

ORIGINAL ARTICLE

Asthma and Rhinitis

Asthma and lung function in adulthood after a viral wheezing episode in early childhood

K. Backman¹  | H. Ollikainen² | E. Piippo-Savolainen¹ | K. Nuolivirta³ | M. Korppi⁴¹Department of Pediatrics, Kuopio University Hospital, Kuopio, Finland²Child Welfare Clinic and School Health Care, Health Care Center, Pediatrics, Kuopio, Finland³Department of Pediatrics, Seinäjoki Central Hospital, Seinäjoki, Finland⁴Pediatric Research Centre, Tampere University and Tampere University Hospital, Tampere, Finland**Correspondence**Katri Backman, Department of Pediatrics, Kuopio University Hospital, Kuopio, Finland.
Email: katri.backman@kuh.fi**Funding information**

Kuopio University Hospital (EVO grant, code 440076), The National Foundation for Pediatric Research in Finland, The National Graduate School of Clinical Investigation in Finland, and Tampere Tuberculosis Foundation

Summary**Background:** Viral aetiology of infection has a significant role in the long-term outcome of early-childhood wheezing.**Objective:** This study examines asthma and lung function in adulthood after early-childhood wheezing induced by respiratory syncytial virus (RSV) and rhinovirus (RV).**Methods:** A total of 100 children were hospitalized for a wheezing episode at less than 24 months of age from 1992 to 1993 in Kuopio University Hospital (Finland). Adenovirus, influenza A and B virus, parainfluenza (1-3) virus, and RSV were tested on admission using antigen detection and antibody assays, and RSV and RV were tested by polymerase chain reaction (PCR). In 2010, 49 cases and 60 population controls attended a follow-up study, which included spirometry with bronchodilation test and fractionally exhaled nitric oxide (FE_{NO}) measurements.**Results:** Current asthma was present in 64% of the cases with RV-induced wheezing (OR 17.0 [95%CI 3.9-75.3] vs controls), in 43% of the cases with RSV-induced wheezing episode (6.1 [1.5-24.9] vs controls), and in 12% of the controls. The RV group showed significantly higher mean FE_{NO} values than the RSV group and controls. RV-positive cases had lower MEF50 before bronchodilation and higher MEF50, FEV1, and FEV1/FVC bronchodilation responses than controls. RSV-positive cases had lower FVC than controls before bronchodilation.**Conclusion:** Cases with RV- and RSV-induced early-childhood wheezing had increased risk for asthma in adulthood, and RV-positive cases had significantly higher FE_{NO} values than RSV-positive cases and controls. Compared to controls, RV-positive cases showed more bronchial reactivity, and RSV-positive cases showed lower FVC before bronchodilation in lung function testing.**Clinical relevance:** Children with RV- or RSV-induced wheezing in early childhood have an increased risk for asthma and lung function abnormalities in adulthood.**KEYWORDS**

asthma, child, lung function, outcome, respiratory syncytial virus, rhinovirus, wheezing

1 | INTRODUCTION

Hospitalization for wheezing in early childhood has been associated with the development of asthma and reduced lung function in adulthood.¹⁻⁴ Respiratory syncytial virus (RSV) and rhinovirus (RV) are the

most common viruses that cause wheezing in young children.⁵ In most previous studies, viral aetiology of the first wheezing episode has been crucial when evaluating later outcomes in children with wheezing in early childhood.⁶⁻¹⁰ There is strong evidence that the prevalence of asthma is increased during childhood after RSV-

induced wheezing,⁶⁻¹⁰ but later outcomes are controversial.^{4,11,12} Wheezing induced by RV appears to be linked to individual predisposition to asthma and atopic diseases,^{6,13} and there is an even higher risk of asthma in childhood compared to wheezing induced by RSV or other viruses.⁸ However, it is not known whether this association is still present in adults.

We have prospectively followed a cohort of children who were hospitalized for wheezing from 1992 to 1993 in Kuopio University Hospital, Finland.¹⁴ This cohort has been evaluated in several follow-up visits from early childhood to adolescence.¹⁴⁻¹⁷ We previously documented an increased risk for childhood asthma after hospitalization for wheezing at age under 2 years and demonstrated that the risk was highest among children with a history of RV-induced wheezing.⁸ The aim of this study was to evaluate asthma and lung function 18 years after the first hospitalization for wheezing. In addition, we evaluated whether or not these outcomes are related to viral aetiology of the early-childhood wheezing episode.

2 | SUBJECTS AND METHODS

2.1 | Original study design and previous follow-up

A total of 100 children were hospitalized for wheezing at age less than 24 months from 1992 to 1993 in Kuopio University Hospital.¹⁸ All study subjects presented with wheezing and respiratory distress during respiratory tract infection, which was severe enough to require hospitalization. Of these children, 85% had presented with wheezing for the first time, and all were hospitalized for the first time.¹⁴

Seven viruses were studied using antigen detection in the nasopharyngeal aspirate (NPA) on admission and by antibody assays in paired sera. Adenoviruses, influenza A and B virus, parainfluenza 1, 2, and 3 virus, and RSV were assayed.¹⁴ Later, 81 frozen NPA samples taken on admission were used in polymerase chain reaction (PCR) to test for RSV and picornaviruses like RV.⁸ After infancy, this cohort was evaluated in several clinical studies at mean ages of 4, 7 and 12 years.^{8,15,17}

2.2 | Follow-up study in 2010

In 2010, 49 (49%) cases with a history of early-childhood wheezing attended the clinical follow-up study. Viral PCR had been performed for 40 of them during the initial wheezing episode. A questionnaire about asthma and allergy symptoms was mailed to all attendees. Doctoral interviews and examinations, flow-volume spirometry including both a pre-bronchodilation (pre-BD) and post-BD measurements, and two-week monitoring of home peak expiratory flow (PEF) were performed for all study subjects. An invitation to the study was also sent with a ratio of 4:1 to unselected population-based controls matched by sex and age who were born in the hospital district of Kuopio University Hospital. Of those invited, 60 control subjects participated in the study. Characteristics of cases with early-childhood wheezing

episode who attended and did not attend were compared. There were no significant differences between groups in viral aetiology of the initial wheezing episode, age in admission to hospital, sex distribution, presence of atopic dermatitis in admission, or parental characteristics including parental asthma and atopy. There was no possibility to compare the characteristics of controls who attended or did not attend.

