

Rhinovirus bronchiolitis, maternal asthma, and the development of asthma and lung function impairments

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Abstract

Background: Children with a history of rhinovirus (RV) positive bronchiolitis have a high risk of developing subsequent asthma. Maternal asthma might also increase this risk. The aim of this study was to investigate the combined effects of hospitalization for RV positive bronchiolitis in infancy and a history of maternal asthma on the development of asthma at preschool age.

Methods: This is a prospective cohort study of 139 preschool-aged children, with a history of hospital admission for bronchiolitis in infancy, followed-up to ascertain asthma and asthma-like symptoms, skin prick allergy test positivity, and lung function measured pre- and post-bronchodilator using impulse oscillometry.

Results: Children with a past hospitalization for RV positive bronchiolitis (42.4% of all) and a history of maternal asthma (36.7% of all) had the greatest prevalence and risk ratio (RR) for doctor-diagnosed asthma (prevalence 81.8% and RR 2.10, 95% confidence interval [CI] 1.37–3.19, $p = .001$), use of inhaled corticosteroids (68.2% and RR 2.17, 95% CI 1.19–3.99, $p = .001$) and short-acting β -agonists in the last 12 months (95.2% and RR 1.49, 95% CI 1.17–1.89, $p = .001$), as compared to those with RV negative bronchiolitis and no maternal asthma history. More children in this group had an abnormal airway resistance (33.3% and adjusted risk ratio [aRR] 3.11, 95% CI 1.03–9.47, $p = .045$) and reactance (27.8% and aRR 2.11, 95% CI 1.06–4.26, $p = .035$) at 5 Hz, as compared to those with RV negative bronchiolitis and no maternal asthma history.

Conclusion: Hospitalization for RV positive bronchiolitis in early life combined with a history of maternal asthma identifies a subgroup of children with a high asthma

burden while participants with only one of the two risk factors had intermediate risk for asthma.

KEYWORDS

asthma in childhood, bronchiolitis, lung function, maternal asthma, rhinovirus

1 | INTRODUCTION

Asthma is the most common chronic disease among children¹ and adversely affects quality of life. An asthma diagnosis in young children is more uncertain than at school age. However, preschoolers have the highest proportion of emergency department visits and hospital admissions for asthma-like symptoms when compared to other age groups.^{2,3} A better understanding of the risk factors that are associated with the development of asthma in early life may be relevant to its prevention, diagnosis, and treatment. In this regard, the development of asthma is thought to be a complex interaction between genetic, epigenetic, and environmental factors.⁴

Bronchiolitis in infancy is a virus-induced lower respiratory tract infection involving the terminal airways and previously associated with negative respiratory health outcomes later in life.^{5,6} The most common pathogen found in infants with bronchiolitis is respiratory syncytial virus (RSV), followed by human rhinovirus (RV), which commonly causes wheezy illnesses in preschoolers and asthma exacerbations.⁷

Sigurs et al.⁵ demonstrated that infants hospitalized with RSV bronchiolitis had a greater prevalence of asthma and recurrent wheezing, airway hyperresponsiveness, and allergic sensitization at the ages of 3, 7, 13, and 18 years compared to a control group.⁵ One in five children with a history of RSV infant bronchiolitis requiring hospitalization will be admitted again for respiratory illness such as asthma, wheezing, or respiratory infections.⁸

While the clinical manifestations of bronchiolitis might not differ according to virus type, the host immune response, moderated by gene–environment interactions, may predispose to, and be altered by, RV infection. This may establish an association between RV-induced bronchiolitis in infancy and the development of childhood asthma. For instance, the Childhood Origins of Asthma study showed that in cases of bronchiolitis managed at home in early life, RV-induced bronchiolitis was a stronger predictor of later wheezing at 3 years and asthma development at 6 years of age than RSV-induced bronchiolitis.⁹

Maternal asthma increases the risk for both hospital admissions due to bronchiolitis^{10,11} and an asthma diagnosis in childhood.^{12–14} Several studies have investigated the relationship between the severity of the bronchiolitis episode and later onset of asthma,^{8,15–17} and the association of RSV bronchiolitis in infancy and lung function later in life.^{18–20} However, the role of hospital admission for RV-induced bronchiolitis and its combined effect with maternal asthma for the development of asthma and lung function changes in childhood is yet to be determined.

