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ORIGINAL ARTICLE

RSV hospitalization in infancy increases the risk of current wheeze at age 6 in late preterm born children without atopic predisposition

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Abstract

Severe respiratory syncytial virus (RSV) infection during infancy is associated with ongoing respiratory morbidity. In a large birth cohort of 2210 healthy preterm infants born at 32–35 weeks of gestation, we aimed to determine the role of atopy in the link between RSV hospitalization and current wheeze at age 6. We defined current wheeze as parent-reported wheeze or the use of respiratory medication in the past 12 months. Based on a positive family history of atopic disease, we distinguished between children with and without atopic predisposition. Six-year follow-up data was obtained in 997/1559 (64%) children of which 102 (10.2%) children had been hospitalized with RSV during infancy. Current wheeze was present in 184/997 (18.6%) children. RSV hospitalization was an independent risk factor for current wheeze in children without atopic predisposition (aOR 4.05 [95% CI 1.22–12.52]) but not in children with this atopic background (aOR 1.50 [95% CI 0.81–2.71]).

Conclusion: This is the largest published birth cohort demonstrating that in late preterm infants, atopic predisposition defines the relationship between RSV hospitalization and current wheeze. Future RSV prevention trials aiming to prevent ongoing respiratory symptoms should be analyzed separately for atopic status.

What is Known:
- *RSV infection is responsible for a significant burden of disease in young children worldwide.*
- *Severe RSV infection in early life is associated with asthmatic symptoms later in life.*

What is New:
- *This is the largest published birth cohort reporting about the role of atopic predisposition in the link between severe RSV infection and current wheeze at school age.*
- *We show that RSV hospitalization in infancy is an independent risk factor for current wheeze in late preterm children without atopic predisposition at age 6. This was not seen in children with atopic predisposition.*

Keywords RSV · Respiratory syncytial virus · Wheeze · Atopy · Preterm

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Abbreviations

OR	Odds ratio
aOR	Adjusted odds ratio
CI	Confidence interval
LRTI	Lower respiratory tract infection
RSV	Respiratory syncytial virus
RSVH	RSV hospitalization
wGA	Weeks gestational age

Introduction

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infection (LRTI) in infants globally and is responsible for a vast burden of disease in early childhood [7, 8, 22]. Severe RSV infection is not only responsible for morbidity in early childhood but can also cause ongoing respiratory morbidity up to early adulthood [11, 19, 25]. This ongoing respiratory morbidity is characterized by persistent wheezing [3, 14, 23–25, 30], decreased lung function [11, 25, 30], and is suggested to influence the development of asthma [9, 19, 24, 25, 30]. However, the association between severe RSV infection and ongoing symptoms seems to decrease with age which raises doubt about whether this respiratory morbidity is permanent or merely transient [17]. Additionally, we lack definitive proof that shows that severe RSV infection is causal in the development of ongoing respiratory morbidity or simply reflects an underlying predisposition for respiratory morbidity caused by other pathophysiological mechanisms such as atopy [20]. While we know that atopic children have an increased risk of developing asthma, we are unaware of the precise interplay between atopy and severe RSV infection in infancy in causing persistent respiratory morbidity. Few studies have investigated this specific relation and results are conflicting [9, 23, 30]. These studies were often underpowered in subgroup analysis which made it difficult to draw robust conclusions. We aimed to determine the role of atopy in the link between severe RSV infection in early childhood in late preterm infants and ongoing respiratory symptoms at school age.

Materials and methods

Study design

This study is a prospective follow-up study of the RISK study, a multicenter, prospective birth cohort study to investigate risk factors for RSV hospitalization (RSVH) in otherwise healthy late preterm infants of 32^{+1}–35^{+6}-week gestational age. The study design and data collection of the RISK study have been explained in detail in previous publications [4, 12]. In summary, otherwise healthy children born between 32^{+1} and 35^{+6} weeks of gestation were included in 41 participating hospitals in the Netherlands between June 2008 and February 2015. Children with major congenital abnormalities (such as Down syndrome), children who received palivizumab for any reason, and children hospitalized for clinical bronchiolitis without a viral test result were excluded from analysis. In total, 4088 children were included in the RISK study of which 181 (4.4%) were hospitalized in the first year of life with RSV-bronchiolitis [12]. In the current study, we prospectively followed up children from this cohort that reached the age of 6 years, using an online parental questionnaire.