2.3 | Methods

PEF was measured using a Mini-Wright PEF meter (Clement-Clarke International LTD, Harlow, Essex, UK) three times every morning and every evening for 2 weeks, and after bronchodilator inhalations (Salbutamol 0.4 mg, Buventol Easyhaler 0.1 mg/dos, Orion Pharma, Espoo, Finland) in the morning during the second week.¹⁹ Daily PEF variability of 20% or more or an improvement in PEF of 15% or more after bronchodilator inhalation at least twice during the monitoring period was considered as abnormal.²⁰

FE_{NO} was measured with a NIOX MINO Airway Inflammation Monitor (Aerocrine AB, Solna, Sweden) according to current standards in all subjects except for one control.²¹ Skin prick tests (SPTs) (ALK Soluprick, Copenhagen, Denmark) were performed with the following allergens: birch, common alder, timothy grass and mugwort pollen, dog, cat, horse and cow dander, three dust mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae* and *Acarus siro*), and spores of one mould (*Cladosporium herbarum*). Allergic rhinitis and conjunctivitis were defined as the presence of seasonal symptoms or symptoms triggered by animal contacts during the preceding 12 months. Atopic eczema was defined as itchy eczema at typical locations. Current allergy was defined by the presence of allergic rhinitis, conjunctivitis, or atopic eczema, in combination with atopic sensitization (one or more positive SPT results).

Spirometry measurements (SpiroStar USB spirometer Medikro, Kuopio, Finland) that met the standards used was obtained from all 49 cases and 58 controls.¹⁹ The measured indices were forced vital capacity (FVC), forced expiratory volume in one-second (FEV₁), and maximum expiratory flow at 50% FVC (MEF₅₀). The spirometry indices are presented as percentages of the means of age- and sex-specific, height-related reference values that were used in Finland at the time of the clinical study.²² Spirometry was performed before (pre-BD values) and 15 minutes after (post-BD values) inhalations of 0.4 mg of salbutamol (Ventoline Evohaler 0.1 mg/dos, GlaxoSmithK-line).

Repeated wheezing episodes (more than 2 episodes during the last 12 months), chronic night cough, and prolonged cough for more than 4 weeks apart from infection were regarded as asthma-presumptive symptoms. For current asthma, previously diagnosed asthma combined with asthma symptoms or ongoing regular maintenance medication with inhaled corticosteroids (ICS), during the last 12 months, were required. In addition, study subjects were regarded as having asthma if they presented an abnormal result in the home PEF monitoring, and also reported asthma-presumptive symptoms or repeated use of bronchodilators.

2.4 | Statistics

The data were analysed using SPSS 21.0 software (SPSS Inc., Chicago, IL, USA). Chi-square and Fisher's exact tests were used in the analyses of the categorized data. Logistic regression was used in the multivariate analyses of categorized data, and the results are presented as odds ratios (OR) and their 95% confidence intervals (95% CI). Analysis of variance (ANOVA) was used in the analysis of continuous lung function test data. Study subjects with early-childhood wheezing were divided into three groups positive for RV, RSV, and other viruses. Those 40 study subjects with PCR tests performed during the initial wheezing episode were included in the post hoc analysis to compare these viral wheezing groups. In post hoc analyses, all groups were compared to the control group, and viral wheezing groups were also compared to each other in paired comparisons.

2.5 | Ethics

The study was approved by the Ethics Committee of the Pohjois-Savo Health Care District (Permission number 76/2009, dated 20th January 2010). Informed written consent was obtained from all study subjects.

3 | RESULTS

3.1 | Respiratory symptoms and asthma

There were no statistically significant differences between cases and controls in terms of age and sex distribution or current daily smoking (Table 1). Likewise, there were no statistically significant differences in asthma-presumptive symptoms between cases with early-childhood wheezing and controls (Table 1). However, the use of on-demand bronchodilators and the use of continuous ICS during the past 12 months were more common in cases than in controls (Table 1). Atopic sensitization to animal dander but not to seasonal pollens was more common in cases than in controls (Table 1).

Current asthma was present in 53% of cases compared to 12% of controls (Table 1). In line with this, cases had significantly higher FE_{NO} values (mean [95%CI]; 29.2 ppb [19.0-39.6 ppb]) compared to controls (18.0 [14.5 - 21.3], $P = .027$). Pathological findings in the home PEF monitoring were present in 19% of cases and 9% of controls ($P = .184$).