Here, we report an analysis of a prospective follow-up cohort of preschool-aged children who were hospitalized for moderate to severe bronchiolitis in infancy and participated in the high-flow warm humidified oxygen (HFWHO) randomized controlled trial (RCT).²¹ This analysis aims to investigate the combined effects of RV-induced bronchiolitis and history of maternal asthma on the development of asthma, asthma-like symptoms, and lung function changes at preschool age.

2 | METHODS

This is a prospective cohort study of preschool-aged children who were admitted as infants or young children (≤ 24 months) with a clinical diagnosis of moderate or severe bronchiolitis to the John Hunter Children's Hospital, Newcastle, Australia from July 2012 to September 2015. Infants with moderate bronchiolitis at admission participated in the HFWHO RCT (ANZ Clinical Trials Registry, number ACTRN12612000685819).²² Infants and children with severe bronchiolitis at admission requiring transfer to the pediatric intensive care unit (PICU) were excluded from participating in the HFWHO RCT but were instead invited to participate in a nested observational HFWHO substudy. All children were offered longitudinal prospective follow-up through the Growing into Asthma–Bronchiolitis (GIAB) cohort study (ANZ Clinical Trials Registry, number 12607000561482).

We obtained informed written consent from parents and caregivers, and all studies were approved by the Hunter New England Health and the University of Newcastle Human Research Ethics Committees.

2.1 | Bronchiolitis diagnosis

During the HFWHO RCT, a diagnosis of bronchiolitis was made following the NSW Health Clinical practice guideline that states that children with moderate bronchiolitis need to be admitted to a hospital and be seen by a pediatrician.²³ They usually presented with an unwell appearance, moderate tachypnea, mild or moderate work of breathing, with oxygen saturation between 90% and 95% in room air, mild tachycardia, and some feeding difficulty. In severe bronchiolitis, children had an unwell appearance, apnea, severe tachypnea (>70 breaths per minute [bpm]) or bradypnoea (<30 bpm), moderate to severe grunting, may have been cyanosed or pale with oxygen saturation less than 90% on room air, had a significant feeding

difficulty (e.g., take in <50% of normal feeds), and required transfer to a tertiary PICU.²³

2.2 | Viral diagnostics

RSV direct immunofluorescence was performed on nasopharyngeal aspirate (NPA) samples at the time of hospital admission. Infants were also screened for the following other respiratory viruses employing Multiplex10 PCR (AusDiagnostics): RSV, influenza A, influenza B, human metapneumovirus, adenovirus, picornavirus (rhinovirus), enterovirus, and parainfluenza virus type 1, 2, and 3. Infants with bronchiolitis were separated into two groups based on the research aim: the RV positive group was compared to the RV negative group.

2.3 | Procedures and outcomes

During attendance at follow-up preschool visits, the parent/caregiver completed the ISAAC core questionnaire (wheezing, cough, rhinitis, and eczema modules)²⁴ and additional standardized respiratory symptom questions validated for preschoolers that included information on medication use.^{25–27} Parental history of asthma was collected as part of the initial cohort and confirmed at a follow-up visit. A clinical examination was conducted by a medical doctor, specialized or experienced at the level of an advanced trainee in pediatrics, including an interview of the primary care person to determine if the participant had doctor-diagnosed asthma.

2.4 | Lung function measurements

Lung function measurement was attempted in all cooperative participants during the follow-up visit. Impulse oscillometry (IOS) was conducted using the combined MasterScreen system (Jaeger Co). Testing was conducted in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines.^{28,29} Abnormal lung function was categorized according to ≥ 1.65 standard deviation of the predicted value for resistance and reactance of the respiratory system at 5 Hertz (Rrs5 and Xrs5, respectively).³⁰ After the measurement of the pre-IOS children received four puffs of salbutamol administered through a spacer, and 15 min later post-IOS measurements were performed.²⁸ Bronchodilator response (BDR) was measured as the percentage change between post-measurement and pre-measurement of Rrs5.²⁸

2.5 | Skin prick test

Skin allergy tests on the forearm were also performed if the parent/caregiver consented. Atopy was defined as a positive response (≥ 3 mm wheal) to any one of the common aeroallergens:

Dermatophagoides pteronyssinus, *Dermatophagoides farinae*, cat, dog, *Aspergillus fumigatus*, five grass mix, and standard food allergens; whole peanut extract, egg yolk, and egg white. Histamine was the positive control. The wheal size of the negative control (saline) was subtracted from the allergen wheal size. To be positive, a response ≥ 3 mm of the adjusted wheal size was required.

