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Risk factors for respiratory syncytial virus-associated acute lower respiratory infection in children under 5 years: An updated systematic review and meta-analysis

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ABSTRACT

Objectives: Respiratory syncytial virus (RSV) is a leading cause of acute lower respiratory infection (ALRI) in young children. With substantial advances in RSV research, we aimed to conduct an updated systematic review of risk factors for RSV-ALRI in children under 5 years.

Methods: We updated our previously published literature search to November 2022 among three English databases and additionally searched three Chinese databases (from January 1995) to identify all relevant publications. We performed random-effects meta-analyses to estimate the pooled odds ratio (OR) and 95% confidence interval (CI) for each risk factor and each outcome (RSV-ALRI in the community and RSV-ALRI hospitalization).

Results: A total of 47 studies were included (26 from the updated search). Indoor air pollution was identified as a possible risk factor for RSV-ALRI in the community (OR 1.45, 95% CI: 1.10-1.90). The identified risk factors for RSV-ALRI hospitalization fall into four categories: demographic (male sex, Māori and Pacific ethnicities vs European or other ethnicities), pre- and post-neonatal (prematurity, low birth weight, small for gestational age, maternal smoking during pregnancy or lactation, maternal age <30 years vs 30-34 years, multiparity, caesarean section vs vaginal), household and environmental (having siblings, passive smoking, maternal asthma, daycare centre attendance) and health and medical conditions (any chronic diseases, bronchopulmonary dysplasia, HIV infections, congenital heart disease, Down syndrome, cystic fibrosis, previous asthma). The pooled ORs ranged from 1.14 to 4.55.

Conclusion: Our findings on the risk factors for RSV-ALRI help identify RSV high-risk groups, which has important implications for RSV prevention at both individual and population levels.

Introduction

Respiratory syncytial virus (RSV) is the most common viral pathogen identified in children with acute lower respiratory infection (ALRI), posing a substantial public health burden worldwide [1,2]. It is estimated that there were 33.0 million RSV-ALRI episodes among children younger than 5 years globally in 2019, of which 3.6 million were hospitalized, and up to 101,400 deaths could be attributed to RSV [3]. In addition to proximal acute health events, growing evidence has shown that RSV-ALRI in early life is associated with an increased risk of long-term respiratory diseases, including recurrent wheezing, asthma, impaired lung function and even with premature adult death from respiratory disease [4-7].

Despite the absence of specific RSV treatments, significant advances have been made in prophylactic immunization for protecting infants. Beyfortus (nirsevimab), a long-acting, single-dose monoclonal antibody developed by AstraZeneca/Sanofi, has secured

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approval in the European Union (EU), US and UK, providing prolonged RSV prevention for at least 5-6 months during infancy [8-10]. Pfizer's ABRYSVO, standing as the first maternal RSV vaccine, was recently licensed in the EU and US, offering neonates protection from birth to 6 months [11,12]. These developments marked significant milestones in RSV prophylaxis, underscoring the strides in paediatric protective strategies.

It is therefore important to identify children with risk factors for developing RSV-ALRI for optimizing RSV prevention and control strategies and for raising awareness of RSV among the general public. We previously published a systematic review and meta-analysis in 2015 on the potential risk factors for developing RSV-ALRI in children under 5 years, based on 27 studies published between January 1995 and July 2015 [13]. However, there were several aspects in that review that required further improvement. First, for the association between potential risk factors and RSV-ALRI, studies that reported only odds ratio (OR) obtained from univariate analysis (i.e. not accounting for common confounders) were also included in the analysis due to the limited evidence obtained from studies that used multivariable analysis. Second, there was no differentiation for RSV-ALRI occurring in the community and being hospitalized. Moreover, no subgroup analyses were performed, yet differences in risk factors for developing RSV-ALRI may exist between different populations; for instance, risk factors and their association with RSV-ALRI could vary by different income regions or age groups.

Since the publication of the previous review, a number of new studies have been published, adding substantially to the understanding of risk factors for RSV-ALRI. To this end, we conducted an updated systematic literature review and meta-analysis to improve the understanding of risk factors for developing RSV-ALRI among young children.

Methods

The systematic review was reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA 2020) reporting checklist (Supplementary Table S1). The study protocol was registered with PROSPERO (CRD42021271398).

Literature search

Based on the previous systematic review [13], we conducted an updated literature search among three English databases (MEDLINE, EMBASE and Web of Science) to identify relevant studies published after 1 August 2015 that reported the association between individual-level risk factors and RSV-ALRI. In addition, we included three comprehensive and authoritative Chinese databases (CNKI, Wanfang Data and Chongqing VIP) and identified relevant studies from 1 January 1995. All literature searches in above mentioned databases were conducted on 30 November 2022. No language restrictions were applied. Our search strategy incorporated terms related to RSV, respiratory infection, child and risk factors, as well as their synonyms. The complete search strategies for all databases are presented in Supplementary Text S1.

