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Received: 16 September 2022 | Revised: 2 December 2022 | Accepted: 9 January 2023

DOI: 10.1111/apa.16666

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

ORIGINAL ARTICLE

Blood eosinophils during bronchiolitis: Associations with atopy, asthma and lung function in young adults

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Funding information
Stavanger University Hospital; The Kloster Foundation; The Norwegian Allergology and Immunopathology Association; The Norwegian Asthma and Allergy Association; The Western Norway Regional Health authority, Grant/Award Number: Grant number F-12502

Abstract

Aim: To study if blood eosinophils during bronchiolitis were associated with atopy, asthma and lung function in young adults and if these associations differed between respiratory syncytial virus (RSV) bronchiolitis and non-RSV bronchiolitis.

Methods: This historical cohort enrolled 225 subjects. Blood eosinophils were measured during bronchiolitis in infancy, and the subjects were invited to a follow-up at 17–20 years of age including questionnaires for asthma and examinations of lung function and atopy.

Results: The level of eosinophils was positively associated with subsequent atopy in the unadjusted analysis, but not in the adjusted analysis, and not with asthma. There was a negative association between the level of eosinophils and forced vital capacity (FVC) (−0.11; −0.19, −0.02) and forced expiratory volume in first second (FEV_1) (−0.12; −0.21, −0.03) (regression coefficient; 95% confidence interval). The non-RSV group had higher levels of eosinophils during bronchiolitis, but there was no interaction between the level of eosinophils and RSV status for any outcome.

Conclusions: The level of eosinophils during bronchiolitis was negatively associated with lung function in young adult age, but we found no associations with atopy or asthma. These associations were not different after RSV bronchiolitis compared to non-RSV bronchiolitis.

KEYWORDS
asthma, atopy, bronchiolitis, eosinophils, lung function

1 | INTRODUCTION

Bronchiolitis is a common viral lower respiratory tract infection in early childhood.[1,2] Children hospitalised for bronchiolitis have an increased risk of asthma and impaired lung function persisting into young adulthood,[3–6] but the underlying mechanisms of these associations are less understood.

Suppression of blood eosinophils is the expected response to an acute viral infection,[7] but a subset of infants with bronchiolitis have normal or even elevated levels.[8] Recently, it has been indicated that the 'bronchiolitis' diagnosis clinically and pathophysiologically comprises more than one condition,[9] which may be related to the atopic status of the individual, age at hospitalisation and the virus involved. Whereas non-respiratory syncytial virus (RSV) bronchiolitis,

Abbreviations: β, regression coefficient; BMI, body mass index; CI, confidence interval; FEF_{25-75}, forced expiratory flow between 25% and 75% of the forced vital capacity; FEV_1, forced expiratory volume in first second; FVC, forced vital capacity; OR, odds ratio; RRR, relative risk ratio; RSV, respiratory syncytial virus; SD, standard deviation; Th, T-helper cell.

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especially bronchiolitis due to human rhinovirus, has been connected to a T-helper cell (Th) 2-driven eosinophilic inflammation, RSV bronchiolitis is more often linked to a type-1 response and a neutrophilic inflammation.[9–11]

Asthma is a heterogeneous disease with various mechanistic pathways (endotypes) and variable clinical presentations (phenotypes).[12,13] Based on endotypes, asthma may be divided into asthma dominated by a Th-2-high eosinophilic airway inflammation, and asthma dominated by a Th-2-low neutrophilic inflammation.[12] Asthma in children and adolescents is most often linked to a concomitant eosinophilic inflammation, whereas up to 25% of asthmatic adults have neutrophilic inflammation.[13]

As both bronchiolitis and asthma show diversity linked to different expressions of eosinophilic inflammation, it is interesting to study if the level of eosinophils during bronchiolitis is associated with subsequent atopy and respiratory morbidity. Studies investigating this association in childhood found associations between the level of eosinophils during bronchiolitis and subsequent asthma.[14–16] In a follow-up at 11 years of age after bronchiolitis in infancy, increasing levels of eosinophils were associated with an increased risk of asthma and lower lung function.[16] There is little published data on associations between the level of eosinophils during bronchiolitis and respiratory outcomes in young adult age. In a Finnish post-bronchiolitis study, the level of eosinophils during bronchiolitis did not predict subsequent asthma at 18–20 years of age,[17] but low levels of eosinophils during bronchiolitis predicted low asthma risk at 28–31 years.[14]

We aimed to study if the level of blood eosinophils during bronchiolitis in infancy was associated with atopy, asthma and lung function in young adults and if these associations differed between RSV bronchiolitis and non-RSV bronchiolitis.