2.6 | Statistical analyses

Categorical measures were described using counts and percentages, while continuous measures were characterized using means with standard deviation (SD) if normally distributed, and medians with interquartile range (IQR) if non-normally distributed. Statistical significance for continuous secondary outcome variables were determined using a nonparametric, two-tailed Mann–Whitney *U* test or the parametric Student *t* test as appropriate. Categorical variables were compared using a χ^2 test. Poisson regression was used for the analysis of the association between having RV positive bronchiolitis and maternal asthma and the development of asthma, asthma-like symptoms, and lung function impairments at preschool age. Results are expressed as risk ratio (RR) and adjusted risk ratio (aRR) with 95% confidence intervals (CIs) based on robust variance estimation.³¹ To investigate potential confounders, adjustment was made for gender, prematurity, breastfeeding, maternal asthma, paternal asthma, bronchiolitis severity, time on O₂ in hospital, length of stay in hospital (in days), age at hospital admission (in months), additional bronchiolitis episode(s), PICU presentation during bronchiolitis admission, and age at the visit (in months). All data during hospital admission were collected as part of the HFWHO trial described elsewhere,²¹ while information at the preschool visit was collected through an interview at the time of the visit and through questionnaires completed by parents. Since all children had bronchiolitis, the potential risk of maternal asthma is not independent but is assessed as the combined effect of maternal asthma and RV bronchiolitis.

3 | RESULTS

The initial cohort was composed of 234 infants who were hospitalized for bronchiolitis. In all, 202 infants had moderate bronchiolitis and 32 children had severe bronchiolitis (Figure 1). Infants who had an RV infection ($n = 109$ out of 234; 46.6%) were significantly older and more likely male than non-RV infected infants (Table 1). The majority of non-RV infected infants were RSV positive ($n = 98$ out of 125; 73.1%; Table 1). No differences in other clinical parameters collected during the acute hospital admission were observed between the RV positive and negative groups of infants (Table 1).

Of the 234 hospitalized infants, 139 children were prospectively followed-up at preschool age (participation 59.4%, Figure 1). Children who attended the follow-up were more likely to have been breastfed in the past (83.3% vs. 72.4%, $p = .021$) and admitted to the Pediatric

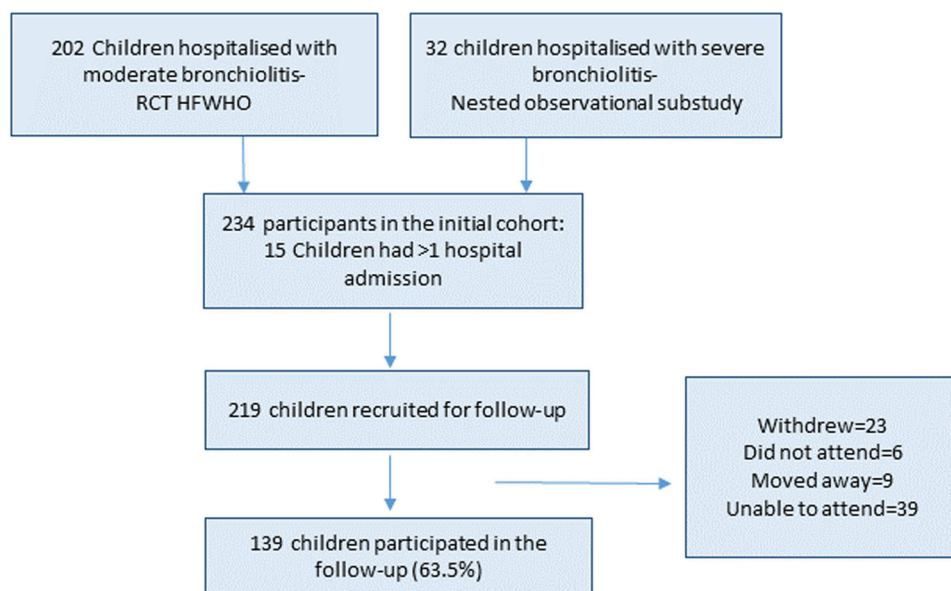


FIGURE 1 Flow chart of the subjects included in the studies from the initial cohort to the follow-up cohort. HFWHO, high-flow warm humidified oxygen; RCT, randomized controlled trial [Color figure can be viewed at wileyonlinelibrary.com]