3.2 | Viral findings in early childhood as risk factors for asthma and allergy

Among the 40 cases hospitalized for wheezing in early childhood with viral PCR available, RSV was detected in 14 cases (8 single RSV and 6 mixed infections). RV was detected in 18 cases (14 single RV and 4 mixed infections). Other detected viruses were parainfluenza 3 virus in 7 cases (4 single and 3 mixed infections), enterovirus in 3 cases (1 single and 2 mixed infections), and adenovirus in 3 cases (all mixed infections). The associations between viral aetiology of

TABLE 1 Basic characteristics, allergy, and asthma at age 17-20 years in study subjects with history of early-childhood wheezing episode compared to controls

	Early-childhood wheezing episode (N = 49) N (%)	Controls (N = 60) N (%)	OR (95% CI) ^a
Age, mean (95%CI)	18.8 (18.6-19.1)	18.7 (18.5-19.0)	$P = .403$
Sex (female)	19 (39)	33 (55)	0.52 (0.24-1.12)
Current daily smoking	16 (33)	18 (30)	1.97 (0.81-4.80)
Repeated wheezing ^b	16 (33)	12 (20)	2.72 (1.05-7.05)
Prolonged cough ^c	6 (12)	7 (12)	1.21 (0.35-4.22)
Repeated or chronic night cough	5 (10)	7 (12)	0.68 (0.18-2.54)
On-demand bronchodilators ^d	23 (47)	8 (13)	6.92 (2.57-18.62)
Inhaled corticosteroids ^e	10 (20)	5 (8)	3.38 (1.03-11.13)
Allergic rhinitis	27 (55)	30 (50)	1.53 (0.68-3.43)
Allergic conjunctivitis	24 (49)	25 (42)	1.56 (0.71-3.46)
Atopic eczema	16 (33)	14 (23)	1.97 (0.79-4.87)
Atopic sensitization ^f	34 (69)	31 (52)	2.08 (0.90-4.79)
Sensitization to animal dander ^f	30 (61)	18 (30)	3.51 (1.54-7.99)
Sensitization to seasonal pollens ^f	25 (51)	28 (47)	1.06 (0.48-2.38)
Current allergy ^g	28 (57)	27 (45)	1.72 (0.78-3.82)
Current asthma	26 (53)	7 (12)	11.4 (3.8-34.2)

^aOR, odds ratio; CI, confidence interval; all variables are adjusted for age, sex, current daily smoking, and in case of current asthma adjusted for age, sex, current daily smoking, and current allergy.

^bmore than 2 episodes during the last 12 mos.

^c4 wks or more apart from infection.

^duse of on-demand bronchodilators during the preceding 12 mos.

^euse of continuous inhaled corticosteroids during the preceding 12 mos.

^fpositive skin prick test reaction.

^gallergic disease and atopic sensitization combined.

early-childhood wheezing and asthma or atopy in adulthood were studied in three groups. The RV group consisted of 14 cases with RV alone. The RSV group consisted of 8 cases with RSV alone and 6 cases with mixed infections (parainfluenza 3 virus in 2 cases, enterovirus in 2 cases, RV in 1 case, and adenovirus and parainfluenza 3 virus in 1 case). The other viral aetiology group consisted of 4 cases with parainfluenza 3 infection, 2 cases with adenovirus and RV infection, 2 cases with enterovirus and RV infection, 1 case with enterovirus infection, and 4 cases with no detected viral aetiology.

Compared to controls, there was a higher risk for current asthma in study subjects with RV aetiology, RSV aetiology, and other viral

TABLE 2 Adulthood outcomes of early-childhood wheezing in relation to viral aetiology of initial wheezing episode in early childhood

	Viral aetiology of the wheezing episode			Controls N = 60 N (%)
	RV ^a N = 14 N (%) OR (95%CI)	RSV ^b N = 14 N (%) OR (95%CI)	Other viruses N = 12 N (%)OR (95%CI)	
Current asthma ^c	9 (64) 17.0 (3.9-75.3)	6 (43) 6.1 (1.5-24.9)	7 (58) 16.3 (2.9-91.4)	7 (12)
Atopic sensitization ^d	10 (71) 2.2 (0.6-8.0)	8 (57) 1.3 (0.4-4.2)	7 (75) 2.0 (0.5-8.8)	31 (52)
Sensitization to animal dander ^d	9 (64) 4.1 (1.2-14.1)	7 (50) 2.3 (0.7-7.7)	8 (67) 3.5 (0.9-14.0)	18 (30)
Sensitization to seasonal pollens ^d	7 (50) 1.1 (0.3-3.5)	6 (43) 0.9 (0.3-2.9)	7 (58) 1.1 (0.3-4.2)	28 (47)
Current allergy ^e	7 (50) 1.2 (0.4-4.0)	7 (50) 1.2 (0.4-4.0)	8 (67) 2.3 (0.6-8.9)	27 (45)

^aRhinovirus.^brespiratory syncytial virus.^cadjusted with age, sex, current allergy, and current daily smoking.^dpositive skin prick test reaction, logistic regression adjusted for age and sex.^eallergic disease and atopic sensitization combined, logistic regression adjusted for age and sex.

aetiology of early-childhood wheezing (Table 2). There were no statistically significant differences between viral wheezing groups in paired comparisons (data not shown). Sensitization to animal dander was more common in study subjects with RV aetiology of initial wheezing compared to controls, but there were no statistically significant differences between the viral wheezing groups in atopic sensitization or current allergy (Table 2). FE_{NO} values were significantly higher in cases with RV aetiology of early-childhood wheezing compared to controls and to the RSV aetiology group (Figure 1).