Key Notes

- Children hospitalised for bronchiolitis have an increased risk of asthma and impaired lung function persisting into young adulthood, but the underlying mechanisms including the role of eosinophilic inflammation are less known.
- The level of eosinophils during bronchiolitis in infancy was negatively associated with lung function in young adult age, but not associated with atopy or asthma.
- These associations did not differ between respiratory syncytial virus (RSV) bronchiolitis and non-RSV bronchiolitis.

2 | PATIENTS AND METHODS

2.1 | Study design and subjects

This is a historical cohort study enrolling young adults hospitalised for bronchiolitis below the age of 12 months in Stavanger and Bergen, Norway between October 1996 and May 2001. Eligible subjects were invited to a follow-up at 17–20 years of age as described in more detail previously.[6,18] Bronchiolitis was defined based on European guidelines as an acute viral respiratory tract infection during the first year of life with fever, tachypnoea, dyspnoea, prolonged expiration and wheeze on auscultation.[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 diseases, and prematurity with gestational age at birth <32 weeks. 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.

2.2 | Exposures

The level of eosinophils was analysed in blood samples drawn from the infants as a part of the routine tests immediately after admission to the hospital for bronchiolitis as previously described.[19]

2.3 | Outcomes

Atopy was defined as either a positive skin prick test[20] and/or a positive allergen panel or specific immunoglobulin E for at least one common allergen. Asthma ever was defined as a positive answer to the question *have you ever been diagnosed with asthma by a doctor?* Current asthma was defined as asthma ever combined with symptoms of asthma and/or use of asthma medication during the last 12 months. Lung function was measured by spirometry according to established guidelines.[21] Clinical examinations were performed from April 2015 to March 2020, and methods for recording outcomes at follow-up are described in more detail previously.[6]

Subjects were divided into four phenotypes based on the occurrence of atopy and current asthma at follow-up: (1) healthy: no asthma, no atopy; (2) atopic non-asthmatic: atopy, no asthma; (3) non-atopic asthma: asthma, no atopy and (4) atopic asthma: asthma and atopy.

2.4 | Covariates/confounders

Factors possibly influencing both the exposure and outcomes were identified as potential confounders as illustrated in a directed acyclic graph (Figure S1).

Clinical data from the hospital stay for bronchiolitis were obtained retrospectively by review of medical records. Birthweight and gestational age at birth were collected from birth protocols and supplemented by information from medical records. Subjects with no information of prematurity were defined as having a gestational age at birth >36 weeks. Data regarding atopic dermatitis ever, early life exposure to household smoking and family history of asthma and

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atopy were obtained retrospectively by review of medical records from the hospitalisation for bronchiolitis and supplemented by information from questionnaires at follow-up.

Anthropometry at follow-up was measured by study nurses or collected from questionnaires for those not participating in the clinical examinations. Personal smoking was defined based on questionnaires, and missing responses from two subjects were interpreted as negative answers in the analyses.

2.5 | Statistics

Continuous data were presented as means with standard deviations (SD) and compared by Student's *t* test if normally distributed or as medians and interquartile ranges and compared by Mann–Whitney *U* test if not normally distributed. Categorical data were presented as counts and percentages and compared by Pearson chi-square test. Multiple imputation by iterative chained equations resulting in 100 completed data sets (random seed 123456) was performed to handle missing data on the virus (RSV vs. non-RSV), weight and the level of eosinophils during hospitalisation for bronchiolitis, birthweight, atopic dermatitis, household smoking, body mass index (BMI), asthma, atopy and lung function. Sex, age at hospitalisation for bronchiolitis, gestational age at birth <36 weeks, family history of atopy, age at follow-up and personal smoking were included as auxiliary variables. When analysing phenotypes of combinations of asthma and atopy, an otherwise equal separate multiple imputation was performed including the four-category phenotype variable instead of separate variables for asthma and atopy. Linear, logistic and multi-nominal logistic regressions were performed to study the associations between the level of eosinophils and different outcomes. The distribution of the levels of eosinophils was highly skewed and