First year follow-up

Clinical data about pregnancy and birth characteristics were obtained from medical records retrieved from the hospital where the child was born. Additionally, parents filled out a questionnaire at birth about risk factors of RSV infection including the presence of siblings, planned day care attendance, atopy in first degree family members, and parental smoking. After the first year of life, a second parental questionnaire was completed. This questionnaire recorded information about hospitalization for respiratory infection, presence of wheezing, the use of respiratory medicine, breastfeeding, day care attendance, and eczema. If hospitalization for respiratory infection was indicated by the parents at 1-year follow-up, we retrospectively verified whether RSV infection was the cause of hospitalization in the medical records of the attended hospital.

Six-year follow-up

Follow-up at 6 years of age was performed using an online parental questionnaire. Data was collected about asthma, wheezing, and the use of respiratory medication. This questionnaire was based on the standardized core questions from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire [1]. The questionnaire was completed in an online survey tool (NetQ healthcare software https://www.netqhealthcare.nl/en). Participants received an invite for follow-up by email and were reminded to participate once more after 2 weeks if they had not responded. To increase statistical power, we enriched the cohort with active telephonic follow-up of additional RSVH cases from the non-responders.

Definitions

Severe RSV infection was defined as hospitalization for respiratory tract infection with proven RSV infection as determined by routine practice laboratory testing in the participating hospitals [4, 12]. Our primary outcome was current wheeze at the age of 6 years. We defined current wheeze as parent-reported

wheeze or the use of respiratory medication, or both, within the past 12 months. Parent-reported wheeze was defined as at least one reported episode of wheeze in the past 12 months, whereas reported use of respiratory medication was defined as the use of inhaled respiratory medication (either inhaled steroids or beta-mimetics) at least once in the past 12 months. Atopic predisposition was defined as a positive history of atopic disease (asthma, eczema, or hay fever) in at least one of the parents.

Statistical analysis

First, crude odds ratios for the association between RSVH and current wheeze were calculated for children with complete follow-up data using logistic regression analysis. Second, we compared baseline characteristics between the response and non-response group using the Student's t test and Mann-Whitney U test for continuous variables and the χ^2 test or Fisher exact test for discrete variables with a significance level of < 0.05. Statistically significant variables that indicated non-response or 'missingness' were included in the logistic regression model in order to adjust for this non-response. Third, we adjusted for potential confounding bias by including potential confounders from literature to the model. We performed an extensive literature search to identify risk factors for RSV and asthma that could potentially confound the results (supplemental Table S1). Fourth, we stratified the results by atopic predisposition in order to obtain estimates for children with and without atopic predisposition.

Last, we performed a sensitivity analysis in which the missing outcome data was imputed for children without 6-year follow-up. We used multiple imputation with 100 iterations per imputed dataset to obtain 30 imputed datasets. Analyses were performed on the 30 imputed datasets and Rubin's rules were applied to obtain overall estimates. All analyses were performed using R version 3.1.1 for Windows and multiple imputation was performed with the mice package.

Results

Participants

A total of 2307 children from the RISK birth cohort were eligible for follow-up at age 6 because they were born between June 2008 and April 2011. We excluded 78 children receiving palivizumab, 6 children with major congenital abnormalities, and 13 patients hospitalized with clinical bronchiolitis but in whom no viral testing was performed. The remaining 2210 children were contacted for participation in the online survey. A total of 651 (29%) of the participants could not be reached because of incorrect contact details. A total of 1559 participants received the invitation, of which 961 (62%) completed the online questionnaire. With active telephonic follow-up, we included 36 additional RSVH cases from the non-response group, resulting in a total of 997 children with 6-year follow-up data (Fig. 1). Hospitalization because of RSV infection occurred in 102 children during their first year of life. Baseline characteristics of children with and without 6-year follow-up are shown in Table 1. Various differences were seen between children with and without complete follow-up [Table 1]. These differences remained significant when the 36 cases which were included by active follow-up were analyzed in their original group (data not shown).

Current wheeze

At 6 years of age, wheeze was reported in 119/997 (12%) children and the use of respiratory medication was reported in 159/988 (16%) children. In nine children, data about the use of respiratory medication was missing resulting in eight undetermined values for the composite endpoint of current wheeze (1 indicated wheezing in past 12 months and was classified as having current wheeze for the composite endpoint). The composite endpoint current wheeze was present in 184 of 989 (18.6%) children with available data.

