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Asthma, atopy and lung function in young adults after hospitalisation for bronchiolitis in infancy: impact of virus and sex

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ABSTRACT

Background Hospitalisation for bronchiolitis is a risk factor for asthma and impaired lung function during childhood, but outcomes in young adults are poorly described. Our primary aim was to study the prevalence of asthma and atopy, and lung function at 17–20 years of age after bronchiolitis in infancy and, secondarily, the impact of viral aetiology (respiratory syncytial virus (RSV) vs non-RSV) and sex on these outcomes.

Methods This Norwegian cohort study enrolled 225 young adults hospitalised for bronchiolitis in infancy during 1996–2001 and 167 matched control subjects. The follow-up included questionnaires for asthma and examinations of lung function and atopy. Outcomes were analysed by mixed effects regressions.

Results Current asthma was more frequent in the postbronchiolitis group versus the control group: 25.1% (95% CI 19.0% to 31.2%) vs 13.1% (95% CI 7.9% to 18.2%), but not atopy: 44.3% (95% CI 37.1% to 51.5%) vs 48.2% (95% CI 40.5% to 55.8%), adjusted predicted proportions (95% CIs). Asthma prevalence did not differ between the RSV group and the non-RSV group: 24.0% (95% CI 16.1% to 32.0%) vs 23.8% (95% CI 12.8% to 34.7%) nor between sexes. Forced expiratory volume in 1 s (FEV_1), the ratio FEV_1/forced vital capacity (FVC), and forced expiratory flow between 25% and 75% of FVC, were lower in the postbronchiolitis group.

Conclusion Young adults hospitalised for bronchiolitis had higher prevalence of asthma, but not atopy, and a more obstructive lung function pattern than control subjects. The asthma prevalence was high after both RSV bronchiolitis and non-RSV bronchiolitis, and there was no difference between sexes. Bronchiolitis in infancy is associated with respiratory morbidity persisting into young adulthood.

Key messages

- Key question: What are the long-term outcomes of bronchiolitis in infancy regarding the prevalence of asthma and atopy, and lung function at 17–20 years of age, and how do viral aetiology (respiratory syncytial virus (RSV) vs non-RSV) and sex impact on these outcomes?
- Young adults hospitalised for bronchiolitis had more asthma and a more obstructive lung function pattern, but similar prevalence of atopy compared with control subjects. The asthma prevalence was high after both RSV bronchiolitis and non-RSV bronchiolitis, and there was no difference between sexes.
- This is the largest cohort study of respiratory outcomes in young adults after hospitalisation for bronchiolitis in infancy, and shows that bronchiolitis is associated with respiratory morbidity persisting into young adulthood. This is important as even mild lung function impairment may be a predictor of later cardiorespiratory morbidity and mortality.

INTRODUCTION

Bronchiolitis is a viral lower respiratory tract infection commonly seen in children less than 1 year of age.[1 2] Bronchiolitis constitutes a substantial health burden worldwide, and is the most common reason for admission to hospital during infancy in high-income countries.[3 4] Children hospitalised for bronchiolitis have increased risk of subsequent asthma and impaired lung function later in childhood.[2 5–8]

The risk of asthma after bronchiolitis is related to the virus involved.[2 7] The highest risk of asthma has been observed in children with bronchiolitis caused by other viruses than respiratory syncytial virus (RSV),[7] and particularly by human rhinovirus (HRV).[9 10] Whereas asthma after RSV bronchiolitis seems to be linked to a T-helper cell (Th)1 dominated inflammatory response and structural airway damage, asthma after non-RSV bronchiolitis such as HRV bronchiolitis, is probably more related to atopy and a Th2 dominated eosinophilic inflammation.[11–13]

Few studies have evaluated the impact of sex on respiratory outcomes in young adults with a previous history of bronchiolitis, but in general the risk of asthma is related to sex. During childhood the prevalence of asthma is higher in males, but after a switch during

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puberty females have a higher prevalence in adulthood.[14 15]

Knowledge regarding long-term respiratory morbidity in adults with former bronchiolitis is limited, but a few small studies have reported a sustained increased risk of asthma and lower lung function.[6 16 17] A Finnish study reported irreversible airway obstruction at 30 years of age after severe bronchiolitis in infancy,[18] which may suggest permanent structural alterations in the airways, in line with studies indicating that bronchiolitis predisposes to the development of chronic obstructive pulmonary disease (COPD).[19–21] COPD is a major public health problem,[22] and improved insights into how early life respiratory tract infections influence subsequent development of respiratory morbidity is therefore of great importance.