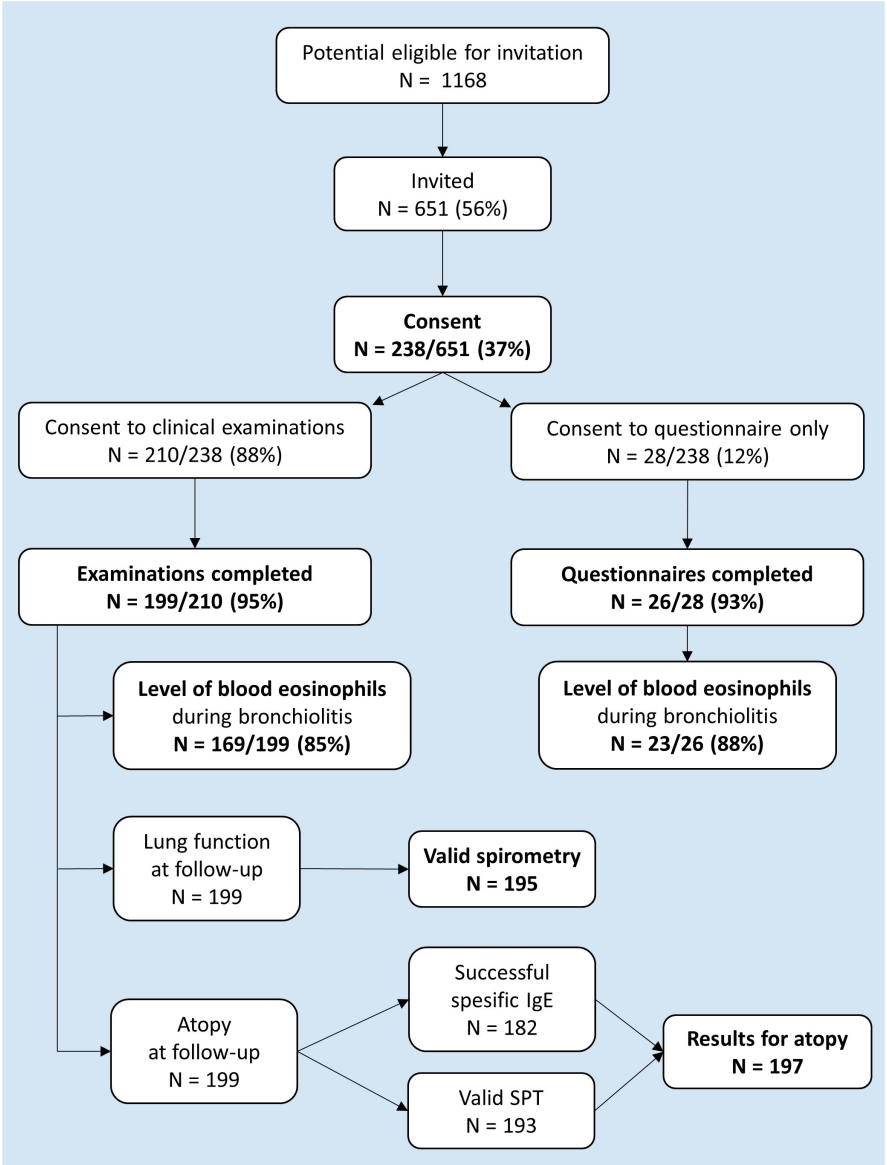

FIGURE 1 Overview of study subjects. SPT, skin prick test.

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TABLE 1 Background and clinical characteristics at the hospitalisation for bronchiolitis