Intensive Care Unit (PICU; 35.3% vs. 21.4%, $p = .005$) in infancy (Table 1). Hospitalization for RV positive bronchiolitis was present in 42.4% of children and 36.7% of children had a history of maternal asthma (Table 1). We did not observe an association between the

allocated treatment (HFWHO vs. low flow oxygen) and doctor-diagnosed asthma at preschool age (57.7% vs. 75.5%, $p = .417$, respectively) in the children who participated in the HFWHO RCT ($n = 99$).

TABLE 1 Subject characteristics of the initial (HFWHO) and follow-up (GIAB) cohort

Characteristics	Initial cohort				Follow-up cohort				Initial versus follow-up p value
	Total ($n = 234$)	RV ($n = 109$)	Non-RV ($n = 125$)	p value	Total ($n = 139$)	RV ($n = 59$)	Non-RV ($n = 80$)	p value	
Males ^a	67.5%	78.9%	57.6%	.001	64.8%	76.3%	56.3%	.019	.650
Prematurity ^a	21.4%	18.4%	24%	.339	20.1%	22%	18.8%	.408	.895
Maternal asthma ^a	41.1%	41.8%	40.5%	.890	36.7%	37.3%	36.3%	.900	.436
Breastfeeding ^a	72.4% (163/225)	67.6% (74/105)	76.7% (92/120)	.138	83.3%	81%	85%	.348	.021
ICU presented ^a	21.4%	22%	20.8%	.874	35.3%	39%	32.5%	.270	.005
Age at admission in months ^b	6 (3–11)	8 (4–11)	4 (2–9)	<.001	7 (2–11)	9 (5–13)	5 (2–10)	.002	.615
Age at a visit in months ^b	–	–	–	–	47 (42–51)	48 (43–53)	47 (41–50)	.104	–
Length of stay in days ^b	2 (1–3)	2 (1–3)	2 (1–3)	.340	2 (1–3)	2 (1–3)	2 (1–3)	.565	.336
Time on O ₂ in hours ^b	24 (12–50)	22.5 (11.5–42.5)	28 (12–59)	.084	28.5 (12–53)	28.5 (11–47)	27.5 (12–61)	.346	.615
RSV ^a	57.7%	26.9%	73.1%	<.001	54.6%	11.8%	88.2%	<.001	.666
Other viruses ^a	19.7%	33.0%	24.8%	.880	7.2%	25.4%	12.5%	.072	.157

Note: Values in bold are values with statistical significant difference between groups.

Abbreviations: GIAB, Growing into Asthma-Bronchiolitis; HFWHO, high-flow warm humidified oxygen; ICU, intensive care unit; IQR, interquartile range; RSV, respiratory syncytial virus; RV, rhinovirus.

^aCategorical variables; counts and % (χ^2 test).

^bContinuous variables non-normally distributed, used median (IQR) (Mann–Whitney test).