Atopic predisposition

Baseline data about atopic predisposition was available in 828 children. Atopic predisposition was present in 506/828 (61%) of the children. This reflects that at least one of the parents of the child has indicated having eczema, hay fever, or asthma. When we stratified for atopic predisposition, we saw that 118/506 (23.3%) of the children with atopic predisposition had current wheeze compared to 40/322 (12.4%) of children without atopic predisposition.

RSV, atopic predisposition, and current wheeze

At the age of 6, 28/101 (27.7%) of RSVH cases had current wheeze compared to 156/888 (17.6%) children who were not hospitalized [Table 2]. The unadjusted odds ratio for RSVH and current wheeze at 6 years of age was 1.80 (95% CI 1.11–2.85). This association was stable after subsequent adjustment for non-response (adjusted OR 1.97; 95% CI 1.11–3.39), and after adjustment for confounding (aOR 1.89; 95% CI 1.06–3.32) [Table 2].

After stratification for atopic predisposition, the association between RSVH and current wheeze was statistically significant in children without atopic predisposition (aOR 4.05; 95% CI 1.22–12.52) but was not significant in children with atopic predisposition (aOR 1.50; 95% CI 0.81–2.71) [Table 2]. When sensitivity analysis was performed in the total study population with imputation of missing data, the association

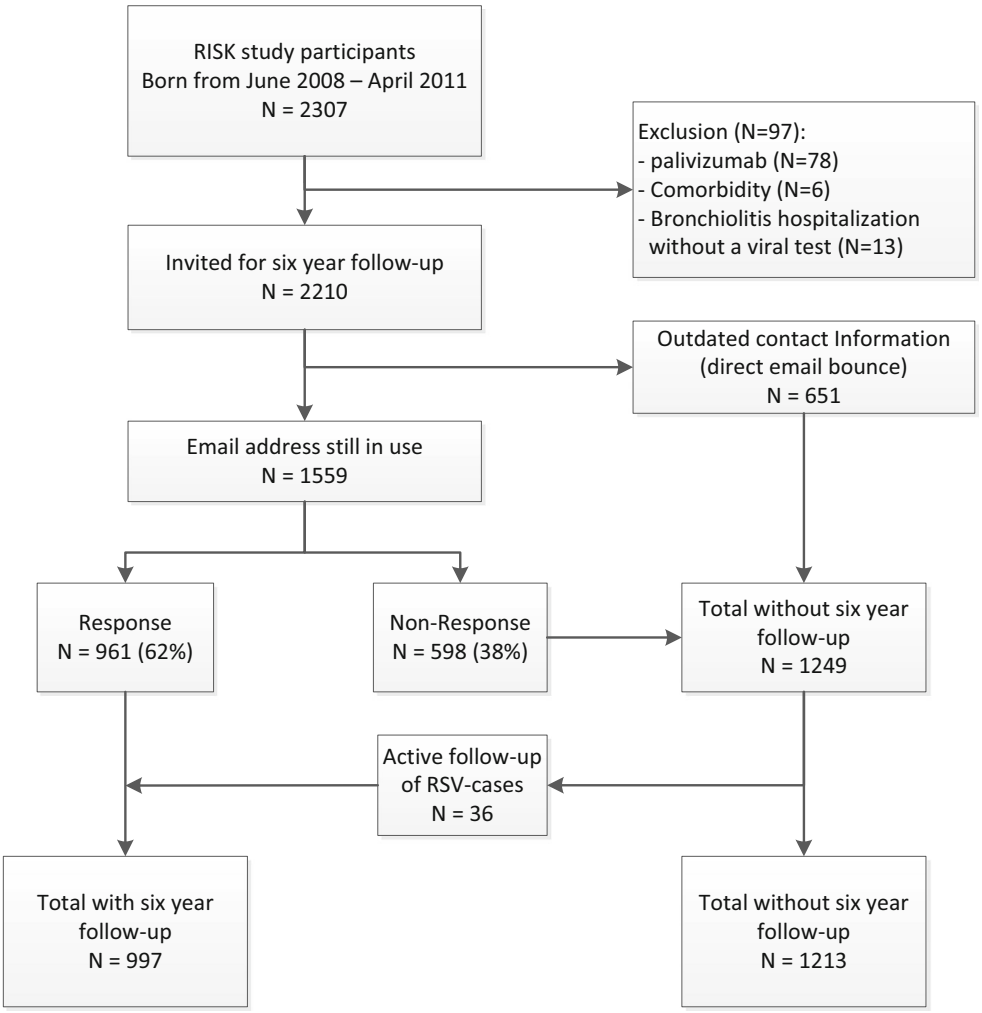

Fig. 1 Study population flow chart

between RSVH and current wheeze was confirmed only in children without atopic predisposition [Table 3].