	All subjects		RSV		Non-RSV		
Background	***N***		***N***		***N***		***p* value***
Male, *n* (%)	225	117 (52.0)	128	62 (48.4)	64	34 (53.1)	0.540
Gestational age at birth <36 weeks, *n* (%)	225	4 (1.8)	128	3 (2.3)	64	1 (1.6)	0.721
Birth weight, grams, mean (SD)	197	3526 (619)	110	3515 (667)	58	3528 (530)	0.898
Early life exposure to household smoking, *n* (%)	182	39 (21.4)	105	22 (21.0)	48	9 (18.8)	0.753
Family history of atopy, *n* (%)	225	165 (73.3)	128	90 (70.3)	64	49 (76.6)	0.361
Atopic dermatitis ever, *n* (%)	217	55 (25.4)	125	24 (19.2)	62	19 (30.7)	0.080
At hospitalisation for bronchiolitis							
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
History of bronchopulmonary obstruction, *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
Leukocytes count/μL, mean (SD)	212	12 303 (3851)	119	12 295 (3868)	62	12 976 (3943)	0.266
Eosinophils % of leukocytes, median (quartiles)	192	1.0 (0.3, 2.2)	108	0.7 (0.3, 1.5)	57	1.8 (0.7, 2.8)	**<0.001**
Eosinophils count/μL, median (quartiles)	192	110 (40, 234)	108	80 (32, 169)	57	190 (74, 407)	**<0.001**
Eosinophils count >300/μL, *n* (%)	192	41 (21.4)	108	14 (13.0)	57	19 (33.3)	**0.002**
Eosinophils count >100/μL, *n* (%)	192	103 (53.7)	108	47 (43.5)	57	40 (70.2)	**0.001**

Abbreviations: *N*, number of subjects with available data; *n*, number of subjects with the characteristic described; RSV, respiratory syncytial virus; SD, standard deviation.

**p* values comparing the RSV and the non-RSV group from Student's *t* test for normally distributed variables given as mean (SD), Mann–Whitney *U* test for continuous variables not normally distributed given as median (quartiles) and Pearson chi-squared test for dichotomous variables.

Bold values denote statistical significance at the $p < 0.05$ level.

therefore transformed using the natural logarithm after adding 0.1 to all values to include subjects with a level of eosinophils at zero. Unadjusted and adjusted odds ratios (OR), relative risk ratios (RRR) or regression coefficients (β) with 95% confidence intervals (CI) were calculated. We adjusted for the following pre-specified variables: age at follow-up, sex, family history of atopy, RSV status and age at hospitalisation for bronchiolitis. Other potential confounders were handled by sensitivity analyses (Figure S1). The impact of viral aetiology was assessed by including an interaction term between the level of eosinophils and RSV status.

Stata version 17.0 (*Stata Corp LLC*, *TX*, *USA*) was used for all analyses. *p* values of <0.05 were considered statistically significant.

2.6 | Ethics

The study was approved by the Norwegian Regional Committee on Medical Research Ethics (2014/1930/REK west). Signed statements of informed consent were obtained from all subjects and also from parents if the subjects were younger than 18 years of age.

3 | RESULTS

3.1 | Study subjects

An overview of the inclusion process is given in Figure 1 and described in more detail previously.[6] In total, 1168 eligible infants were admitted for bronchiolitis in the study region during the inclusion period, of whom 651 (56%) were invited to the follow-up at 17–20 years of age. Of the invited subjects, 238 (37%) consented to participate, 199 completed the clinical examinations and 26 returned the questionnaire only, without taking part in the examinations. The level of blood eosinophils was measured during the hospitalisation for bronchiolitis in 192 of the consenting subjects.

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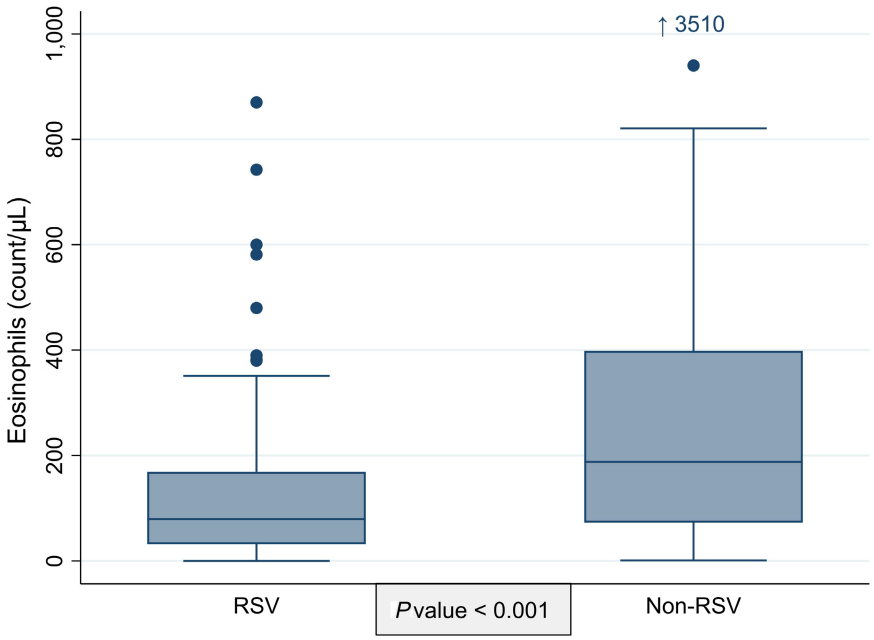