Study selection

After duplicate records were removed, two review groups consisting of four reviewers (SD, ME, FDW and BC) independently screened all records by title and abstract to exclude ineligible studies. The remaining full-text articles and all included articles from the previous review were assessed for eligibility according to our prespecified inclusion and exclusion criteria (Table 1). Unlike the previous review, which focused on socio-demographic factors, this update included all individual-level risk factors to provide more comprehensive evidence. For the latter step, all excluded studies (at this stage) and the reasons for their exclusion were documented (Supplementary Table S2). Any discrepancies that could not be resolved by consensus were adjudicated by a third reviewer (YL).

Data extraction

For all studies that met the inclusion criteria, one reviewer (SD) used a customized spreadsheet to extract and clean the required data, concerning study characteristics (e.g. study period, study design, study site, World Bank income classification [14]), participant characteristics (e.g. subject age, case and control definition, respiratory specimen and RSV identification methods, sample size) and information on risk factors (e.g. definition, reference group, effect size). RSV-associated ALRI episodes were identified through laboratory tests or RSV-specific ICD-9/10 codes (Supplementary Table S3). The effect sizes were reported as unadjusted and/or adjusted estimates of relative ratios, hazard ratios and ORs, as well as corresponding 95% confidence intervals (CIs) for developing RSV-associated ALRI in the community or hospital admission among high-risk individuals compared with those not at high risk. We calculated unadjusted effect sizes if only frequency data were reported. Continuous correction was implemented by adding 0.5 to each cell in a 2 by 2 table with at least one zero cell to avoid infinite estimates [15]. In the data cleaning process, risk factors with identical or nearly identical definitions were classified into one category; for example, bronchopulmonary dysplasia (BPD) and chronic lung disease arising during the neonatal period were both classified as BPD (see Supplementary Table S4 for details). For certain risk factors, we switched the reference categories to align them with those in the majority of studies for meta-analysis and recalculated the effect size [16]. Factors reported in only one study were not included in the analysis. A second reviewer (BC) double-checked the entered data for accuracy, with disagreements resolved through discussions within the review group.

Quality assessment

Studies were assessed for methodological quality using a self-designed quality scoring form across the following six domains: study design, study subjects, study size, quality of 'control' group ('control' refers to the control group in case-control studies, as well as the non-case group in cohort studies and randomized controlled trials), control of confounders and diagnostic test (Supplementary Table S5). Each domain is scored 1 (higher quality) or 0 points (lower quality). Based on the total score, studies were graded as low ($\leq$2 points), moderate (3-4 points) or high quality (5-6 points) of evidence. Regardless of the quality of evidence, all studies were included in the main meta-analysis.

Data analysis

Outcomes were categorized into two groups: RSV-ALRI in the community and RSV-ALRI hospital admission. For each risk factor associated with each outcome, random-effects meta-analyses were conducted if two or more studies were available. When the incidence rate is low (<5%), ORs can be regarded as a valid approximation of RRs [3]. Therefore, we approximated RRs and HRs as ORs to combine effect estimates. We calculated pooled ORs along with their corresponding 95% CIs to measure the association between each risk factor and each RSV-ALRI outcome. Only ORs reported from multivariable analyses were included in the main analysis. For each meta-analysis, a forest plot was generated to visualize the estimated effect sizes of individual risk factors. Heterogeneity was assessed using the I^2 statistic, categorized as negligible (0%),

Table 1
Inclusion and exclusion criteria.

Inclusion criteria
Published between 1 August 2015 (1 January 1995 for Chinese databases) and 30 November 2022
Reporting data in children younger than 5 years
Including children with a diagnosis of ALRI and laboratory-confirmed RSV illness
Reporting association between individual-level risk factors and RSV–associated ALRI
Including at least 50 children under 5 years
Observational studies using analytic epidemiological study design (i.e. case–control or cohort studies) or randomized controlled trials (placebo arm only)
Reporting results on risk factors based on univariable (considered only for sensitivity analysis) or multivariable analysis
Exclusion criteria
Definitions for ALRI or risk factors not clearly stated or inconsistently applied
RSV infections confirmed solely by serology
Reporting risk factors solely among high-risk study population (e.g. preterm babies, children with congenital heart disease, chronic lung disease and immunosuppression)
Ineligible control group (e.g. RSV negative ALRI cases, children hospitalized for acute infections)
Methods for analysis not clearly reported

ALRI, acute lower respiratory infections; *RSV*, respiratory syncytial virus.

low (<25%), moderate (25-75%) and high (>75%). Publication bias was assessed visually by funnel plots and was examined by Egger's regression tests for risk factors reported in more than 10 studies. A two-sided *P*-value <0.05 was considered statistically significant. Subgroup analyses were performed according to finer age groups, World Bank income groups (high-income countries, HICs vs low- and middle-income countries, LMICs), study periods (1990-2000 vs 2000-2010 vs 2010-2020), study designs (cohort vs case-control vs randomized controlled trial), case definitions (ALRI vs pneumonia vs bronchiolitis) and RSV identification methods (PCR vs other methods).