We hypothesised that young adults hospitalised for bronchiolitis in infancy have a higher risk of asthma and lower lung function, but similar prevalence of atopy compared with control subjects. Our primary aim was to study the prevalence of asthma and atopy, and lung function at 17–20 years of age after bronchiolitis in infancy and, secondarily, the impact of viral aetiology (RSV vs non-RSV) and sex on these outcomes.

METHODS

Study design

This is a historical cohort study of young adults hospitalised for bronchiolitis in infancy and a matched control group.

Postbronchiolitis group

Between October 1996 and May 2001, 1168 children under 1 year of age were discharged from the University Hospitals in Stavanger and Bergen, Norway with a diagnosis of acute bronchiolitis, and were potentially eligible for invitation to this study (figure 1). Exclusion criteria were use of inhaled or systemic corticosteroids prior to the hospitalisation, previous hospitalisation for bronchiolitis, severe neonatal or other pre-existing chronic lung disease and prematurity <32 weeks of gestation. Among eligible subjects, 131 have previously participated in a longitudinal prospective follow-up study at 11 years of age.[7 23] Information regarding eligibility and data from the hospital stay for bronchiolitis were obtained retrospectively by review of medical records.

Control group

A control group not hospitalised for bronchiolitis, but matched on date of birth, sex and gestational age at birth was established by searching the hospital's birth protocols. The next-born eligible person to each individual index postbronchiolitis participant was invited. If the first invited person declined, the next was invited and so on until one control was recruited for each index or a maximum of ten invitations were sent.

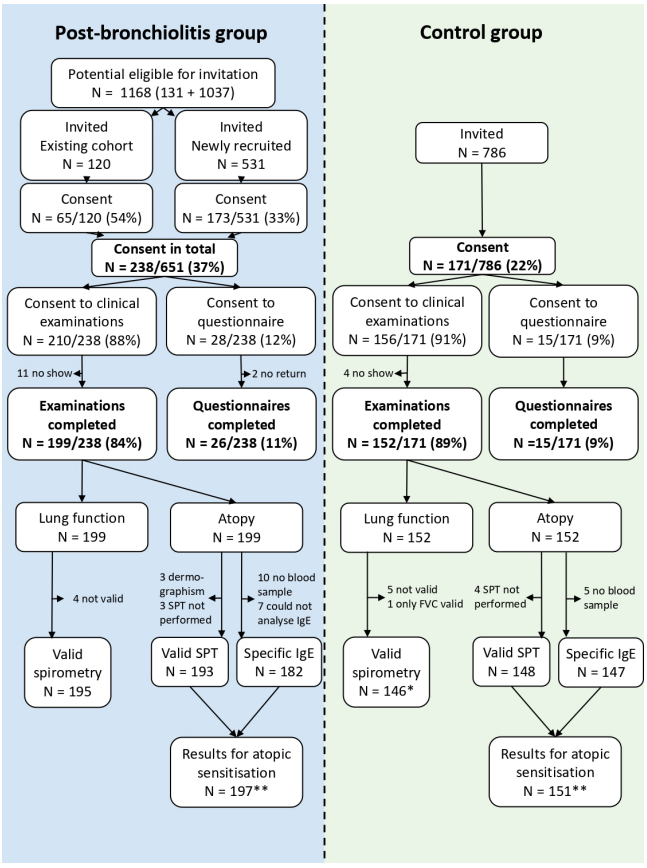

Figure 1 Overview of participants in the postbronchiolitis group and the control group. *N=147 for FVC. **Three subjects in the postbronchiolitis group and one control subject had positive allergen panels (Phadiatop and/or fx5E), but no tested specific IgEs>0.35 kU/L. These were defined as atopic subjects. FVC, forced vital capacity; SPT, skin prick test.

Exposures

Bronchiolitis was defined as an acute viral respiratory tract infection during the first year of life with fever, tachypnoea, dyspnoea, prolonged expiration and wheeze on auscultation.[1] During hospitalisation for bronchiolitis, nasopharyngeal mucus was examined for RSV by direct immunofluorescence (*BioMèrieux, Marcy-l'Ètoile, France*). Other viruses were not systematically tested for. Infants testing positive for RSV were defined as having RSV bronchiolitis and infants testing negative as having non-RSV bronchiolitis.