FIGURE 2 Box plot depicting levels of eosinophils during respiratory syncytial virus (RSV) bronchiolitis and non-RSV bronchiolitis. Within each box, the horizontal lines denote median values; boxes extend from the 25th to the 75th percentile; whiskers denote adjacent values (i.e. values within the 1.5 interquartile range of the 25th and 75th percentile of each group); dots denote observations outside the range of adjacent values. Differences are tested by Mann–Whitney *U* test.

TABLE 2 Clinical characteristics at follow-up of 225 young adults hospitalised for bronchiolitis in infancy

	All subjects		RSV		Non-RSV		
	N		*N*		*N*		*p* value*
Age, years, median (quartiles)	225	19.4 (18.6, 20.3)	128	19.0 (18.3, 19.8)	64	19.5 (18.7, 20.2)	**0.045**
BMI, kg/m^2, median (quartiles)	223	23.5 (21.0, 27.4)	127	23.4 (21.0, 26.9)	63	23.2 (21.0, 27.1)	0.900
Height, cm, median (quartiles)	224	172.5 (167.0, 181.8)	127	171.7 (165.1, 181.3)	64	172.7 (168.0, 181.0)	0.489
Weight, kg, median (quartiles)	224	70.0 (63.1, 83.4)	128	68.5 (62.1, 81.6)	63	70.0 (63.1, 83.7)	0.498
Personal smoking, *n* (%)	225	20 (8.9)	128	10 (7.8)	64	7 (10.9)	0.472
Atopy, *n* (%)	197	90 (45.7)	110	34 (30.9)	55	32 (58.2)	**0.001**
Asthma ever, *n* (%)	223	81 (36.3)	127	41 (32.3)	64	25 (39.1)	0.352
Current asthma, *n* (%)	224	58 (25.9)	128	31 (24.2)	64	17 (26.6)	0.724
Phenotypes	196		110		55		
Healthy, *n* (%)		82 (41.8)		62 (56.4)		15 (27.3)	**<0.001**
Atopic non-asthmatic, *n* (%)		64 (32.7)		22 (20.0)		25 (45.5)	**0.001**
Non-atopic asthma, *n* (%)		25 (12.8)		14 (12.7)		8 (14.6)	0.746
Atopic asthma, *n* (%)		25 (12.8)		12 (10.9)		7 (12.7)	0.730
Lung function							
FVC z-score, mean (SD)	195	0.02 (0.94)	110	−0.08 (0.96)	54	0.10 (0.93)	0.261
FEV_1 z-score, mean (SD)	195	−0.38 (1.03)	110	−0.44 (1.02)	54	−0.42 (1.10)	0.913
FEV_1/FVC z-score, mean (SD)	195	−0.67 (0.99)	110	−0.62 (1.01)	54	−0.88 (0.87)	0.107
FEF_{25-75} z-score, mean (SD)	195	−0.70 (1.00)	110	−0.68 (1.01)	54	−0.85 (1.00)	0.316

Abbreviations: BMI, body mass index; FEF_{25-75}, forced expiratory flow between 25% and 75% of the forced vital capacity; FEV_1, forced expiratory volume in first second; FVC, forced vital capacity; N, number of subjects with available data; n, number of subjects with the characteristic described; RSV, respiratory syncytial virus; SD, standard deviation.

*p values comparing the RSV and the non-RSV group from Student's t test for normally distributed variables given as means (SD), Mann–Whitney U test for continuous variables not normally distributed given as median (quartiles) and Pearson chi-squared test for dichotomous variables.

Bold values denote statistical significance at the $p < 0.05$ level.