To verify the robustness of our main findings, we conducted several one-way sensitivity analyses: (1) adding ORs reported in univariable analyses; (2) including exclusively ORs reported from univariable analyses (even if ORs from multivariable analysis were available); (3) excluding studies considered to be of low quality (defined as quality score ≤2 points).

All data analyses were conducted by R software (version 4.1.2).

Results

Study identification and characteristics

The updated literature search initially identified 5924 records. After excluding duplicates, the titles and abstracts of 3637 studies were screened and 121 studies were subsequently reviewed for full texts, of which 26 studies [17–42] were included. In addition, the 27 studies included in the previous systematic review were reassessed, and 21 ([43–61] and data contributed by Rasmussen and Zar [13]) met our eligibility criteria for inclusion in this analysis. As a result, a total of 47 studies were finally included in this systematic review (Figure 1).

The included 47 studies were conducted in 37 sites from 22 countries, mostly from HICs (34/47, 72%). Cohort study was the most common study design (34/47, 72%). The majority of the studies were hospital-based (40/47, 85%). The general characteristics of the included studies are summarized in Supplementary Table S6. Overall, the methodological quality of the included studies was acceptable, with 33 (70%) studies considered to be of moderate (29 studies) to high (4 studies) quality (Supplementary Table S7). Only one risk factor for RSV-ALRI hospital admission, male sex, was reported by more than 10 studies (15 in total). The funnel plot and the result of Egger's test indicated no publication bias (Supplementary Figure S1; $P = 0.88$).

Risk factors for RSV-ALRI

A total of 4 potential risk factors for developing RSV-ALRI in the community and 24 potential risk factors for hospitalization due to RSV-ALRI were assessed in the main meta-analysis. For ease of reporting, all risk factors (detailed definitions in Supplementary Table S4) were categorized into four groups: demographic factors, pre- and post-neonatal factors, household and environmental factors and health and medical conditions. Detailed results are presented in Tables 2 and 3, with corresponding forest plots available in Supplementary Figures S2 and S3.

Risk factors for developing RSV-ALRI in the community

Demographic factors

Based on two studies ([31] and Rasmussen [13]), the pooled OR for male sex compared to females was 0.70 (95% CI: 0.22-2.24, $I^2 = 50.4\%$). Sensitivity analyses yielded consistent results (Table 2; Supplementary Table S8).

Household and environmental factors

Indoor air pollution was found to be a possible risk factor for developing RSV-ALRI in children under five (OR 1.45, 95% CI: 1.10-1.90, $I^2 = 0\%$; 3 studies). Neither passive smoking (0.90, 0.72-1.13, $I^2 = 0\%$; 2 studies) nor having one or two siblings compared to none (1.35, 0.69-2.66, $I^2 = 81.2\%$; 2 studies) was significantly associated with RSV-ALRI. All sensitivity analyses yielded consistent results with the main findings (Table 2; Supplementary Table S8).

In subgroup analyses conducted based on income levels, study periods, study designs, case definitions and RSV identification methods, the results were generally consistent with the main analysis (Supplementary Figures S4 and S6-S9).

Risk factors for RSV-ALRI hospital admission

Demographic factors. Male sex was associated with higher risks for RSV-ALRI hospitalization (OR 1.23, 95% CI: 1.19-1.27, $I^2 = 7.4\%$; 15 studies). Māori (4.55, 3.84-5.39, $I^2 = 0\%$; 2 studies) and Pacific (3.42, 2.93-3.98, $I^2 = 0\%$; 2 studies) ethnicities were at higher risks for RSV-ALRI hospitalization compared to European or other ethnicities. Rural residence was not associated with higher risks for RSV-ALRI hospitalization (1.09, 0.87-1.37, $I^2 = 9.4\%$; 4 studies) compared to urban residence; the sensitivity analysis that used ORs from univariable analysis yielded borderline results (1.15, 1.002-1.33, $I^2 = 81.2\%$; 4 studies). All other sensitivity analyses showed consistent findings with the main analysis (Table 3; Supplementary Table S9).