Outcomes

Asthma symptoms were recorded by a questionnaire based on the International Study of Asthma and Allergies in Childhood.[24] Asthma ever was defined as a positive answer to have you ever been diagnosed with asthma by a doctor? Current asthma was defined as asthma ever and a positive answer to at least one of the two questions: (1) Have you during the last 12 months had heavy breathing or wheezing/chest-tightness (2) Have you during the last 12 months used any asthma medications (inhaled

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corticosteroids (ICS), long-acting or short-acting beta-2-agonists, montelukast, ipratropium bromide; any combination).

Atopy was defined as either a positive skin prick test defined as a weal diameter ≥3 mm larger than the negative control (Soluprick allergens (ALK Albello, Hørsholm, Denmark)),[25] and/or a positive allergen panel or specific immunoglobuline E (IgE) >0.35 kU/L for one of the following allergens: Dermatophagoides pteronyssinus, dog and cat dander, Cladosporium herbarium, birch, timothy, egg white, milk, peanut, hazelnut and codfish. Serum were analysed for ImmunoCAP hazelnut and the allergen panels Phadiatop and fx5E (Thermo Fisher Scientific, Phadia AB, Uppsala, Sweden). If positive panels, specific IgE was analysed.

Lung function was measured by spirometry according to established guidelines,[26] using V_{max} Encore 229D spirometer (Sensor Medics, Anaheim, USA). Variables recorded were forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), FEV_1/FVC-ratio and forced expiratory flow between 25% and 75% of the FVC (FEF_{25-75}), all standardised for age, height and sex[27] and presented as z-score and percentage of predicted.

Clinical examinations were performed from April 2015 to March 2020.

Covariates/confounders

Prior to the analyses, factors possibly influencing both the exposure and outcomes were identified as potential confounders as illustrated in a directed acyclic graph (online supplemental figure 1).

Birth weight and gestational age at birth were collected retrospectively from birth protocols. Anthropometry was measured by study nurses or collected from questionnaires for those not participating in the clinical examinations. Use of asthma medication, personal and family history of atopy, and smoking were collected through questionnaires. Personal smoking was defined as a positive answer to do you smoke. Ever household smoking was defined as a positive answer to do/did anyone smoke in your home. Missing values were interpreted as negative answer. Atopic dermatitis was defined as a positive answer to have you ever had atopic dermatitis, and family history of atopy as a positive answer to do you know if your mother, father or siblings have or have had atopic dermatitis, asthma or positive allergy tests.

Statistical analysis

Continuous data were presented as mean with SD and compared by Student's t-test if normally distributed, or as median and IQR and compared by Mann-Whitney U-test if not normally distributed. Categorical data were presented as count and percentage, and compared by Pearson χ^2 test. Categorical outcomes were analysed by mixed effects logistic regression and presented as OR with 95% CI and predicted proportion with 95% CI. Continuous outcomes were analysed by mixed effects linear regression and presented as regression coefficient (β) with 95% CI and predictive margin with 95% CI. P values from Wald test are given for OR and β. Potential correlations between matched individuals were allowed for by including a random intercept term in the models. All effect estimates were adjusted for age and potential confounders. The impact of sex was assessed by including an interaction term between sex and group (ie, postbronchiolitis vs control), whereas the RSV group and non-RSV group were directly compared with each other.

To investigate possible confounding and mediating effects of various variables on the association between bronchiolitis and subsequent asthma, one by one of these variables were added to the model. Changes in OR ≥10% were considered clinically important.[28]

SPSS V.26.0 (IBM) and Stata V.16.1 (StataCorp) were used for analyses. Values of $p<0.05$ were considered statistically significant.

Power

Statistical power analyses were performed prior to study start using SPSS Sample Power V.3 (IBM) with power set to 80% and significance level to 0.05. To detect an absolute difference of 10% in the occurrence of asthma or atopy in the postbronchiolitis group compared with the control group, 199 subjects were needed in each group. We assumed this to be clinically relevant and reasonable considering the results from other studies.[16 29] To detect a clinically relevant absolute difference of 5% in FEV_1, 64 subjects needed to be included in each group.[18]

Ethics

Signed statements of informed consent were obtained from all participants and from parents if the participants were younger than 18 years of age.

RESULTS

Participants

A detailed overview of the inclusion process is given in figure 1. Of 651 invited participants to the postbronchiolitis group, 238 (37%) consented, 199 completed the clinical examinations, and 26 returned the questionnaire only. Of 786 invited control subjects, 171 (22%) consented, 152 completed the clinical examinations, and 15 returned the questionnaire only.

Background and clinical characteristics

Baseline characteristics of the postbronchiolitis group and control group are presented in table 1A. Except lower birth weight and more use of ICS at follow-up in the postbronchiolitis group, there were no baseline differences between the two groups.