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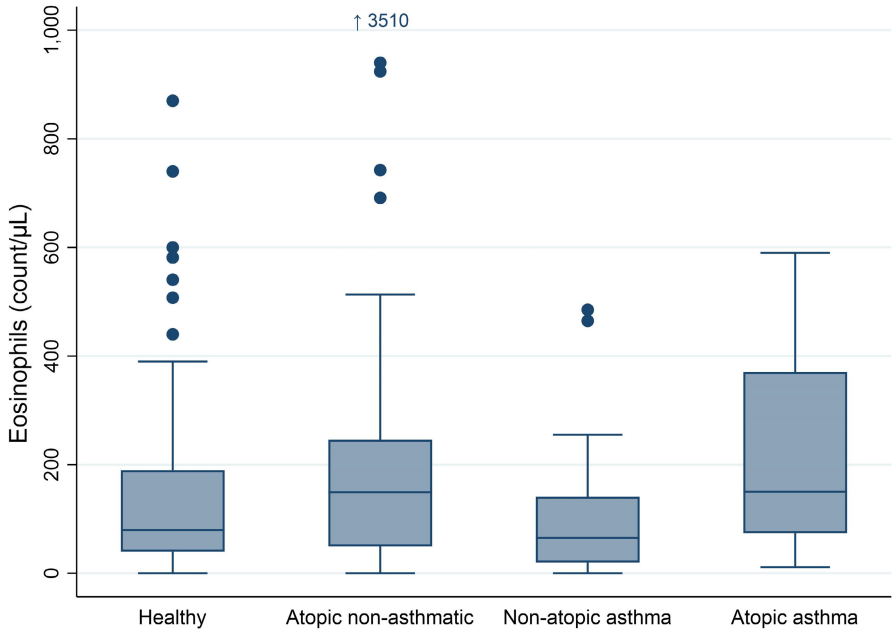

FIGURE 3 Box plot depicting levels of blood eosinophils during bronchiolitis for different phenotypes regarding asthma and atopy at follow-up. Within each box, the horizontal lines denote median values; boxes extend from the 25th to the 75th percentile; whiskers denote adjacent values (i.e. values within the 1.5 interquartile range of the 25th and 75th percentile of each group); dots denote observations outside the range of adjacent values.

3.2 | Background factors and clinical characteristics

The background characteristics did not differ between the RSV group and the non-RSV group (Table 1). As previously described,[6] the non-RSV group were older at hospitalisation and had a shorter length of hospital stay than the RSV group (Table 1). The non-RSV group had higher levels of eosinophils during the hospitalisation for bronchiolitis than the RSV group (Figure 2, Table 1). Also, more subjects in the non-RSV group had a level of eosinophils exceeding a cut-off set to 300 or 100/µL (Table 1).

Subjects in the non-RSV group had a higher prevalence of atopy and were older at follow-up compared to the RSV group, but anthropometry, personal smoking, the prevalence of asthma and lung function variables did not differ between the virus groups (Table 2).[6] The atopic non-asthmatic phenotype was more frequent in the non-RSV group and the healthy phenotype was more frequent in the RSV group, but the frequency of the other phenotypes did not differ between the two virus groups (Table 2). The level of eosinophils during bronchiolitis for each phenotype based on current asthma and atopy at follow-up is illustrated in Figure 3.

3.3 | Associations between the level of eosinophils and atopy and respiratory morbidity

Associations between the level of blood eosinophils during bronchiolitis and different outcomes in young adult age are shown in Table 3 for imputed data.

3.3.1 | Atopy, asthma and phenotypes

The level of eosinophils during bronchiolitis was positively associated with atopy at follow-up in the unadjusted analysis, but not after adjusting for potential confounders (Table 3). There were no associations between the level of eosinophils during bronchiolitis in infancy and asthma ever or current asthma in young adult age (Table 3). A negative association was found between the level of eosinophils during bronchiolitis and the non-atopic asthmatic phenotype, but we found no associations between the level of eosinophils during bronchiolitis and the other phenotypes (Table 3).

3.3.2 | Lung function

The level of eosinophils during bronchiolitis was negatively associated with forced vital capacity (FVC) and forced expiratory volume in first second (FEV_1) at follow-up, but there was no association between the level of eosinophils and FEV_1/FVC (Table 3 and Figure 4). There was a tendency for a negative association between the level of eosinophils and forced expiratory flow between 25% and 75% of the forced vital capacity (FEF_{25-75}) (Table 3 and Figure 4).

3.3.3 | Impact of viral aetiology

We found no interactions between the level of eosinophils and RSV status for atopy, asthma, different phenotypes or lung function parameters, meaning that the associations between the level of eosinophils and the various outcomes did not differ between the RSV group and the non-RSV group (data not shown).