Pre- and post-neonatal factors. Despite reporting variations in the gestational age groupings, prematurity was associated with higher risks for RSV-ALRI hospitalization. The pooled ORs ranged from 1.76 (1.62-1.91, $I^2 = 6.7\%$; 5 studies) in those of 33-36 weeks of gestational age (wGA) to 2.49 (2.33-2.66, $I^2 = 3.3\%$; 3 studies) in

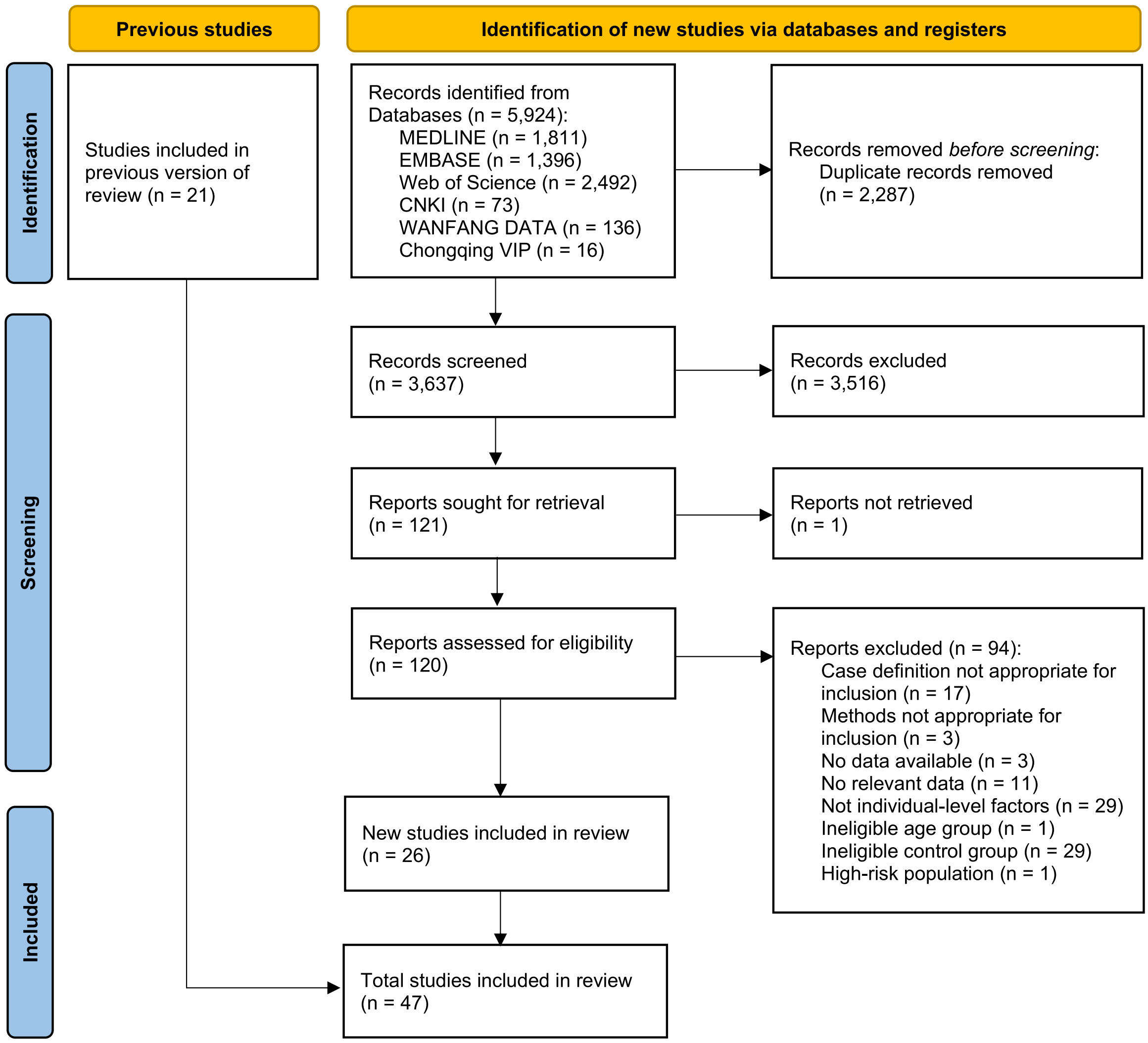

Figure 1. PRISMA flow diagram of study selection.

Table 2
Risk factors for RSV-ALRI in the community.