Clinical characteristics during the hospitalisation for bronchiolitis are given in table 1B. Subjects in the non-RSV group were older at hospitalisation. The RSV group had longer length of hospital stay.

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Table 1 Background and clinical characteristics in the postbronchiolitis group and the control group.

(A) Background and clinical characteristics of young adults hospitalised for bronchiolitis in infancy compared with control subjects.

	Postbronchiolitis		Control		P value*
	N		N		
Males, n (%)	225	117 (52.0)	167	82 (49.1)	0.57
Gestational age at birth <36 weeks, n (%)	204	4 (2.0)	164	1 (0.6)	0.266
Birth weight, grams, mean (SD)	197	3526 (619)	164	3661 (515)	**0.024**
At follow-up					
Age, years, median (quartiles)	225	19.4 (18.6, 20.3)	167	19.2 (18.6, 20.6)	0.241
BMI, kg/m^2, median (quartiles)	223	23.5 (21.0, 27.4)	166	22.7 (21.2, 25.5)	0.076
Height, cm, median (quartiles)	224	172.5 (167.0, 181.8)	166	175.0 (167.6, 182.0)	0.218
Weight, kg, median (quartiles)	224	70.0 (63.1, 83.4)	166	71.0 (63.0, 80.1)	0.651
Use of inhaled corticosteroids the last 12 months, n (%)	223	25 (11.2)	166	9 (5.4)	**0.046**
Personal smoking, n (%)	225	20 (8.9)	167	8 (4.8)	0.119
Household smoking ever, n (%)	225	74 (32.9)	167	41 (24.6)	0.073
Atopic dermatitis, n (%)	215	50 (23.3)	164	35 (21.3)	0.658
Family history of atopy, n (%)	225	155 (68.9)	167	107 (64.1)	0.316

(B) Clinical variables at hospitalisation for bronchiolitis for all postbronchiolitis subjects and for the RSV group compared with the non-RSV group.

	All postbronchiolitis		RSV		Non-RSV		P value†
	N		N		N		
Age at hospitalisation, months, median (quartiles)	225	4.2 (2.3, 6.8)	128	3.8 (2.0, 5.8)	64	4.5 (2.4, 7.8)	**0.041**
Weight at hospitalisation, grams, mean (SD)	197	6911 (1905)	112	6539 (1823)	54	7107 (1818)	0.062
Previous history of BPO, n (%)	225	32 (14.2)	128	13 (10.2)	64	12 (18.8)	0.095
Length of hospital stay, days, median (quartiles)	225	3.0 (1.0, 4.0)	128	3.0 (2.0, 5.5)	64	2.0 (1.0, 3.0)	**0.001**
Corticosteroids (inhaled/systemically) given during admission, n (%)	225	15 (6.7)	128	6 (4.7)	64	6 (9.4)	0.206

P values are from Student's t-test for normally distributed variables given as means (SDs), Mann-Whitney U test for continuous variables not normally distributed given as medians (quartiles) and Pearson χ^2 test for dichotomous variables. Bold values denote statistical significance at the p<0.05 level.
*P values comparing the postbronchiolitis group and the control group.
†P values comparing the RSV group and the non-RSV group.
BMI, body mass index; BPO, broncopulmonal obstruction; n, number of participants with the characteristic described; N, number of participants with available data; RSV, respiratory syncytial virus.

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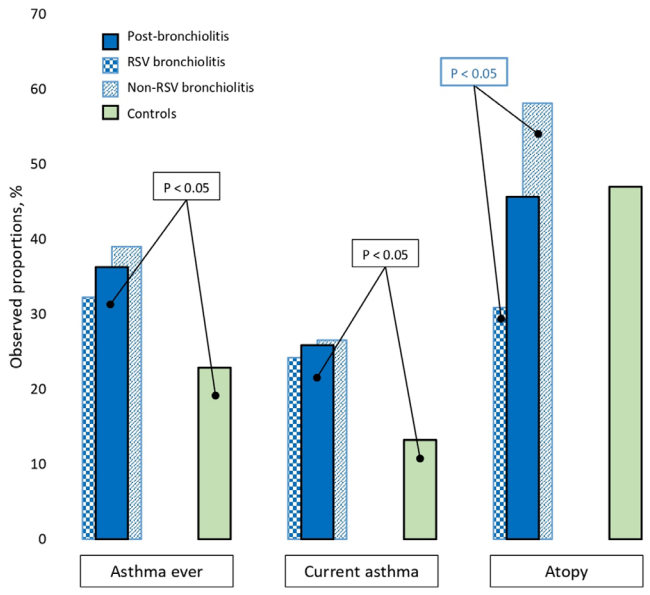

Figure 2 Asthma and atopy in the postbronchiolitis group and the control group including separate columns for RSV bronchiolitis and non-RSV bronchiolitis. Figures are observed proportions. Differences are tested by Pearson χ^2 test and p<0.05 are marked. RSV, respiratory syncytial virus.