3.1 | Prevalence of asthma and respiratory symptoms

Preschool-aged children hospitalized with RV positive bronchiolitis had a higher risk of doctor diagnosed asthma (aRR 1.46; 95% CI, 1.06–2.01, $p = .021$; Table 2). Other asthma-like symptoms, Rrs5 and Xrs5 and BDR were not significantly different between the groups (Table 2). In the adjusted model there were significant other predictors of these outcomes. For instance, maternal asthma was a predictor of doctor-diagnosed asthma (aRR 1.40; 95% CI, 1.01–1.93, $p = .043$), use of inhaled corticosteroids (ICS; aRR 1.59; 95% CI, 1.02–2.43, $p = .040$) and short-acting bronchodilators (SABA) in past 12 months (aRR 1.24; 95% CI, 1.03–1.51, $p = .027$), and having a high airway resistance at 5 Hz [Rrs5] (aRR 3.61; 95% CI, 1.45–8.98, $p = .006$). In the adjusted analysis, recurrent bronchiolitis episodes were also a significant predictor of doctor diagnosed asthma (aRR 1.88; 95% CI, 1.25–2.82, $p = .002$), wheeze in the last 12 months (aRR 1.78; 95% CI, 1.29–2.46, $p < .001$), ICS use (aRR 2.04; 95% CI, 1.21–3.44, $p = .008$) and SABA use in past 12 months (aRR 1.73; 95% CI, 1.30–2.30, $p < .001$). Further, breastfeeding reduced the relative risk for having a high airway resistance at 5 Hz (aRR 0.25; 95% CI, 0.09–0.68, $p = .007$; Table S1).

3.2 | Combined effect of RV positive bronchiolitis and maternal asthma for doctor-diagnosed asthma

Next, we stratified the cohort into four subgroups based on a history of RV bronchiolitis and maternal asthma. When compared to the reference group (RV negative bronchiolitis, no maternal asthma), the children with a history of RV positive bronchiolitis and maternal asthma had an increased RR of having doctor-diagnosed asthma (aRR 2.10, 95% CI 1.37–3.19, $p = .001$), use of ICS (aRR 2.17, 95% CI 1.19–3.99, $p = .001$) and SABA (aRR 1.49, 95% CI 1.17–1.89, $p = .001$) in the last 12 months, and having a higher R5 and reactance at 5 Hz [X5] (Table 3). A higher Rrs5 was also observed in children born to a mother with asthma but without a history of RV positive bronchiolitis (Table 3). Other predictors for a high Rrs5 were bronchiolitis severity (aRR 6.20; 95% CI, 1.64–23.3, $p = .007$) and breastfeeding (aRR 0.25; 95% CI, 0.09–0.68, $p = .007$).

4 | DISCUSSION

To our knowledge, this is the first study to show that hospitalization for RV positive bronchiolitis in combination with a history of

TABLE 2 Risk ratio for respiratory and lung function outcomes stratified by RV positive bronchiolitis

Outcomes	RV % (n = 59)	Non-RV % (n = 80)	RR (95% CI) p value	aRR (95% CI) p value
Doctor-diagnosed asthma	69.0% (40/58)	42.9% (30/70)	1.60 (1.17–2.22) $p = .004$	1.46 (1.06–2.01) $p = .021^{a,b}$
Wheeze (last 12 months)	66.7% (38/57)	59.2% (45/76)	1.12 (0.86–1.46) $p = .374$	1.08 (0.86–1.40) $p = .449^{b,c}$
SABA use (last 12 months)	80.4% (44/56)	63.5% (47/74)	1.23 (0.99–1.54) $p = .058$	1.21 (0.99–1.50) $p = .066^{a,b}$
ICS use (last 12 months)	50% (28/56)	33.8% (23/68)	1.47 (0.96–2.26) $p = .070$	1.41 (0.91–2.20) $p = .122^{a,b}$
Rrs at 5 Hz > 1.65 SD, Z-score	26.5% (13/49)	25.9% (14/58)	1.10 (0.57–2.12) $p = .777$	0.86 (0.41–1.81) $p = .698^{a,d,e}$
Xrs at 5 Hz > –1.65 SD, Z-score	16% (8/50)	5.2% (3/58)	3.09 (0.86–11.10) $p = .083$	4.71 (0.82–27.05) $p = .082$
Bronchodilator response $\geq 27\%$	27.7% (13/47)	22.8% (13/57)	1.13 (0.56–2.28) $p = .728$	1.37 (0.60–3.17) $p = .452$

Note: p values and RRs were calculated using unadjusted and adjusted Poisson regression models adjusted for gender, prematurity, breastfeeding, maternal asthma, severity, time on O₂, LOS, age at admission, age at visit, additional bronchiolitis episodes, paternal asthma, ICU presentation; if significant. Values in bold are values with statistical significant difference between groups.