Risk factor	Main analysis: ORs from multivariable analysis only		Sensitivity analysis: ORs from multivariable and univariable analysis		Sensitivity analysis: ORs from univariable analysis only	
	No. of studies	Pooled OR (95% CI)	No. of studies	Pooled OR (95% CI)	No. of studies	Pooled OR (95% CI)
Demographic factors						
Male sex	2	0.70 (0.22-2.24)	5	1.04 (0.86-1.24)	4	1.05 (0.88-1.26)
Pre- and post-neonatal factors						
Prematurity (<37 wGA vs ≥37 wGA)	1	1.00 (0.30-3.00)	2	0.79 (0.40-1.56)	2	0.77 (0.39-1.49)
Low birth weight (birth weight <2.5 kg)	1	0.90 (0.60-1.40)	3	0.93 (0.68-1.26)	3	0.92 (0.69-1.24)
Lack of breastfeeding (not exclusive breastfeeding)	1	1.70 (0.60-5.00)	2	1.16 (0.66-2.05)	2	1.16 (0.66-2.05)
Household and environmental factors						
Indoor air pollution	3	**1.45 (1.10-1.90)**	4	**1.46 (1.12-1.91)**	2	**1.63 (1.19-2.24)**
Passive smoking	2	0.90 (0.72-1.13)	4	0.95 (0.78-1.15)	2	1.19 (0.68-2.08)
Crowding (>7 persons in the household)	1	1.10 (0.80-1.30)	2	1.13 (0.89-1.43)	2	1.13 (0.91-1.40)
Having siblings (1-2 vs 0)	2	1.35 (0.69-2.66)	2	1.35 (0.69-2.66)	2	1.22 (0.63-2.37)
Having siblings (1 vs 0)	1	1.10 (0.90-1.50)	2	1.07 (0.86-1.34)	2	1.21 (0.96-1.52)

ALRI, acute lower respiratory infection; *CI*, confidence interval; *OR*, odds ratio; *RSV*, respiratory syncytial virus; *wGA*, weeks of gestational age.
OR **in bold** indicates statistical significance.

Table 3
Risk factors for RSV-ALRI hospital admission.