Asthma

Directly observed proportions of asthma and atopy are presented in figure 2, whereas table 2A,B presents unadjusted and adjusted results from regression analyses.

At follow-up, the postbronchiolitis group had higher prevalence of both asthma ever and current asthma compared with the control group (figure 2, table 2A). There was no significant interaction between sex and group (ie, postbronchiolitis vs control) regarding asthma (table 2A), and the prevalence of asthma did not differ between the RSV group and the non-RSV group (figure 2, table 2B).

When adding age and potential confounders (sex, family history of atopy, atopic dermatitis, household smoking, birth weight, gestational age at birth) and mediators (atopy, body mass index, personal smoking) one by one to a regression analysis studying the association between group (ie, postbronchiolitis vs control) and current asthma, none of the variables individually changed the OR more than 10% (data not shown).

Atopy

In the postbronchiolitis group, 90 (45.7%) subjects were atopic. Of these 55 (61.1%) were sensitised to two or more allergens, 51 (56.7%) were sensitised to airborne allergens only, 5 (5.6%) to food allergens only, and 34 (37.8%) were sensitised to both airborne and food allergens. In the control group 71 (47.0%) subjects were atopic. Of these 44 (62.0%) were sensitised to two or more allergens, 42 (59.2%) were sensitised to airborne allergens only, 2 (2.8%) to food allergens only, and 27 (38.0%) were sensitised to both.

There was no difference in the prevalence of atopy between the postbronchiolitis and control group (figure 2, table 2A). We found no significant interaction between sex and group (ie, postbronchiolitis vs control) regarding atopy (table 2A). The RSV group had lower prevalence of atopy compared with the non-RSV group (figure 2, table 2B).

Among subjects with asthma ever, a lower proportion in the postbronchiolitis group than in the control group were atopic (46% vs 70%; p=0.027). The same tendency was seen for current asthma (50% vs 74%; p=0.076).

Lung function

Lung function is presented as z-scores in table 3A,B with the corresponding % predicted in the online supplemental table 1 A,B. Participants in the postbronchiolitis group had a more obstructive lung function pattern with lower FEV_1, FEV_1/FVC ratio and FEF_{25-75} compared with control subjects.

We found a significant interaction between sex and group (ie, postbronchiolitis vs control) for FVC (β −0.42; 95% CI −0.82 to −0.02; p=0.039), but not for other lung function variables (table 3A). Analyses for FVC stratified by sex showed lower FVC in the postbronchiolitis group compared with control subjects in males (β −0.32; 95% CI −0.58 to −0.06, p=0.017), but no difference between the two groups in females (β 0.15; 95% CI −0.14 to 0.44; p=0.313).

The non-RSV group had lower FEV_1/FVC-ratio compared with the RSV group, otherwise lung function did not differ between these two groups (table 3B, online supplemental table 1B).

DISCUSSION

This is to date the largest cohort study of respiratory outcomes in young adults after hospitalisation for bronchiolitis during infancy, also including a large control group. We found a higher prevalence of asthma in the postbronchiolitis group, with no difference between the RSV group and the non-RSV group nor between sexes. We found no difference in atopy between the postbronchiolitis group and the control group, but the prevalence of atopy was lower in subjects with former RSV bronchiolitis compared with subjects with former non-RSV bronchiolitis. A lower proportion of children with asthma were atopic in the postbronchiolitis group than in the control group. The postbronchiolitis group had a more obstructive lung function pattern than the control group.

Strengths and limitations

The main strengths of this study were the high number of participants with clinical data on lung function and atopy, as well as inclusion of children hospitalised for both RSV bronchiolitis and non-RSV bronchiolitis. Only

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Table 2 Asthma and atopy at follow-up in the postbronchiolitis group and the control group with separate results for RSV bronchiolitis and non-RSV bronchiolitis.