3.3 | Lung function

There were no significant differences between subjects hospitalized for wheezing in early childhood and controls in FVC, FEV1, or FEV1/FVC before or after bronchodilator inhalation (Figure 2). Pre-BD MEF50 was significantly lower in cases than in controls (Figure 2). In the bronchodilation test, the mean FVC response was 0.3% (95% CI, -0.5 - 1.1) in cases and -0.2% (-1.0 - 0.6) in controls ($P = .367$, adjusted for current daily smoking). Respective responses in FEV1 were 4.7% (3.3 - 6.2) in cases and 3.2% (1.7 - 4.6) in controls ($P = .109$), in FEV1/FVC 4.5% (3.2 - 5.9) in cases and 3.7% (2.3 - 5.0) in controls ($P = .344$), and in MEF50 16.8% (11.9 - 21.7) in cases and 12.0% (7.2 - 16.9) in controls ($P = .140$).

3.4 | Lung function in relation to viral aetiology of early-childhood wheezing illness

Lung function was evaluated in relation to the causative viral agent of early-childhood wheezing. Rhinovirus-positive cases had significantly lower pre-BD MEF50 (Table 3) and significantly higher

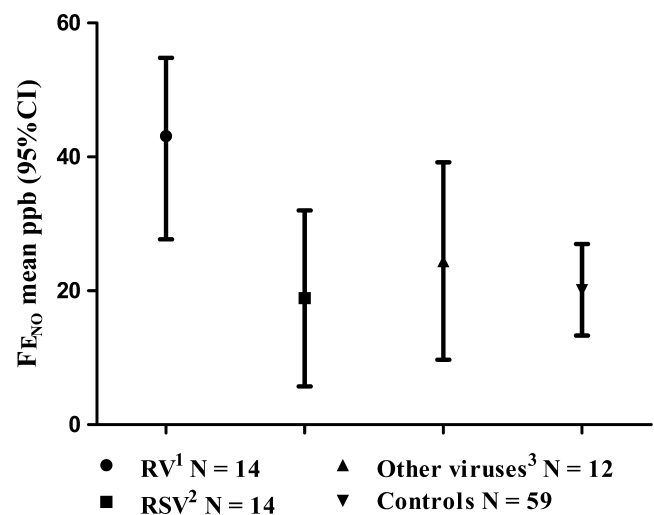


FIGURE 1 Fractionally exhaled nitric oxide (FE_{NO}) values (mean ppb, 95%CI) in adulthood in relation to viral aetiology of the initial wheezing episode in early childhood. ¹Rhinovirus vs controls $P = .002$, vs RSV $P = .015$, vs other viruses $P = .061$, ²respiratory syncytial virus vs controls $P = .924$, vs other viruses $P = .646$, ³other viruses vs controls $P = .518$; all P -values are adjusted with age, sex, current smoking, and current allergy

MEF50 responses to bronchodilators than controls (Table 4). Furthermore, FEV1 and FEV1/FVC responses to bronchodilators were higher in cases with RV-induced wheezing in early childhood compared to controls (Table 4). RSV-positive cases had significantly lower pre-BD FVC values compared to controls (Table 3), but there were no significant differences between RSV group and controls in responses to bronchodilators (Table 4). There were no significant differences in lung function between the three viral wheezing groups (data not shown).

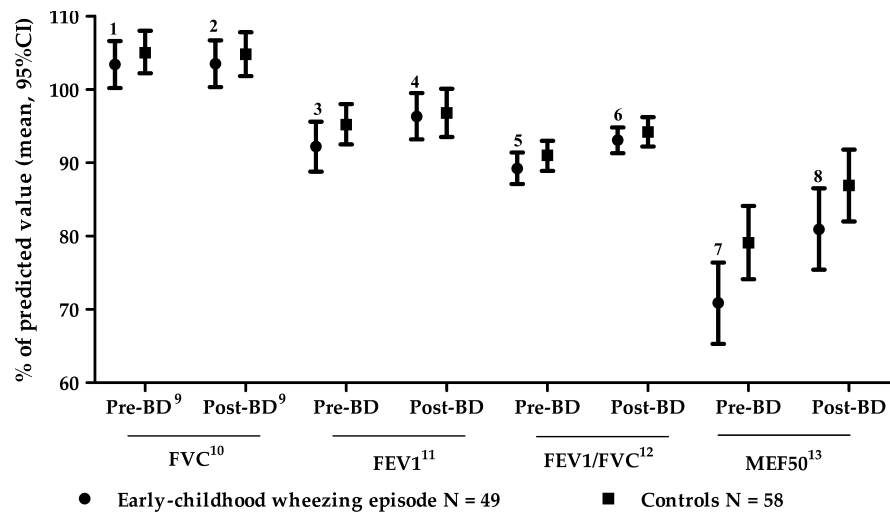


FIGURE 2 Lung function at the age of 17-20 years in study subjects hospitalized for wheezing in early childhood compared to population controls. Comparison between cases with an early-childhood wheezing episode and controls adjusted for current smoking; *P*-values: ¹0.405, ²0.515, ³0.156, ⁴0.365, ⁵0.285, ⁶0.444, ⁷**0.030**, ⁸0.100. ⁹Pre-BD, pre-bronchodilation test; post-BD, post-bronchodilation test, ¹⁰FVC, forced vital capacity (% of predicted value), ¹¹FEV1, forced expiratory volume in one-second (% of predicted value), ¹²FEV1/FVC, FEV1/FVC ratio presented as % of predicted value, ¹³MEF50, maximum expiratory flow after 50% of expired FVC (% of predicted value)

TABLE 3 Lung function at the age of 17-20 years in relation to viral aetiology of the initial wheezing episode in early childhood

