;10:e0121906.



- 61 Noble V, Murray M, Webb MS, *et al.* Respiratory status and allergy nine to 10 years after acute bronchiolitis. *Arch Dis Child* 1997;76:315–9.
- 62 Riikonen R, Lauhkonen E, Törmänen S, *et al.* Prospective study confirms that bronchiolitis in early infancy increases the risk of reduced lung function at 10–13 years of age. *Acta Paediatr* 2019;108:124–30.
- 63 Chatkin MN, Menezes AMB, Victora CG, *et al.* High prevalence of asthma in preschool children in southern Brazil: a population-based study. *Pediatr Pulmonol* 2003;35:296–301.
- 64 Pereira MU, Sly PD, Pitrez PM, *et al.* Nonatopic asthma is associated with helminth infections and bronchiolitis in poor children. *Eur Respir J* 2007;29:1154–60.
- 65 Lee E, Kwon J-W, Kim H-B, *et al.* Association Between Antibiotic Exposure, Bronchiolitis, and *TLR4* (rs1927911) Polymorphisms in Childhood Asthma. *Allergy Asthma Immunol Res* 2015;7:167–74.
- 66 Carroll KN, Wu P, Gebretsadiq T, *et al.* The severity-dependent relationship of infant bronchiolitis on the risk and morbidity of early childhood asthma. *J Allergy Clin Immunol* 2009;123:1055–61.
- 67 Lorente F, Laffond E, Moreno E, *et al.* [Viral infection and asthma: immunologic mechanisms]. *Allergol Immunopathol* 2001;29:126–33.
- 68 Lotz MT, Peebles RS. Mechanisms of respiratory syncytial virus modulation of airway immune responses. *Curr Allergy Asthma Rep* 2012;12:380–7.
- 69 Caixia L, Yang X, Yurong T, *et al.* Involvement of epigenetic modification in epithelial immune responses during respiratory syncytial virus infection. *Microb Pathog* 2019;130:186–9.
- 70 Brandão HV, Vieira GO, Vieira TO, *et al.* Acute viral bronchiolitis and risk of asthma in schoolchildren: analysis of a Brazilian newborn cohort. *J Pediatr* 2017;93:223–9.
- 71 Mansbach JM, Luna PN, Shaw CA, *et al.* Increased *Moraxella* and *Streptococcus* species abundance after severe bronchiolitis is associated with recurrent wheezing. *J Allergy Clin Immunol* 2020;145:518–27.
- 72 Guilbert TW, Bacharier LB. Controversies in the treatment of the acutely wheezing infant. *Am J Respir Crit Care Med* 2011;183:1284–5.
- 73 Ralston SL, Lieberthal AS, Meissner HC, *et al.* Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics* 2014;134:e1474–502.
- 74 Ricci V, Delgado Nunes V, Murphy MS, *et al.* Bronchiolitis in children: summary of NICE guidance. *BMJ* 2015;350:h2305.
- 75 Scheltema NM, Nibbelke EE, Pouw J, *et al.* Respiratory syncytial virus prevention and asthma in healthy preterm infants: a randomised controlled trial. *Lancet Respir Med* 2018;6:257–64.
- 76 Mochizuki H, Kusuda S, Okada K, *et al.* Palivizumab prophylaxis in preterm infants and subsequent recurrent wheezing: six-year follow-up study. *Am J Respir Crit Care Med* 2017;196:29–38.
- 77 Prais D, Kaplan E, Klinger G, *et al.* Short- and long-term pulmonary outcome of Palivizumab in children born extremely prematurely. *Chest* 2016;149:801–8.
- 78 O'Brien KL, Chandran A, Weatherholtz R, *et al.* Efficacy of motavizumab for the prevention of respiratory syncytial virus disease in healthy native American infants: a phase 3 randomised double-blind placebo-controlled trial. *Lancet Infect Dis* 2015;15:1398–408.
- 79 Jones LL, Hashim A, McKeever T, *et al.* Parental and household smoking and the increased risk of bronchitis, bronchiolitis and other lower respiratory infections in infancy: systematic review and meta-analysis. *Respir Res* 2011;12:5.
- 80 Thomsen SF, van der Sluis S, Stensballe LG, *et al.* Exploring the association between severe respiratory syncytial virus infection and asthma: a registry-based twin study. *Am J Respir Crit Care Med* 2009;179:1091–7.
- 81 Olkin I. Re: "A critical look at some popular meta-analytic methods". *Am J Epidemiol* 1994;140:297–9.