(A) Asthma and atopy at 19 years in the postbronchiolitis group compared with the control group

	Effect estimate			Predicted proportion, % (95% CI)		Interaction sex*group§
	N	OR (95% CI)	P value*	Postbronchiolitis	Control	P value*
Asthma ever						
Asthma ever†	389	1.92 (1.22 to 3.02)	**0.005**	36.3 (30.0 to 42.6)	22.9 (16.5 to 29.3)	
Asthma ever‡	346	1.89 (1.12 to 3.21)	**0.017**	34.8 (28.0 to 41.5)	22.7 (16.2 to 29.1)	0.925
Current asthma						
Current asthma†	390	2.61 (1.41 to 4.82)	**0.002**	25.8 (20.1 to 31.5)	13.3 (8.1 to 18.4)	
Current asthma‡	347	2.75 (1.32 to 5.73)	**0.007**	25.1 (19.0 to 31.2)	13.1 (7.9 to 18.2)	0.972
Atopy						
Atopy†	348	0.95 (0.62 to 1.45)	0.805	45.7 (38.7 to 52.6)	47.0 (39.1 to 55.0)	
Atopy‡	310	0.84 (0.52 to 1.36)	0.472	44.3 (37.1 to 51.5)	48.2 (40.5 to 55.8)	0.776

(B) Asthma and atopy at 19 years after RSV bronchiolitis compared with non-RSV bronchiolitis.

	Effect estimate			Predicted proportion to % (95% CI)	
	N	OR (95% CI)	P value*	RSV	Non-RSV
Asthma ever					
Asthma ever†	191	0.74 (0.40 to 1.39)	0.353	32.3 (24.2 to 40.4)	39.1 (27.1 to 51.0)
Asthma ever‡	162	0.86 (0.42 to 1.77)	0.685	32.8 (24.0 to 41.7)	36.0 (23.5 to 48.5)
Current asthma					
Current asthma†	192	0.88 (0.44 to 1.76)	0.724	24.2 (16.8 to 31.6)	26.6 (15.7 to 37.4)
Current asthma‡	163	1.02 (0.45 to 2.29)	0.971	24.0 (16.1 to 32.0)	23.8 (12.8 to 34.7)
Atopy					
Atopy†	165	0.32 (0.16 to 0.63)	**0.001**	30.9 (22.3 to 39.5)	58.2 (45.1 to 71.2)
Atopy‡	139	0.35 (0.16 to 0.75)	**0.007**	31.4 (22.2 to 40.7)	53.8 (40.6, 67.0)

Results from mixed effects logistic regression analyses including calculations of predicted proportions.
The predicted proportions are products of the regression analyses and correspond to the expected proportions of the outcomes if everyone had a previous history of bronchiolitis (A) or RSV bronchioltis (B), or if everyone had no history of bronchiolitis (A) or a history of non-RSV bronchiolitis (B), with all other covariates kept at their original value.
*P values for OR from Wald test. Bold values denote statistical significance at the p<0.05 level.
† Unadjusted model.
‡Adjusted for sex, age, birth weight, gestational age at birth, household smoking ever, atopic dermatitis, family history of atopy.
§Interaction term between sex and group (ie, postbronchiolitis vs control).
RSV, respiratory syncytial virus.

children hospitalised during their first year of life were included, ensuring a homogeneous study population.[4] The main weaknesses were the modest participation rate potentially increasing the risk of selection bias, and lack of specific viral aetiologies in the non-RSV group. Nevertheless, the study population was drawn from all children hospitalised for bronchiolitis in the two participating hospitals during the inclusion period, and we, therefore, hold that the results are generalisable for children hospitalised for bronchiolitis under 1 year of age in comparable high-income countries.

Interpretation

Asthma

The higher prevalence of asthma in the postbronchiolitis group compared with the control group is in line with previous research.[6 16–18 30 31] In an earlier publication including a subgroup from this study, 21% in the postbronchiolitis group had current asthma at 11 years of age,[7] a figure also in line with this study. This underlines that bronchiolitis in infancy is associated with long-term respiratory morbidity not only during childhood, but also persisting into young adult age.

Surprisingly, the prevalence of asthma in young adults did not differ between the RSV group and the non-RSV group, but were high in both groups. These results are in line with a Swedish postbronchiolitis study reporting asthma prevalence at 17–20 years of age of 48% after RSV bronchiolitis and 41% after non-RSV bronchiolitis (p=0.53),[17] but differ from two Finnish studies which found a tendency for higher prevalence in adults after non-RSV bronchiolitis compared with RSV bronchiolitis.[30 32] Most follow-up studies reporting outcomes during childhood find a higher risk of subsequent asthma after bronchiolitis with HRV or other non-RSV viruses compared with RSV bronchiolitis.[7 9 10 30] In our previous publication from the 11-year follow-up, 36% of children with former non-RSV bronchiolitis vs 16% with former RSV bronchiolitis reported current asthma.[7]

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Table 3 Lung function at follow-up in the postbronchiolitis group and the control group with separate results for RSV bronchiolitis and non-RSV bronchiolitis.