	Viral aetiology of the wheezing episode			Controls N = 60 mean % (95% CI)
	RV ^a N = 14 mean % (95% CI) P-value ^c	RSV ^b N = 14 mean % (95% CI) P-value ^c	Other viruses N = 12 mean % (95% CI) P-value ^c	
FVC ^d				
Pre-BD ^e	104 (98-110) .649	98 (92-104) .041	107 (100-114) .654	105 (102-108)
Post-BD ^e	104 (98-110) .794	99 (93-104) .059	107 (101-114) .579	105 (102-108)
FEV1 ^f				
Pre-BD ^e	90 (84-96) .135	90 (84-96) .139	96 (90-103) .723	95 (92-98)
Post-BD ^e	96 (90-102) .511	93 (87-99) .134	100 (94-106) .571	98 (95-101)
FEV1/FVC ^g				
Pre-BD ^e	87 (83-91) .120	91 (87-95) .811	90 (85-95) .821	91 (88-93)
Post-BD ^e	92 (88-96) .439	94 (90-98) .815	93 (89-97) .717	94 (92-96)
MEF50 ^h				
Pre-BD ^e	64 (54-75) .015	75 (65-86) .548	76 (65-88) .676	79 (73-84)
Post-BD ^e	76 (65-86) .051	85 (75-96) .749	88 (77-96) .818	87 (82-92)

^aRhinovirus-positive cases.

^brespiratory syncytial virus-positive cases.

^canalysis of variance, comparisons vs control group adjusted with current daily smoking.

^dFVC, forced vital capacity (% of predicted value).

^epre-BD, pre-bronchodilation test, post-BD, post-bronchodilation test.

^fFEV1, forced expiratory volume in one-second (% of predicted value).

^gFEV1/FVC, FEV1/FVC ratio presented as % of predicted value.

^hMEF50, maximum expiratory flow after 50% of expired FVC (% of predicted value).

TABLE 4 Bronchial responses in the bronchodilation test at the age of 17-20 years in relation to viral aetiology of the initial wheezing episode in early childhood

	Viral aetiology of the wheezing episode			Controls N = 60 mean % (95% CI)
	RV ^a N = 14 mean % (95% CI) P-value ^c	RSV ^b N = 14 mean % (95% CI) P-value ^c	Other viruses N = 12 mean % (95% CI) P-value ^c	
FVC ^d BD response	0.6 (−0.8-2.0) .337	0.5 (−0.9-1.9) .394	0.4 (−1.1-1.9) .527	−0.1 (−0.9-0.6)
FEV1 ^e BD response	6.9 (4.1-9.6) .019	3.8 (1.2-6.5) .699	3.9 (1.1-6.8) .670	3.2 (1.9-4.6)
FEV1/FVC ^f BD response	6.5 (4.0-9.0) .041	3.5 (1.1-6.0) .927	3.5 (0.9-6.2) .911	3.7 (2.4-4.9)
MEF50 ^g BD response	22.7 (13.6-31.7) .037	15.9 (7.1-24.7) .450	16.2 (6.6-25.8) .448	12.2 (7.6-16.7)

^aRhinovirus-positive cases.^brespiratory syncytial virus-positive cases.^canalysis of variance, comparisons vs control group adjusted with current daily smoking.^dFVC, forced vital capacity (% of predicted value).^eFEV1, forced expiratory volume in one-second (% of predicted value).^fFEV1/FVC, FEV1/FVC ratio presented as % of predicted value.^gMEF50, maximum expiratory flow after 50% of expired FVC (% of predicted value).

4 | DISCUSSION

The main objective of this controlled study was to evaluate the long-term outcome of early-childhood wheezing in relation to viral aetiology of the initial wheezing episode. At the age of 17-20 years, the prevalence of current asthma and measured FE_{NO} values were significantly higher in cases compared to controls. RV, RSV, and other viral aetiology of the wheezing episode were associated with increased risk for asthma in young adulthood with no significant differences between these three viral wheezing groups. However, RV aetiology was associated with higher FE_{NO} values in adulthood compared to controls or to the RSV aetiology group. Study subjects with early-childhood wheezing showed more bronchial reactivity to bronchodilators in lung function testing, and these changes were more pronounced in cases with the RV-induced wheezing episode. Compared to controls, RSV-induced wheezing in early childhood was associated with lower pre-BD FVC in young adulthood, without significant differences in responses in the bronchodilation test).

The majority of children who suffer from wheezing in early childhood are asymptomatic later in life.^{2,3,23,24} However, many prospective cohorts have demonstrated that early-childhood wheezers have an increased risk of suffering from asthma later in childhood,^{15,16,25-29} adolescence,^{4,17,30,31} and even in adulthood.^{2,3,32} In this follow-up, current asthma was present in 53% of cases and 12% of controls. Thus, the prevalence of asthma after early-childhood wheezing observed in the present study is in line with a few comparable prospective studies which have demonstrated a 30%-64% prevalence of asthma at the age of 15-20 years after hospitalization for early-childhood wheezing.^{4,9,30,31} This difference in the prevalence of asthma was reinforced by significantly higher FE_{NO} values in the wheezing group compared to controls. In line with this, the use of

on-demand bronchodilators and continuous ICS was significantly more common in cases compared to controls. The rather similar prevalence of asthma-presumptive symptoms may at least partly reflect the high proportion of treated asthma in cases.