Risk factor	Main analysis: ORs from multivariable analysis only		Sensitivity analysis: ORs from multivariable and univariable analysis		Sensitivity analysis: ORs from univariable analysis only	
	No. of studies	Pooled OR (95% CI)	No. of studies	Pooled OR (95% CI)	No. of studies	Pooled OR (95% CI)
Demographic factors						
Male sex	15	**1.23 (1.19-1.27)**	21	**1.22 (1.19-1.26)**	14	**1.24 (1.20-1.30)**
Rural residence	4	1.09 (0.87-1.37)	5	1.14 (0.93-1.40)	4	**1.15 (1.002-1.33)**
Ethnicity (Māori vs European/Other)	2	**4.55 (3.84-5.39)**	2	**4.55 (3.84-5.39)**	1	**5.00 (3.35-7.44)-**
Ethnicity (Pacific vs European/Other)	2	**3.42 (2.93-3.98)**	2	**3.42 (2.93-3.98)**	1	**4.79 (3.12-7.35)**
Pre- and post-neonatal factors						
Apgar score at 5 min (0-7 vs 8-10)	1	1.11 (0.95-1.29)	2	1.48 (0.85-2.59)	2	**1.88 (1.68-2.10)**
Intrauterine growth restriction	1	**1.26 (1.12-1.42)**	2	1.12 (0.82-1.52)	1	0.91 (0.64-1.30)
Prematurity (<37 wGA vs ≥37 wGA)	3	**1.85 (1.74-1.97)**	9	**2.33 (1.82-2.98)**	9	**2.41 (1.93-3.03)**
Prematurity (<33 wGA vs ≥37 wGA)	3	**2.32 (1.75-3.09)**	8	**3.46 (2.43-4.94)**	6	**4.29 (3.06-6.04)**
Prematurity (33-36 wGA vs ≥37 wGA)	5	**1.76 (1.62-1.91)**	12	**1.92 (1.63-2.25)**	9	**1.99 (1.61-2.46)**
Prematurity (29-32 wGA vs ≥37 wGA)	3	**2.49 (2.33-2.66)**	4	**2.87 (2.14-3.87)**	3	**3.53 (1.93-6.45)**
Prematurity (<29 wGA vs ≥37 wGA)	3	**2.32 (1.73-3.13)**	5	**3.26 (2.10-5.06)**	4	**4.49 (2.57-7.88)**
Maternal smoking during pregnancy or lactation	8	**1.33 (1.22-1.45)**	11	**1.34 (1.21-1.48)**	5	**1.73 (1.13-2.66)**
Maternal alcohol during pregnancy or lactation	1	0.91 (0.80-1.05)	2	0.91 (0.80-1.02)	1	0.89 (0.69-1.13)
Maternal gestational diabetes mellitus	1	1.06 (1.00-1.12)	2	1.05 (0.99-1.12)	1	0.93 (0.73-1.20)
Maternal age at delivery (<25 vs 30-34 years)	3	**1.46 (1.39-1.53)**	2	**1.45 (1.38-1.52)**	1	**2.32 (1.63-3.29)**
Maternal age at delivery (25-29 vs 30-34 years)	3	**1.14 (1.10-1.17)**	3	**1.14 (1.10-1.17)**	1	0.95 (0.91-1.00)
Maternal multiparity	2	**2.51 (1.05-5.99)**	2	**2.51 (1.05-5.99)**	1	**1.62 (1.18-2.22)**
Multiple births	5	1.03 (0.82-1.30)	7	1.19 (0.91-1.54)	4	**1.77 (1.53-2.04)**
Mode of delivery (caesarean section vs vaginal)	2	**1.19 (1.07-1.33)**	2	**1.19 (1.07-1.33)**	-	**-**
Mode of delivery (emergency caesarean section vs vaginal)	1	**1.09 (1.01-1.17)**	2	**1.11 (1.06-1.15)**	2	**1.11 (1.06-1.15)**
Low birth weight (birth weight <2.5 kg)	3	**2.07 (1.51-2.85)**	3	**2.07 (1.51-2.85)**	3	**3.00 (2.73-3.30)**
Small for gestational age	3	**1.16 (1.02-1.33)**	3	**1.16 (1.02-1.33)**	1	**1.25 (1.14-1.38)**
Large for gestational age	3	1.00 (0.93-1.08)	3	1.00 (0.93-1.08)	1	0.95 (0.86-1.04)
Lack of breastfeeding (not predominantly breastfeeding)	1	**2.05 (1.08-3.03)**	2	**2.43 (1.80-3.30)**	1	**2.67 (1.83-3.89)**
Household and environmental factors						
Having siblings (≥1 vs 0)	4	**1.68 (1.14-2.49)**	4	**1.68 (1.14-2.49)**	2	1.75 (0.56-5.45)
Having siblings (1 vs 0)	4	**2.20 (1.69-2.87)**	4	**2.20 (1.69-2.87)**	3	**1.76 (1.56-2.00)**
Having siblings (≥2 vs 0)	3	**3.42 (1.68-6.97)**	3	**3.42 (1.68-6.97)**	2	**2.81 (1.39-5.69)**
Having siblings (≥2 vs <2)	1	1.10 (0.92-1.35)	2	1.67 (0.64-4.39)	2	1.85 (0.92-3.70)
Having siblings (≥3 vs <3)	2	**1.47 (1.16-1.87)**	2	**1.47 (1.16-1.87)**	2	**1.60 (1.30-1.98)**
Passive smoking	3	**1.93 (1.30-2.87)**	5	**1.63 (1.33-1.98)**	4	**1.64 (1.33-2.02)**
Maternal asthma	3	**1.49 (1.32-1.68)**	4	**1.50 (1.33-1.70)**	1	8.00 (1.00-64.00)
Low maternal education (<12 years)	1	**1.20 (1.10-1.30)**	2	1.41 (0.91-2.19)	1	**1.92 (1.14-3.24)**
Daycare centre attendance	2	**1.59 (1.29-1.96)**	2	**1.59 (1.29-1.96)**	-	-
Single parenthood	3	**1.15 (1.06-1.25)**	3	**1.15 (1.06-1.25)**	1	**1.67 (1.21-2.31)**
Health and medical conditions						
Any chronic diseases	4	**2.27 (1.79-2.87)**	4	**2.27 (1.79-2.87)**	2	**2.46 (1.23-4.89)**
BPD	4	2.38 (0.84-6.75)	6	**3.21 (1.52-6.79)**	5	**5.38 (3.02-9.58)**
Cardiomyopathy	1	**2.78 (1.78-4.34)**	2	**3.03 (2.02-4.54)**	1	**4.53 (1.73-11.88)**
Cystic fibrosis	2	**2.07 (1.43-2.98)**	3	**3.13 (1.49-6.57)**	2	**4.82 (2.72-8.55)**
CHD	1	**2.80 (2.30-3.30)**	4	**4.07 (2.82-5.87)**	4	**4.04 (2.76-5.90)**
HS-CHD	4	**2.59 (1.07-6.26)**	5	**3.00 (1.43-6.28)**	4	**3.86 (2.39-6.22)**
Down syndrome	3	**3.10 (2.73-3.53)**	5	**4.21 (2.85-6.21)**	4	**6.26 (5.48-7.15)**
HIV infections (HIV-infected vs HIV-uninfected [exposed or unexposed])	3	**3.74 (2.65-5.27)**	5	**3.56 (2.69-4.72)**	4	**3.44 (2.45-4.85)**
HIV infections (HIV-infected vs HIV-unexposed uninfected)	1	**2.80 (2.00-3.90)**	2	**2.32 (1.59-3.40)**	2	**1.94 (1.40-2.69)**
Pulmonary hypertension	1	**3.26 (2.44-4.34)**	2	**4.97 (1.98-12.46)**	1	**8.38 (4.28-16.41)**
Previous asthma	2	**4.09 (3.01-5.55)**	2	**4.09 (3.01-5.55)**	-	-