Abbreviations: aRR, adjusted risk ratio; ICS, inhaled corticosteroids; ICU, intensive care unit; LOS, length of stay; RR, risk ratio; RV, rhinovirus; SABA, short-acting bronchodilator.

^aMaternal asthma.

^bAdditional bronchiolitis episode(s).

^cAge at visit.

^dBreastfeeding.

^eICU.

TABLE 3 Respiratory and lung function outcomes stratified by RV positive bronchiolitis and maternal asthma

Outcomes	Non-RV/non-asthmatic mother (n = 51)	Non-RV/asthmatic mother (n = 37)	RV/non-asthmatic mother (n = 29)	RV/asthmatic mother (n = 22)
Doctor-diagnosed asthma (n = 120)	35.4%	59.1%	61.1%	81.8%
	REF	1.30 (0.77–2.21)	1.44 (0.90–2.30)	2.10 (1.37–3.19)
		<i>p</i> = .322	<i>p</i> = .127	<i>p</i> = .001
Wheeze (n = 126) (last 12 months)	54%	69.2%	60%	77.2%
	REF	1.24 (0.86–1.78)	1.09 (0.75–1.58)	1.26 (0.90–1.76)
		<i>p</i> = .241	<i>p</i> = .642	<i>p</i> = .171
SABA use (n = 123) (last 12 months)	57.5%	74.1%	68.6%	95.2%
	REF	1.14 (0.85–1.56)	1.10 (0.80–1.53)	1.49 (1.17–1.89)
		<i>p</i> = .365	<i>p</i> = .558	<i>p</i> = .001
ICS use (n = 117) (last 12 months)	25.6%	48%	38.2%	68.2%
	REF	1.58 (0.80–3.10)	1.34 (0.65–2.77)	2.17 (1.19–3.99)
		<i>p</i> = .182	<i>p</i> = .425	<i>p</i> = .012
Rrs at 5 Hz > 1.65 SD, Z-score (n = 101)	18%	36.8%	22.6%	33.3%
	REF	3.60 (1.13–11.51)	0.90 (0.30–2.67)	3.11 (1.03–9.47)
		<i>p</i> = .030	<i>p</i> = .845	<i>p</i> = .045
Xrs at 5 Hz > -1.65 SD, Z-score (n = 106)	5.1%	9.4%	5.3%	27.8%
	REF	1.23 (0.19–7.82)	0.85 (0.09–8.04)	2.11 (1.06–4.23)
		<i>p</i> = .824	<i>p</i> = .887	<i>p</i> = .035
Bronchodilator response $\geq$ 27% (n = 98)	18.4%	31.6%	22.3%	35.3%
	REF	1.45 (0.45–4.70)	1.06 (0.34–3.36)	2.18 (0.83–5.77)
		<i>p</i> = .534	<i>p</i> = .919	<i>p</i> = .116

Note: *p* values and aRRs were calculated using Poisson regression adjusted for gender, prematurity, breastfeeding, severity, time on O₂, length of stay, age at admission, age at visit, additional bronchiolitis episode(s), ICU presented. Values in bold are values with statistical significant difference between groups. Abbreviations: aRR, adjusted risk ratio; ICS, inhaled corticosteroids; ICU, intensive care unit; RR, risk ratio; RV, rhinovirus; SABA, short-acting bronchodilator.

maternal asthma increases the risk for doctor-diagnosed asthma, asthma medication use, and abnormal lung function at preschool-age.

During their bronchiolitis hospitalization, data on clinical parameters and management was meticulously collected in all infants. Interestingly, no difference was found between the RV positive and the RV negative group except for a higher age and a greater proportion of males in the RV positive group, which is in line with previous studies.^{7,32} Thus, any difference in clinical outcomes at preschool age between RV positive and negative infants is unlikely explained by, or associated with, their clinical course during the hospital admission. The follow-up cohort had more children who were breastfed and admitted to PICU than the initial cohort, raising the possibility of bias due to missing observations. Nonetheless, our results could suggest a potential selection bias, where mothers who have breastfed or had a child admitted to PICU in the past were more likely to participate in the follow-up. However, an increased prevalence of breastfeeding might be protective for asthma, whereas more severe bronchiolitis requiring PICU admission might worsen asthma prevalence. Since the potential impact of these effects would

operate in opposite directions, this possible selection bias is unlikely to have a major impact on our outcomes.