It is evident that the viral aetiology of the wheezing episode has a significant role in the long-term outcome after early-childhood wheezing.⁶ RSV-induced wheezing in early childhood has been associated with an increased risk for asthma in childhood.^{11,29,33} However, the later outcome is controversial, and it has been suggested that this association becomes insignificant in school-aged children.¹² In the present study, RV, RSV, and other viral aetiologies of the initial wheezing episode were associated with a higher risk for asthma in adulthood compared to controls. Our results are in line with studies which have demonstrated that increased risk for asthma is still present in adulthood after hospitalization for RSV-induced wheezing in early childhood.^{4,32,34}

In 2003, it was demonstrated for the first time in the current cohort that later asthma risk is even higher if the wheezing episode in early childhood is triggered by viruses other than RSV, especially RV.⁸ This finding has later been verified in other cohorts.^{10,35,36} On the other hand, a Danish study concluded that the number of respiratory infections in the first years of life but not the particular viral trigger was associated with later asthma development until the age of 7 years.³⁷ However, children recruited to that cohort were born to mothers with asthma, and respiratory tract infections were not necessarily associated with wheezing and hospitalization, which may at least partly explain the conflicting results.³⁷ In the present study, the risk of asthma in young adults was higher after RV-induced early-childhood wheezing compared to RSV-induced wheezing, but due to the small group sizes, this difference was not statistically significant.

Atopic children seem to be more prone to wheezing symptoms during RV infection compared to non-atopic children.^{8,33,38,39} Therefore, it has been suggested that RV-induced wheezing in children may merely be a sign of individual predisposition for asthma.^{6,7,40} In the present follow-up, RV aetiology of early-childhood wheezing was associated with higher risk of sensitization to animal dander in adulthood compared to controls, but not with current allergic symptoms. RSV aetiology was not associated with current allergy in adulthood. In both cases, an increased risk for asthma was robust to adjustment for current allergy, and thus independent from current allergy in adulthood.

The value of FeNO in phenotyping of asthma is unknown.⁴¹ However, it is known that eosinophilic inflammation in the airways is most pronounced in atopic asthma, and the concentration of nitric oxide is related to eosinophilic inflammation in the airways.^{41,42} FeNO values were significantly higher in the RV group than in controls and in the RSV group, which may be a sign of higher prevalence of eosinophilic inflammation in the airways in initially RV-positive cases. These results suggest that both RV- and RSV-induced wheezing episodes in early childhood are associated with asthma even in adulthood, but perhaps with different asthma phenotypes. This finding needs to be confirmed in larger cohorts, but it is coherent with previous findings about the association between RV-induced wheezing and atopic diseases.^{8,33,38,39} Our results are also consistent with previous findings that FeNO values are not increased in adulthood after RSV infection of the lower respiratory tract during infancy.^{4,32}

Numerous studies have demonstrated that lung function abnormalities are present later in childhood, in adolescence, and in early adulthood after hospitalization for early-childhood wheezing.^{1,4,11,43-45} In the present study, cases with a history of early-childhood wheezing illness had significantly lower MEF50 values before bronchodilation compared to controls. However, this difference was not seen after bronchodilation, suggesting greater bronchial responses for bronchodilating drugs in small airways. RV aetiology was associated with lower MEF50 values before bronchodilation, while RSV aetiology was associated with lower FVC values before bronchodilation. Study subjects with other viral aetiology did not differ significantly from controls in terms of lung function. FEV1, FEV1/FVC, and MEF50 responses in the bronchodilation test were significantly higher in the RV group compared to controls.

Even though the differences in lung function parameters were small, lower FVC before bronchodilation after RSV-induced wheezing and greater bronchial reactivity after RV-induced wheezing found in the present study seem to reflect permanent patterns of lung function in relation to the viral aetiology of early-childhood wheezing. Similar findings have been demonstrated previously in the same cohort.^{44,46} In addition, other studies have also demonstrated lower lung function, but no bronchial hyperresponsiveness in the bronchodilation test in adolescents and adults after RSV-induced wheezing in early childhood.^{11,32,47} Very few studies have examined the effects of RV infection on future lung function, and they have associated early-childhood RV-induced wheezing with bronchial

hyperresponsiveness in childhood.^{44,48} However, until now, the adulthood outcome has remained unknown. In the current study setting, we are not able to determine whether or not the lung function patterns found in the study subjects with RV- or RSV-induced wheezing histories are induced by early viral infections or merely reflect the lung function patterns already present before the viral infection occurred. However, it seems that lower FVC after RSV infection and signs of increased bronchial reactivity to bronchodilating drugs after RV infection that are already present in childhood remain unchanged up to the age of 17-20 years.⁴⁶

The strengths of the present prospective controlled study are the long follow-up time and careful collection of data during enrolment of study subjects, which included advanced methods of viral detection. At the time of enrolment in the 1990s, Kuopio University Hospital served as the only hospital in the area for children who needed hospitalization, which means that the study population is an unbiased cohort of hospitalized children with early-childhood wheezing in the area. Unselected population controls, matched for age and sex, were recruited from the hospital district for the present study in adulthood. The main shortcoming of the study is that the number of study subjects was small, and this may affect the results and increase the possibility of type 2 statistical error especially in comparison with viral wheezing groups. However, long-term follow-up studies after RV-induced wheezing are scarce, which adds to the importance of the current results. Combining study subjects with no viruses detected in other viral aetiology group can be justified with current findings that viral aetiology can be detected in all children with early-childhood wheezing illness.³⁸ For example, bocavirus and metapneumovirus detections were not available at the time of the primary hospital admission. In our study, the 12% prevalence of asthma and 42% prevalence of allergic rhinitis in unselected controls are well in line with 10% prevalence of asthma and 44% prevalence of allergic rhinitis in Finnish adult population.⁴⁹

In conclusion, study subjects with an early-childhood wheezing episode, induced by RV, RSV, or other viruses have an increased risk for asthma at the age of 17-20 years compared to controls without such wheezing history. Cases with RV aetiology of early-childhood wheezing had significantly higher FE_{NO} values compared to RSV-positive cases and controls, which suggests eosinophilic inflammation in the airways of former RV patients. Compared to controls, cases with RV-induced early-childhood wheezing showed more bronchial reactivity in the bronchodilation test and RSV-induced wheezing in early childhood was associated with lower pre-BD FVC in young adulthood, without significant differences in responses to bronchodilators.