ALRI, acute lower respiratory infection; *BPD*, bronchopulmonary dysplasia; *CI*, confidence interval; *HS-CHD*, hemodynamically significant congenital heart disease; *OR*, odds ratio; *RSV*, respiratory syncytial virus; *wGA*, weeks of gestational age.
OR **in bold** indicates statistical significance. '-' indicates data not reported.

those of 29-32 wGA compared to full-term (≥37 wGA) children. Both low birth weight (2.07, 1.51-2.85, I^2 = 6.0%; 3 studies) compared to birth weight ≥2.5 kg and small for gestational age compared to appropriate for gestational age (1.16, 1.02-1.33, I^2 = 8.0%; 3 studies) were found to be risk factors; by contrast, the pooled OR for large for gestational age was not statistically significant. Multiple births were not associated with higher risks for RSV-ALRI hospitalization (1.03, 0.82-1.30, I^2 = 9.5%; 5 studies). Maternal smoking during pregnancy or lactation, maternal age at delivery <25 years and between 25 and 29 years compared to 30-34 years, maternal multiparity, and caesarean section compared to vaginal were all associated with increased risks for RSV-ALRI hospitalization; the pooled ORs ranged from 1.14 (1.10-1.17, I^2 = 9.6%; 3 studies) for maternal age at delivery between 25 and 29 years to 2.51 (1.05-

5.99, $I^2 = 9.5\%$; 2 studies) for maternal multiparity. Results from sensitivity analyses were generally consistent to the main analysis (Table 3; Supplementary Table S9).

Household and environmental factors. Having siblings, passive smoking, maternal asthma, daycare centre attendance and single parenthood were all found to be significantly associated with increased risks for RSV-ALRI hospitalization; the pooled ORs ranged from 1.15 (1.06-1.25, $I^2 = 5.9\%$; 3 studies) for single parenthood to 3.42 (1.68-6.97, $I^2 = 9.9\%$; 3 studies) for having two or more siblings compared to none. Results from sensitivity analyses generally remained consistent with the main results (Table 3; Supplementary Table S9).

Health and medical conditions. We assessed seven health and medical conditions-related factors in the main analysis: any chronic diseases, BPD, HIV infections, congenital heart disease (CHD), Down syndrome, cystic fibrosis and previous asthma. The point estimates of the pooled ORs of all these seven conditions were greater than 2 and were all statistically significant except for BPD (OR 2.38, 95% CI: 0.84-6.75, $I^2 = 9.8\%$; 4 studies); the pooled OR of BPD was statistically significant in sensitivity analyses that included ORs from both multivariable and univariable analyses, and that included ORs from univariable analyses only (Table 3).

The results of the vast majority of risk factors across all subgroup analyses were consistent with the primary findings, except that in the subgroup analysis based on study periods, rural residence was a significant risk factor during 1990-2000 but was no longer significant in 2010-2020 (Supplementary Figures S4-S9).

Discussion

Based on the latest available evidence, this systematic review and meta-analysis updated the knowledge of risk factors for developing RSV-ALRI among children under five. Although existing evidence from community-based studies is still limited, we identified indoor air pollution as a possible risk factor for developing RSV-ALRI in the community, increasing the risk by 45%. Besides, a wide range of demographic, pre- and post-neonatal, household and environmental and health and medical condition-related factors were identified that increased the risks for RSV-ALRI hospitalization by 14%-355%.