Jackson et al.⁹ showed that RV positive wheezy illnesses in the first 3 years of life were associated with a ninefold increase in the risk of asthma development at the age of 6 years. In contrast, RSV positive wheezy illnesses were associated with a smaller increase in relative risk. Even though our study did not include a cohort of children never admitted to hospital for bronchiolitis, our results are in line with previous data. Specifically, we found an approximately sevenfold increase in prevalence for doctor-diagnosed asthma in children hospitalized with RV positive bronchiolitis in infancy (asthma prevalence 69.0%), and a fourfold increase in those hospitalized with RV negative bronchiolitis in infancy (asthma prevalence 42.9%), when assuming an asthma prevalence of around 10% in a nonselected Australasian child cohort.

Bergroth et al.³³ demonstrated an increase in asthma controller medication use in preschoolers 5 years after a bronchiolitis episode where hospital admission was necessary. They found that bronchiolitis caused by RV infection resulted in an early initiation of asthma

controller medication use (4 months after RV infection vs. 15 months after RSV infection).^{33,34} In addition, at preschool age, 50% of children who had RV infection in infancy were still using asthma controller medication, as compared to only 15% of children who had an RSV infection. Thus the increase in asthma prevalence in children hospitalized with RV positive bronchiolitis in early life is associated with earlier onset and prolonged use of asthma medications.

Our study supports this conclusion and the novel observation of our study is that preschool children with a past history of hospitalization for RV positive bronchiolitis as well as maternal asthma have the highest prevalence for doctor-diagnosed asthma (81.8%), use of ICS (68.2%) and SABA (95.2%) in the past 12 months, as well as abnormal lung function assessed by the measurement of Rrs5 (33.3%). Even if an asthma diagnosis is uncertain and medications may be overprescribed in preschool-aged children, our results highlight a much higher asthma disease burden and greater lung function impairments in this group of children as compared to those without a history of maternal asthma and with RV negative bronchiolitis. Further investigations on a genetic, physiological, molecular, and cellular level are warranted to characterize lung disease in this high-risk group, which may pave the way for more personalized disease monitoring and treatment approaches. As this group of children is easily identifiable, if virus diagnostics are performed, they could be specifically targeted for interventions. This may partially reduce future health care costs that have been reported to be 83% higher in preterm infants admitted to hospital with bronchiolitis over their first 4 years of life in one recent study.³⁵

The higher prevalence of abnormal normal lung function in children with a history of maternal asthma is of particular interest. Birth cohort studies have demonstrated an association between RV bronchiolitis and lower lung function, varying from early childhood to adulthood.^{36–40} Guilbert et al.⁴¹ showed that children who had RV positive wheezing episode in the first 3 years of life, had reduced lung function measured by IOS at 5 years of age. A study conducted by Kotaniemi-Syrj nen et al.⁴² demonstrated increased bronchial responsiveness at school age associated with RV positive wheezing in infancy. Our study suggests that a history of maternal asthma may also be a risk factor for reduced lung function at preschool age, either in its own right (Rrs5) or in combination with a history of RV positive bronchiolitis (Rrs5 and Xrs5). We are currently conducting an analysis of the Breathing for Life Trial⁴³ to determine if asthma in pregnancy affects infant lung function at 6 weeks of age, raising the possibility of effects on fetal lung development. Interestingly, while lung function impairments predispose to bronchiolitis,^{16,44} the Draekenstein cohort have shown that significant viral infection in the first year of life has a detrimental effect on early lung function.⁴⁵ Thus, it is possible that both pre-existent and acquired lung function impairments contribute toward the development of asthma after RV positive bronchiolitis in infancy.

A large recent multicenter study showed, compared to infants hospitalized with RSV positive bronchiolitis, that only those with RV group C positive bronchiolitis in conjunction with IgE sensitization resulted in a significantly higher risk of subsequent asthma

development at age 4 years (HR [hazard ratio], 4.06; 95% CI, 1.17–14.1).⁴⁶ There was a significant interaction between virus groups and IgE sensitization on the risk of recurrent wheeze (p for interaction < .01).⁴⁶ We did not observe an interaction between atopy and RV positive bronchiolitis in our cohort. However, this may be expected as we did not determine the RV species. We, therefore, cannot exclude that some of the risks that maternal asthma confers upon subsequent asthma development in RV group C positive infants may be mediated by IgE.