ACKNOWLEDGEMENTS

The authors are grateful to Satu Korpi, RN, and Anneli Paloranta, RN, for their skilful and professional work during the study. Orion Pharma is acknowledged for providing inhaled bronchodilators for use during the home PEF monitoring.

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

ORCID

K. Backman  <http://orcid.org/0000-0001-5683-407X>

REFERENCES

- Backman K, Piippo-Savolainen E, Ollikainen H, Koskela H, Korppi M. Irreversible airway obstruction in adulthood after bronchiolitis in infancy: evidence from a 30-year follow-up study. *Respir Med*. 2014;108:218-223.
- Backman K, Piippo-Savolainen E, Ollikainen H, Koskela H, Korppi M. Increased asthma risk and impaired quality of life after bronchiolitis or pneumonia in infancy. *Pediatr Pulmonol*. 2014;49:318-325.
- Goksor E, Amark M, Alm B, Ekerljung L, Lundback B, Wennergren G. High risk of adult asthma following severe wheezing in early life. *Pediatr Pulmonol*. 2015;50:789-797.
- Sigurs N, Aljassim F, Kjellman B, et al. Asthma and allergy patterns over 18 years after severe RSV bronchiolitis in the first year of life. *Thorax*. 2010;65:1045-1052.
- Jartti T, Lehtinen P, Vuorinen T, Ruuskanen O. Bronchiolitis: age and previous wheezing episodes are linked to viral etiology and atopic characteristics. *Pediatr Infect Dis J*. 2009;28:311-317.
- Rossi GA, Colin AA. Infantile respiratory syncytial virus and human rhinovirus infections: respective role in inception and persistence of wheezing. *Eur Respir J*. 2015;45:774-789.
- Jartti T, Korppi M. Rhinovirus-induced bronchiolitis and asthma development. *Pediatr Allergy Immunol*. 2011;22:350-355.
- Kotaniemi-Syrjanen A, Vainionpaa R, Reijonen TM, Waris M, Korhonen K, Korppi M. Rhinovirus-induced wheezing in infancy—the first sign of childhood asthma? *J Allergy Clin Immunol*. 2003;111:66-71.
- Ruotsalainen M, Hyvarinen MK, Piippo-Savolainen E, Korppi M. Adolescent asthma after rhinovirus and respiratory syncytial virus bronchiolitis. *Pediatr Pulmonol*. 2013;48:633-639.
- Jackson DJ, Gangnon RE, Evans MD, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med*. 2008;178:667-672.
- Stein RT, Sherrill D, Morgan WJ, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet*. 1999;354:541-545.
- Regnier SA, Huels J. Association between respiratory syncytial virus hospitalizations in infants and respiratory sequelae: systematic review and meta-analysis. *Pediatr Infect Dis J*. 2013;32:820-826.
- Korppi M, Kotaniemi-Syrjanen A, Waris M, Vainionpaa R, Reijonen TM. Rhinovirus-associated wheezing in infancy: comparison with respiratory syncytial virus bronchiolitis. *Pediatr Infect Dis J*. 2004;23:995-999.
- Reijonen TM, Korppi M. One-year follow-up of young children hospitalized for wheezing: the influence of early anti-inflammatory therapy and risk factors for subsequent wheezing and asthma. *Pediatr Pulmonol*. 1998;26:113-119.
- Reijonen TM, Kotaniemi-Syrjanen A, Korhonen K, Korppi M. Predictors of asthma three years after hospital admission for wheezing in infancy. *Pediatrics*. 2000;106:1406-1412.
- Kotaniemi-Syrjanen A, Reijonen TM, Korhonen K, Korppi M. Wheezing requiring hospitalization in early childhood: predictive factors for asthma in a six-year follow-up. *Pediatr Allergy Immunol*. 2002;13:418-425.
- Hyvarinen MK, Kotaniemi-Syrjanen A, Reijonen TM, Korhonen K, Korppi MO. Teenage asthma after severe early childhood wheezing: an 11-year prospective follow-up. *Pediatr Pulmonol*. 2005;40:316-323.
- Reijonen T, Korppi M, Kuikka L, Remes K. Anti-inflammatory therapy reduces wheezing after bronchiolitis. *Arch Pediatr Adolesc Med*. 1996;150:512-517.
- Miller MR, Hankinson J, Brusasco V, et al. ATS/ERS Task Force. Standardisation of spirometry. *Eur Respir J*. 2005;26:319-338.
- Quanjer PH, Lebowitz MD, Gregg I, Miller MR, Pedersen OF. Peak expiratory flow: conclusions and recommendations of a Working Party of the European Respiratory Society. *Eur Respir J Suppl*. 1997;24:2S-8S.
- American Thoracic Society, European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med*. 2005;171:912-930.
- Viljanen AA, Halttunen PK, Kreis KE, Viljanen BC. Spirometric studies in non-smoking, healthy adults. *Scand J Clin Lab Invest Suppl*. 1982;159:5-20.
- Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med*. 1995;332:133-138.
- Morgan WJ, Stern DA, Sherrill DL, et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. *Am J Respir Crit Care Med*. 2005;172:1253-1258.
- Korppi M, Reijonen T, Poysa L, Juntunen-Backman K. A 2- to 3-year outcome after bronchiolitis. *Am J Dis Child*. 1993;147:628-631.
- Kuikka L, Reijonen T, Remes K, Korppi M. Bronchial asthma after early childhood wheezing: a follow-up until 4.5-6 years of age. *Acta Paediatr*. 1994;83:744-748.
- Wennergren G, Hansson S, Engstrom I, et al. Characteristics and prognosis of hospital-treated obstructive bronchitis in children aged less than two years. *Acta Paediatr*. 1992;81:40-45.
- Wennergren G, Amark M, Amark K, Oskarsdottir S, Sten G, Redfors S. Wheezing bronchitis reinvestigated at the age of 10 years. *Acta Paediatr*. 1997;86:351-355.
- Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. *Am J Respir Crit Care Med*. 2000;161:1501-1507.
- Piippo-Savolainen E, Remes S, Kannisto S, Korhonen K, Korppi M. Asthma and lung function 20 years after wheezing in infancy: results from a prospective follow-up study. *Arch Pediatr Adolesc Med*. 2004;158:1070-1076.
- Goksor E, Amark M, Alm B, Gustafsson PM, Wennergren G. Asthma symptoms in early childhood—what happens then? *Acta Paediatr*. 2006;95:471-478.
- Backman K, Piippo-Savolainen E, Ollikainen H, Koskela H, Korppi M. Adults face increased asthma risk after infant RSV bronchiolitis and reduced respiratory health-related quality of life after RSV pneumonia. *Acta Paediatr*. 2014;103:850-855.
- Jackson DJ, Evans MD, Gangnon RE, et al. Evidence for a causal relationship between allergic sensitization and rhinovirus wheezing in early life. *Am J Respir Crit Care Med*. 2012;185:281-285.
- Diez-Domingo J, Perez-Yarza EG, Melero JA, et al. Social, economic, and health impact of the respiratory syncytial virus: a systematic search. *BMC Infect Dis*. 2014;14:544.
- Kusel MM, de Klerk NH, Keadze T, et al. Early-life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma. *J Allergy Clin Immunol*. 2007;119:1105-1110.
- Koponen P, Helminen M, Paasilta M, Luukkaala T, Korppi M. Preschool asthma after bronchiolitis in infancy. *Eur Respir J*. 2012;39:76-80.
- Bonnelykke K, Vissing NH, Sevelsted A, Johnston SL, Bisgaard H. Association between respiratory infections in early life and later asthma is independent of virus type. *J Allergy Clin Immunol*. 2015;136:81, 86.e4.