Compared to the previously published meta-analysis [13], our updated analysis has made several improvements. First, we adopted stricter inclusion criteria to improve the overall quality of the included evidence. Specifically, we excluded cross-sectional studies (which were included in the previous meta-analysis), as they lack predefined comparison groups, making them vulnerable to publication bias. Additionally, while certain factors, such as sex, have a clear temporal order with the outcome, the causal temporality of other potential confounders may be less clear. We also modified the quality assessment approach by incorporating more objective indicators. Despite the use of stricter criteria, with the substantial volume of published studies in the recent 5 years, the total number of included studies in our review increased by 74% (from 27 to 47), and the number of assessed factors based on multivariable evidence increased by more than threefold (from 7 to 25). For risk factors with multiple levels such as number of siblings and prematurity, we managed to assess the risk for each level. For example, we further divided the prematurity group (i.e. <37 wGA) into <29 wGA, 29-32 wGA and 33-36 wGA, and assessed these subgroups individually; by doing so, we confirmed that even late-preterm-born children had a sizeable risk (OR 1.76, 95% CI: 1.62-1.91) for RSV-ALRI hospitalization compared to children born at term.

In addition to the risk factors identified by the previous review [13], several other factors were confirmed as risk factors for RSV-ALRI hospitalization in our review, including Māori or Pacific ethnicity, small for gestational age, maternal age <30 years at delivery, caesarean section and maternal multiparity. We also quantified the effect size of several previously well-recognized health and medical condition-related factors such as BPD [62], Down syndrome [63] and CHD [64].

Moreover, for the first time, we distinguished the risk factors associated with RSV-ALRI in community settings from those leading to RSV-ALRI hospitalization. Interestingly, while male sex was not shown as a risk factor for developing RSV-ALRI in the community in our analysis, it was associated with an approximately 20% increase in the risk for RSV-ALRI hospitalization. Such contrasting results might be a result of the differences in the disease severity between male and female, although we could not rule out the effect of the limited number of community-based studies. Similar to male sex, we found contrasting results for passive smoking, which was shown as a risk factor for hospitalization but not for RSV-ALRI in the community. This suggests that exposure to passive smoking might aggravate RSV diseases. Three studies examined the association between indoor air pollution and developing RSV-ALRI in the community using multivariable analyses; however, the definitions were not entirely consistent (Supplementary Table S4). Among these, only one cohort study found a significant association, which defined indoor air pollution as no window ventilation in the kitchen. Therefore, we considered indoor air pollution as a possible risk factor for developing RSV-ALRI in the community, consistent with the 2019 Global Burden of Disease Study that found household air pollution from solid fuels as the second leading cause of lower respiratory infection mortality in children younger than 5 years (following child wasting) [65].

However, we do acknowledge several limitations in this study. First, the meta-analysis results were largely informed by evidence from HICs (accounting for more than 70% of included studies), although subgroup analysis by country income did not yield substantially different results for risk factors with available data. Second, we acknowledged high heterogeneities among the included studies, including the variations in case definitions of ALRI and RSV identification methods, and variations in defining, measuring and reporting risk factors. Moreover, the number of studies included in the meta-analysis per risk factor was still limited and we could not rule out type II error (i.e. false negative results). Third, although we considered the meta-analysis of individually reported ORs from multivariable analyses as the main analysis to account for confounding bias in each individual study, including only ORs from multivariable analyses could result in false positive results. This is because in some studies, the list of factors included in the multivariable analysis was informed solely by the univariable analysis, that is only factors that showed statistical significance in the univariable analysis (e.g. determined by the P-value) was selected. To help address this limitation, we conducted sensitivity analyses that included results from univariable analysis, which yielded generally consistent findings.

Conclusions

Despite these limitations, our study synthesized the latest evidence on risk factors for RSV-ALRI in children under 5 years. Our findings did not only update the knowledge on the risk factors of RSV-ALRI but also could help raise awareness of RSV prevention among the public, especially parents of high-risk children. The reported effect size of these risk factors in this study provides important input data for estimating the public health impact of reducing or eliminating certain risk factors, such as indoor air pollution. These data could also be used to support the development of individual risk prediction models for RSV-ALRI. With novel RSV prophylactic products targeting protection at infants being available, information on RSV risk factors could help public health authorities identify high-risk populations and prioritize the allocation of RSV prophylactic products in resource-constrained settings.

Declarations of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: YL reports grants from WHO, GSK and Wellcome Trust; and personal fees from WHO and Pfizer, outside the submitted work. HN reports grants from the Innovative Medicines Initiative, WHO, the National Institute for Health Research, Pfizer and Icosavax; and personal fees from the Bill & Melinda Gates Foundation, Pfizer, GSK, Merck, Abbvie, Janssen, Icosavax, Sanofi, Novavax, outside the submitted work.

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Ethical approval

Approval was not required as this is a systematic review.

Author contributions

HN and YL conceptualized the study. SD led the data acquisition with substantial contributions from CB, ME and FDW. SD led the data analysis with input from YL. SD and YL led data interpretation with input from HN, CB, ME and FDW. SD wrote the first draft of the report with substantial input from YL. All co-authors reviewed the draft for intellectual content and approved the final report.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2024.107125.

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