(A) Lung function at 19 years in the postbronchiolitis group compared with the control group.

	Effect estimate			Predictive margin (95% CI)		Interaction sex*group§
	N	β (95% CI)	P value*	Postbronchiolitis	Control	P value*
FVC						
z-score†	342	−0.10 (−0.30 to 0.09)	0.313	0.02 (−0.12 to 0.15)	0.12 (−0.04 to 0.27)	
z-score‡	306	−0.07 (−0.27 to 0.14)	0.532	0.03 (−0.12 to 0.17)	0.09 (−0.07 to 0.25)	**0.039**
FEV1						
z-score†	341	−0.31 (−0.52 to −0.10)	**0.004**	−0.38 (−0.52 to −0.24)	−0.07 (−0.23 to 0.10)	
z-score‡	305	−0.32 (−0.54 to −0.09)	**0.005**	−0.39 (−0.55 to −0.24)	−0.08 (−0.24 to 0.09)	0.174
FEV1/FVC						
z-score†	341	−0.33 (−0.55 to −0.12)	**0.002**	−0.67 (−0.81 to −0.53)	−0.33 (−0.49 to −0.17)	
z-score‡	305	−0.40 (−0.62 to −0.18)	**<0.001**	−0.71 (−0.86 to −0.56)	−0.31 (−0.47 to −0.15)	0.32
FEF_{25-75}						
z-score†	341	−0.37 (−0.57 to −0.16)	**0.001**	−0.70 (−0.83 to −0.56)	−0.33 (−0.48 to −0.17)	
z-score‡	305	−0.40 (−0.62 to −0.19)	**<0.001**	−0.73 (−0.88 to −0.58)	−0.33 (−0.49 to −0.17)	0.78

(B) Lung function at 19 years after RSV bronchiolitis compared with non-RSV bronchiolitis.

	Effect estimate			Predictive margin (95% CI)	
	N	β (95% CI)	P–value*	RSV	Non–RSV
FVC					
z-score†	164	−0.18 (−0.49 to 0.13)	0.256	−0.08 (−0.25 to 0.10)	0.10 (−0.15 to 0.36)
z-score‡	139	−0.27 (−0.61 to 0.07)	0.12	−0.12 (−0.32 to 0.07)	0.14 (−0.13 to 0.42)
FEV1					
z-score†	164	−0.02 (−0.36 to 0.32)	0.912	−0.44 (−0.63 to −0.25)	−0.42 (−0.70 to −0.14)
z-score‡	139	−0.03 (−0.40 to 0.35)	0.888	−0.47 (−0.69 to −0.25)	−0.44 (−0.75 to −0.14)
FEV1/FVC					
z-score†	164	0.26 (−0.05 to 0.57)	0.103	−0.62 (−0.80 to −0.44)	−0.88 (−1.13 to −0.62)
z-score‡	139	0.38 (0.04 to 0.72)	**0.026**	−0.59 (−0.79 to −0.39)	−0.97 (−1.24 to −0.70)
FEF_{25-75}					
z-score†	164	0.17 (−0.16 to 0.50)	0.311	−0.68 (−0.87 to −0.49)	−0.85 (−1.12 to −0.58)
z-score‡	139	0.24 (−0.11 to 0.59)	0.18	−0.68 (−0.89 to −0.48)	−0.92 (−1.21 to −0.64)

Results from mixed effects linear regression analyses including calculations of predictive margins.
The predictive margins are products of the regression analyses and correspond to the predicted mean values of the outcome if everyone had a previous history of bronchiolitis (A) or RSV bronchioltis (B), or if everyone had no history of bronchiolitis (A) or a history of non-RSV bronchiolitis (B), with all other covariates kept at their original value.
*P values for β from Wald test. Bold values denote statistical significance at the p<0.05 level.
†Unadjusted model.
‡Adjusted for birth weight, gestational age at birth, household smoking ever, atopic dermatitis, family history of atopy.
§Interaction term between sex and group (ie, postbronchiolitis vs control).
FEF_{25-75}, forced expiratory flow between 25% and 75% of the forced vital capacity; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; RSV, respiratory syncytial virus.