38. Turunen R, Koistinen A, Vuorinen T, et al. The first wheezing episode: respiratory virus etiology, atopic characteristics, and illness severity. *Pediatr Allergy Immunol*. 2014;25:796-803.
39. Jartti T, Kuusipalo H, Vuorinen T, et al. Allergic sensitization is associated with rhinovirus-, but not other virus-, induced wheezing in children. *Pediatr Allergy Immunol*. 2010;21:1008-1014.
40. Beigelman A, Bacharier LB. The role of early life viral bronchiolitis in the inception of asthma. *Curr Opin Allergy Clin Immunol*. 2013;13:211-216.
41. Lehtimäki L, Csonka P, Mäkinen E, Isojärvi J, Hovi SL, Ahovuo-Saloranta A. Predictive value of exhaled nitric oxide in the management of asthma: a systematic review. *Eur Respir J*. 2016;48:706-714.
42. Petsky HL, Kew KM, Turner C, Chang AB. Exhaled nitric oxide levels to guide treatment for adults with asthma. *Cochrane Database Syst Rev*. 2016;9:CD011440.
43. Sigurs N, Gustafsson PM, Bjarnason R, et al. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. *Am J Respir Crit Care Med*. 2005;171:137-141.
44. Kotaniemi-Syrjänen A, Reijonen TM, Korhonen K, Waris M, Vainionpää R, Korppi M. Wheezing due to rhinovirus infection in infancy: bronchial hyperresponsiveness at school age. *Pediatr Int*. 2008;50:506-510.
45. Goksor E, Gustafsson PM, Alm B, Amark M, Wennergren G. Reduced airway function in early adulthood among subjects with wheezing disorder before two years of age. *Pediatr Pulmonol*. 2008;43:396-403.
46. Hyvärinen MK, Kotaniemi-Syrjänen A, Reijonen TM, Korhonen K, Korppi MO. Lung function and bronchial hyper-responsiveness 11 years after hospitalization for bronchiolitis. *Acta Paediatr*. 2007;96:1464-1469.
47. Korppi M, Piippo-Savolainen E, Korhonen K, Remes S. Respiratory morbidity 20 years after RSV infection in infancy. *Pediatr Pulmonol*. 2004;38:155-160.
48. Guilbert TW, Singh AM, Danov Z, et al. Decreased lung function after preschool wheezing rhinovirus illnesses in children at risk to develop asthma. *J Allergy Clin Immunol*. 2011;128:532.e1-10.
49. Kainu A, Pallasaho P, Piirila P, Lindqvist A, Sovijärvi A, Pietinalho A. Increase in prevalence of physician-diagnosed asthma in Helsinki during the Finnish Asthma Programme: improved recognition of asthma in primary care? A cross-sectional cohort study. *Prim Care Respir J*. 2013;22:64-71.

How to cite this article: Backman K, Ollikainen H, Piippo-Savolainen E, Nuolivirta K, Korppi M. Asthma and lung function in adulthood after a viral wheezing episode in early childhood. *Clin Exp Allergy*. 2017;00:1–9. <https://doi.org/10.1111/cea.13062>