Discussion

We found that in late preterm infants without atopic predisposition, severe RSV infection in early life is an independent risk factor for current wheeze at the age of 6. To our knowledge, this is the largest published birth cohort reporting about the role of atopic predisposition in the link between severe RSV infection and current wheeze at school age.

It is known that atopy increases the risk of developing asthma. In addition, atopy is associated with an increased risk of RSV hospitalization in early life [27]. However, the precise interplay between atopy, RSV infection, and asthma development is still unknown. Multiple explanations exist for the interaction between viral infections and atopy and their link to asthmatic disease. One explanation is that atopic disease alters the immune response towards an impaired response to viral infection which makes individuals more prone to (severe) infection [18]. Additionally, viral infections as well as atopic disease can cause bronchial epithelial damage which makes the lungs more susceptible to bronchial hyperreactivity [18]. Both the epithelial damage and altered immune response are key features in development of asthmatic disease.

Our results are in line with the population-based study of Henderson et al. who showed that RSVH was only a risk factor in children without atopy [9]. However, RSVH did not increase the risk in children without atopy in other cohort studies by Sigurs and Zomer-Kooijker [23, 30]. Inconsistency with our results can potentially be explained by the limited sample size and different outcome definitions used in these studies. The MAKI trial, a randomized controlled trial in a similar patient population of late preterm infants, investigated whether RSV prophylaxis during infancy alters the risk of school age asthma. They found less parent-reported asthma at age 6 in children who received RSV prophylaxis but did not detect a difference in physician-diagnosed asthma or lung function [21]. Subgroup analysis for parental atopic disease showed that RSV prophylaxis significantly reduced the risk of parent-reported current asthma in children without atopic

Table 1 Baseline characteristics stratified by response to 6-year follow-up

	Response ($N = 997$)	No response ($N = 1213$)	P value*
Birth characteristics			
Gender male	561/997 (56.3%)	657/1213 (54.2%)	0.3
wGA (weeks + days)	34 + 2	34 + 2	0.4
Birth weight (in grams (SD))	2219 (434)	2222 (444)	0.9
Multiple birth	317/995 (31.9%)	453/1207 (37.5%)	0.005
Maternal asthma	101/995 (10.2%)	164/1209 (13.6%)	0.01
Paternal asthma	72/995 (7.2%)	162/1209 (13.4%)	< 0.001
Maternal eczema	151/992 (15.2%)	220/1205 (18.3%)	0.06
Paternal eczema	113/992 (11.4%)	176/1205 (14.6%)	0.03
Maternal hay fever	173/762** (22.7%)	238/986 (24.1%)	0.5
Paternal hay fever	149/762** (19.6%)	231/986 (23.4%)	0.08
Maternal smoking during pregnancy	107/997 (10.7%)	161/1212 (13.2%)	0.07
High educational level mother[a]	508/993 (51.2%)	497/1206 (41.2%)	< 0.001
High educational level father[a]	461/985 (46.8%)	478/1195 (40.0%)	0.001
Dutch nationality mother	907/997 (91.0%)	1060/1213 (87.4%)	0.01
Dutch nationality father	902/997 (90.5%)	1052/1213 (86.7%)	0.01
Siblings (at least one)	375/996 (37.7%)	480/1206 (39.8%)	0.3
Follow-up at 1 year of age			
RSVH***	102/997 (10.2%)	19/1213 (1.6%)	< 0.001
Wheeze	297/995 (29.8%)	340/1207 (28.2%)	0.4
Respiratory medicine use (at least once)	255/989 (25.8%)	289/1200 (24.1%)	0.4
Smoking mother	148/995 (14.9%)	240/1210 (19.8%)	0.002
Smoking father	256/993 (25.8%)	365/1209 (30.2%)	0.02
Day-care attendance	608/998 (61.0%)	628/1212 (51.8%)	< 0.001
Eczema	286/994 (28.8%)	369/1209 (30.5%)	0.4
Breastfed[b]	754/997 (75.6%)	863/1210 (71.3%)	0.02

Data are presented as: *n* total number of participants with data (%), unless otherwise specified, *wGA* weeks gestational age, *SD* standard deviation, *RSVH* RSV hospitalization, *N/A* not applicable