The Tucson Children's Respiratory Study reported increased risk of asthma during the first 10 years of life after RSV infection before 3 years of age, but the increased risk rapidly subsided by age and was not present after the age of 13 years.[8] A similar decrease in asthma prevalence by age after hospitalisation for RSV infection was reported in a meta-analysis.[33] However, in this study of young adults, we found no difference between the RSV-group and the non-RSV-group, the prevalence of asthma was high also after RSV bronchiolitis. Our results are in line with the follow-up study at 18 years of age by Sigurs *et al*[16] and some other postbronchiolitis studies suggesting a U-shaped prevalence curve for asthma after RSV bronchiolitis from early childhood to young adult age.[6]

We found no interaction between sex and group (ie, postbronchiolitis vs control) in the adjusted models, meaning that the impact of having bronchiolitis on subsequent asthma did not differ between sexes. Thus, in contrast to the results from a Swedish study reporting increased risk of asthma in female young adults with former wheezing bronchitis under the age of 2 years,[17] we observed no switch to a higher prevalence of asthma in females during adolescence.

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Differences in asthma prevalence between studies could partly be explained by variations in age criteria at inclusion and the definitions of asthma. We included only infants hospitalised for bronchiolitis during their first year of life, whereas others used 2 or 3 years of age as cut-off. Increased age limit for inclusion increases the heterogeneity of the study population by including more participants in whom the bronchiolitis may represent a first episode of asthma. Definitions of asthma used in epidemiological studies are highly inconsistent and make comparisons between studies challenging.[34] Prevalence of asthma must, therefore, be considered in relation to the prevalence in the corresponding control group, which in this study was high, but in line with studies of the general population.[35]

The prevalence of use of ICS was lower than one would expect based on the corresponding prevalence of asthma in both groups. This may indicate suboptimal adherence to recommended treatment,[36] a high number of mild asthma cases, or even other aetiologies with symptoms mimicking asthma.

Atopy

We found no difference in atopy between the postbronchiolitis group and control group, but atopy was less frequent in the RSV group compared with the non-RSV group. This is in line with other similar studies including our previous follow-up at 11 years of age,[7 8 37 38] but contrasting the study by Sigurs *et al*.[16] The prevalence of atopy was high in both groups, but a similar prevalence of 49% was found among 16 years in a prospective population-based birth cohort from Oslo, Norway.[29] In subjects with asthma ever, atopy was less common in the postbronchiolitis group, with the same tendency among those with current asthma. This finding corroborates that non-eosinophilic asthma is common after bronchiolitis, a notion formerly reported particularly after RSV bronchiolitis.[11] Our study did not have sufficient power to evaluate if viral aetiology during bronchiolitis is associated with different phenotypes of asthma in young adults.

Lung function

Consistent with previous research,[18] the postbronchiolitis group had a more obstructive lung function pattern with lower FEV_1, FEV_1/FVC and FEF_{25-75}. Although mean FEV_1 was within a clinically normal range, it is important to emphasise that even mild to moderate impairment of FEV_1 may be a predictor of later cardiorespiratory morbidity and mortality.[39] Lung function was not measured before the episode with bronchiolitis, and we can, therefore, not exclude that genetically determined small airways have contributed to these findings.

In line with previous research in younger children, young adults with former non-RSV bronchiolitis had lower FEV_1/FVC and hence a more obstructive lung function pattern compared with those with former RSV bronchiolitis.[40] This may indicate that different viruses during bronchiolitis in infancy affect lung function in different ways later in life.

We found a significant interaction between sex and group (ie, postbronchiolitis vs control) for FVC indicating that the impact on lung function of having a history of hospitalisation for bronchiolitis is more pronounced in males than in females. Lung development differs between sexes, and boys are in general more vulnerable for respiratory events during childhood, partly due to differences in anatomy and physiology such as airway size, airway muscle bulk, airway reactivity, airway tone and cough reflexes.[41] In analyses stratified by sex, we found decreased FVC in males after bronchiolitis, a result that differs from a study from Sweden reporting only mid-expiratory flow rate lower than control subjects after bronchiolitis in males.[42]

CONCLUSION

Young adults hospitalised for bronchiolitis had higher prevalence of asthma, but not atopy, and a more obstructive lung function pattern than control subjects. The asthma prevalence was high after both RSV bronchiolitis and non-RSV bronchiolitis, and there was no difference between sexes. The study confirms that bronchiolitis in infancy is associated with impaired respiratory health persisting into young adulthood. Further follow-up studies in adult age are needed to explore the potential for subsequent respiratory morbidity including early-onset COPD after this prevalent childhood disorder.

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