Breastfeeding was associated with better lung function outcomes at preschool age in our study, which supplements earlier results showing protective effects of breastfeeding on lung function at school age.⁴⁷ (Table S1).

Limitations of our study include a lack of RV group C status and uncertainty of asthma diagnosis at preschool age discussed earlier. In addition, only 59% of children from the original cohort were followed into the preschool years. Thus, as data was collected from the interview and self-reported questionnaires, the results might have been influenced by response bias. However, the questionnaires used in this study include additional standardized respiratory symptom questions for preschoolers which has strong construct validity, which may have controlled the potential response bias.⁴⁸ Furthermore, we did not have information on parental education in this cohort. In a study conducted by De Meer et al., a protective effect of higher parental education on the development of wheeze was found. However, this effect was only verified in children with non-atopic wheeze. This was associated with lower levels of smoking in the highly educated families.⁴⁹ In our cohort, information on parental education was not collected at the time of the recruitment. This precluded us to verify this association. However, we did control for smoking and breastfeeding, which are the main factors associated with parental education and these factors were not significantly associated with wheeze. Breastfeeding was only significantly protective of lung function. A strength of the present study is that all children participated in the HFWHO study as infants. Thus, clinical data on their hospitalization was collected prospectively, including viral diagnostics.²¹ A cohort size of 139 children who were followed-up after a bronchiolitis hospitalization and tested for lung function makes our study one of the three largest case samples out of 31 studies recently systematically reviewed, most of whom only included RSV positive children.⁵⁰

In conclusion, our data showed that almost half of all infants hospitalized with bronchiolitis were positive for RV during admission and a larger than expected proportion (41%) had a history of maternal asthma. Further, we show that RV positive bronchiolitis in combination with maternal asthma history confer more than twice the risk for the development of subsequent asthma, the use of asthma medications, and lung function impairments at preschool age. Further studies are required to determine the mechanisms underpinning this clinically relevant observation on a genetic, physiological, molecular, and cellular level.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHORS CONTRIBUTIONS

Study concept and design: Elizabeth Kepreotes, Adam Collison, Bruce Whitehead, and Joerg Mattes. *Patient recruitment and data collection:* Carla R. Da Silva Sena, Matthew Morten, Joseph Meredith, and Elizabeth Kepreotes. *Research methods and quality control:* all authors. *Analysis and interpretation of results:* all authors. *Writing first draft of paper:* Carla R. Da Silva Sena, Matthew Morten, Joseph Meredith, and Joerg Mattes. *Editing of manuscript:* all authors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Supplementary Table 1: Significant other predictors of respiratory outcomes in the multivariable analysis.

Doctor-diagnosed asthma	aRR	P-value	95% CI
Maternal asthma	1.40	0.043	1.01 - 1.93
Recurrent bronchiolitis	1.88	0.002	1.25 - 2.82
Wheeze in the last 12 months	aRR	P-value	95% CI
Age at visit	0.97	0.006	0.95 - 0.99
Recurrent bronchiolitis	1.78	<0.001	1.29 - 2.46
ICS use in the last 12 months	aRR	P-value	95% CI
Maternal asthma	1.59	0.040	1.02 - 2.47
Recurrent bronchiolitis	2.04	0.008	1.21 - 3.44
SABA use in last 12 months	aRR	P-value	95% CI
Maternal asthma	1.24	0.027	1.03 - 1.51
Age at visit	0.98	0.030	0.96 - 1.00
Recurrent bronchiolitis	1.74	<0.001	1.31 - 2.31
Resistance at 5HZ >1.65 SD	aRR	P-value	95% CI
Breastfeeding	0.25	0.007	0.09 - 0.68
Maternal asthma	3.61	0.006	1.45 - 8.98
Severity	6.20	0.004	1.80 - 21.42

Results showed as aRR after adjustment for: : gender, prematurity, breast feeding, maternal asthma, severity, time on o2, LOS, age at admission, age at visit, additional bronchiolitis episodes, paternal asthma, and ICU presentation.