**P* value based on univariate comparison between response and non-response group

**Parental hay fever was later added to the parental questionnaire resulting in a higher number of missing values

***Numbers after enrichment by active follow-up of RSVH cases from the non-response group. The original distribution before enrichment was 66/961 (6.9%) vs 55/1249 (4.4%) ($p = 0.01$)

[a] Educational level was dichotomized by using the arbitrary cut-off level of at least obtaining a institute for Higher Profession Education and Training degree (called HBO in the Netherlands)

[b] Received breastfeeding for at least 1 week after birth

parents, which is in line with our study. This reduced risk was also shown in a European/Canadian cohort study where RSV prophylaxis in children without atopic predisposition (absence of a family history of parental atopic disease), decreased the relative risk of recurrent wheezing by 80% [26]. Similar to our study, this reduction was not observed in children with an atopic background. In contrast, in a study in Japanese children, RSV-prophylaxis decreased recurrent wheeze only in children with an atopic background [14]. The discrepancy with the European/Canadian study was suggested to be caused by a fundamental difference between study populations in genetic makeup or the environment. Based on our study, we speculate that regardless of the presence or absence of severe RSV infection, the atopic background on itself is sufficient to predispose children for the development of asthma. However, in the absence of an atopic predisposition, severe RSV infection seems to play a more important role in causing ongoing respiratory morbidity.

The strength of the current study is the prospective birth cohort design and large sample size, which allowed us to differentiate between children with and without atopic predisposition. There are also limitations worth mentioning. First, because we only included late preterm infants in our study, we cannot generalize our results to all infants. Wheezing disorders are known to be more prevalent in preterm infants compared to term born infants, and pathophysiologic mechanisms are likely to be different [2]. Second, bias could have been introduced during follow-up. Confounding bias is a problem

Table 2 The risk of current wheeze at age 6 stratified by atopic predisposition

Outcome	RSVH	No RSVH	Crude OR (95% CI)	Adjusted[b] aOR (95% CI)	Adjusted[c] aOR (95% CI)
Current wheeze (overall)	28/101 (27.7%)	156/888(17.6%)	1.80 (1.11–2.85)	1.97(1.11–3.39)	1.89 (1.06–3.32)
Current wheeze (atopic predisposition)	19/62[a] (30.6%)	99/444[a] (22.3%)	1.54(0.84–2.73)	1.54(0.84–2.76)	1.50(0.81–2.71)
Current wheeze (no atopic predisposition)	6/21[a] (28.6%)	34/301[a] (11.3%)	3.14(1.06–8.31)	3.39(1.12–9.24)	4.05(1.22–12.52)

Data are presented as: *n* total number of participants with data (%), unless otherwise specified, *RSVH* RSV hospitalization, *OR* odds ratio, *aOR* adjusted odds ratio

[a] 169 participants (19 RSVH cases, 150 participants without RSV infection) had missing data on atopic predisposition resulting in 828 participants to be analyzed when we stratified for atopic predisposition (506 atopic, 322 nonatopic)

[b] Adjusted odds ratios were corrected for variables of missingness (multiple birth, parental smoking, parental asthma, parental eczema, parental educational level, non-Dutch nationality, day-care attendance, and breastfeeding), but not for confounding.[c] Adjusted odds ratios were corrected for both variables of missingness and potential confounders (male gender, presence of siblings, birth weight, day care attendance, smoke exposure, parental atopic constitution, breastfeeding, and educational level of the parents)

in observational studies. We performed an extended literature review to select potential confounders for which we adjusted in analyses. Self-selection bias could have caused parents from children with current wheeze to respond more often because the study purpose was explained in the invitation email at 6-year follow-up. This could have resulted in a higher proportion of children with the outcome. In addition, to increase power, we enriched the cohort with complete follow-up with RSVH cases from the non-response group resulting in more participants with the determinant. Additionally, attrition bias due to selective response in follow-up could have occurred since only 62% of the participants with a valid email address completed follow-up. Participants with outdated contact information together with the non-responders comprised 55% of the total eligible study population. Surveys with long-term follow-up showed response rates varying from 41 to 63% [10, 13, 16]. Higher response rates were obtained when updated contact details were available, which was not the case in our study resulting in the inability to contact 651 eligible participants. Differences seen in the baseline characteristics between responders and non-responders indicated this attrition bias. We have corrected for all these biases that were introduced during follow-up by including covariates of 'missingness' and potential confounders in the regression model. Subsequently, we have performed a sensitivity analysis using imputation to correct for missing outcome data in line with methodological literature [6]. All analyses showed comparable results which strengthens our belief that the conclusions drawn are valid. Third, because stratification in analyses was applied for both RSVH as well as atopic predisposition, numbers tend to become smaller. However, we observed consistent results in the complete case analysis and sensitivity analysis of all 2210 participants including 121 RSVH cases. This makes us feel confident that our conclusions are valid. Fourth, parents are known to overestimate wheezing in their child compared to when wheeze is assessed by a physician [15]. We chose parent-reported current wheeze over a doctor's diagnosis of asthma because our national guidelines dictate that no diagnosis of asthma can be ascertained in children below the age of 6 due to their inability to correctly perform spirometry. Moreover, no consent was given to collect medical data for children in the initial RISK study. It is therefore possible that the prevalence of parent-reported wheeze is overestimated in our study. However, if we compare average rates of wheeze at age 6 in literature, which range from 9.7 to 21.2% [5, 9, 14, 30], our average incidence of parent-reported wheeze in the past 12 months (11.9%) is comparable. Moreover, our average incidence of the composite outcome current wheeze of 18.6% is very comparable to the average 19.0% described in the MAKI trial which used the same

Table 3 Sensitivity analysis of the risk of current wheeze at age 6 stratified by atopic predisposition

Outcome	RSVH (%)	No RSVH (%)	Crude OR (95% CI)	Adjusted[a] aOR (95% CI)
Current wheeze (overall)	28%	20%	1.54 (0.96–2.47)	1.53 (0.93–2.53)
Current wheeze (atopic predisposition)	30%	25%	1.31 (0.74–2.30)	1.32(0.85–2.04)
Current wheeze (no atopic predisposition)	22%	13%	1.92(0.81–4.56)	1.88(1.07–3.30)

Data represent the average percentages of the 30 imputed datasets. *RSVH* RSV hospitalization, *OR* odds ratio, *aOR* adjusted odds ratio

[a] Adjusted odd ratios were corrected for potential confounders (male gender, breastfeeding, siblings, day care attendance, smoke exposure, parental atopic constitution, birth weight, and educational level of the parents)

outcome definition [21]. Fifth, we did not collect data about how frequent the children in our study used their respiratory medication and experienced wheezing. The reported outcomes could therefore reflect a broad range of symptoms in the past 12 months. Last, we defined atopy of the child based on a parental history of atopic disease. We have chosen this definition since parental atopy is known to correlate with atopic disease in the offspring [29], and because it is readily available at birth and is therefore a useable prognostic factor in early life when the risk of severe RSV infection is highest.

In conclusion, in this prospective birth cohort study in healthy late-preterm infants, we found that in children without atopic predisposition, severe RSV bronchiolitis in the first year of life is an independent risk factor for current wheeze at age 6. This suggests that RSV is probably of less importance in the development of wheeze for children with an atopic predisposition since these children are already at increased risk. If reduction of ongoing respiratory symptoms in childhood can be realized by preventing severe RSV infection in certain risk groups, this could be a very viable solution to diminish the burden both in infancy as well as in later childhood. Especially in the light of new RSV vaccines currently being developed, future RSV prevention trials aiming to prevent ongoing respiratory symptoms should be analyzed separately for children with and without an atopic predisposition.

Authors' contributions Koos Korsten designed the study, collected the data, drafted the manuscript, performed the analyses, and approved the manuscript to be published.

Maarten O. Blanken designed the study, critically reviewed the manuscript, and approved the manuscript to be published.

Brigitte J.M. Buiteman collected the data, critically reviewed the manuscript, and approved the manuscript to be published.

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Christiana A. Naaktgeboren performed the analyses, critically reviewed the manuscript, and approved the manuscript to be published.

Louis J. Bont designed the study, critically reviewed the manuscript, and approved the manuscript to be published.

Joanne G. Wildenbeest drafted the manuscript, critically reviewed the manuscript, and approved the manuscript to be published.

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Compliance with ethical standards

Ethics statement The RISK study was reviewed and approved by the Institutional Review Board of the University Medical Centre Utrecht and subsequently approved by Institutional Review Boards of all participating hospitals. All parents provided written informed consent for screening of hospital records. The study was conducted in compliance with the Declaration of Helsinki and the standards of Good Clinical Practice. This manuscript was written according to the guidelines from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [28].

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