3.3.4 | Sensitivity analyses

Analyses with the imputed outcomes left out of the data set did not change the results. The results from analyses on complete cases given in Table S1 did not differ notably from the imputed data set. Including atopic dermatitis, gestational age at birth, birthweight

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TABLE 3 Associations between the level of eosinophils during bronchiolitis in infancy and atopy, asthma and lung function in 225 young adults

Atopy and asthma	**OR (95% CI)**	***p* value***
Atopy, unadjusted	1.27 (1.03, 1.56)	**0.026**
Atopy, adjusted[a]	1.18 (0.94, 1.47)	0.144
Asthma ever, unadjusted	1.01 (0.86, 1.20)	0.867
Asthma ever, adjusted[a]	0.99 (0.83, 1.18)	0.934
Current asthma, unadjusted	0.97 (0.81, 1.16)	0.734
Current asthma, adjusted[a]	0.96 (0.79, 1.16)	0.657
Phenotypes	**RRR (95% CI)**	***p* value***
Healthy	Reference	
Atopic non-asthmatic, unadjusted	1.13 (0.89, 1.42)	0.307
Atopic non-asthmatic, adjusted[a]	1.01 (0.77, 1.31)	0.964
Non-atopic asthma, unadjusted	0.81 (0.65, 1.02)	0.068
Non-atopic asthma, adjusted[a]	0.76 (0.60, 0.98)	**0.031**
Atopic asthma, unadjusted	1.44 (0.97, 2.15)	0.072
Atopic asthma, adjusted[a]	1.37 (0.88, 2.11)	0.162
Lung function	***β* (95% CI)**	***p* value***
FVC z- score, unadjusted	−0.09 (−0.17, −0.01)	**0.024**
FVC z- score, adjusted[b]	−0.11 (−0.19, −0.02)	**0.014**
FEV_1 z- score, unadjusted	−0.11 (−0.19, −0.03)	**0.011**
FEV_1 z- score, adjusted[b]	−0.12 (−0.21, −0.03)	**0.010**
FEV_1/FVC z- score, unadjusted	−0.02 (−0.11, 0.07)	0.633
FEV_1/FVC z- score, adjusted[b]	−0.01 (−0.10, 0.08)	0.808
FEF_{25-75} z- score, unadjusted	−0.08 (−0.16, 0.01)	0.074
FEF_{25-75} z- score, adjusted[b]	−0.07 (−0.16, 0.01)	0.098

Note: Results from unadjusted and adjusted logistic, multi-nominal logistic and linear regression analyses. Missing data were handled by multiple imputation.

The distribution of levels of eosinophils was highly skewed and therefore transformed using the natural logarithm after adding 0.1 to all values.

Abbreviations: CI, confidence interval; FEF_{25-75}, forced expiratory flow between 25% and 75% of the forced vital capacity; FEV_1, forced expiratory volume in first second; FVC, forced vital capacity; OR, odds ratio (from logistic regression); RRR, relative risk ratio (from multinominal regression); RSV, respiratory syncytial virus; β, regression coefficient (from linear regression).

[a]Adjusted for age, sex, family history of atopy, RSV status and age at hospitalisation for bronchiolitis.

[b]Adjusted for family history of atopy, RSV status and age at hospitalisation for bronchiolitis.

*p values from Wald tests. Bold values denote statistical significance at the $p < 0.05$ level.

and household smoking in the analyses did not change the results. Removal of the outlier with an eosinophil blood cell count at 3510/μL (Figure 2) also did not change the results notably.

4 | DISCUSSION

In this historical cohort study, we found associations between the level of blood eosinophils during bronchiolitis in infancy and respiratory outcomes measured in young adult age. The level of eosinophils was negatively associated with lung function. We found a positive association with atopy in the unadjusted analysis, but not after adjustment for potential confounders, and not with asthma. However, when studying phenotypes of asthma and atopy, the level of eosinophils was negatively associated with non-atopic asthma. None of these associations differed between the RSV group and the non-RSV group.

The level of eosinophils during bronchiolitis was associated with atopy in young adult age in the unadjusted analysis, but this finding did not remain significant after adjusting for potential confounders. In a prospective study of newborns of whom the majority had atopic heredity, eosinophilia during infancy was associated with atopy during the first 6 years of life.[22] However, if these associations also apply to a post-bronchiolitis population is less studied. In our follow-up at 11 years, the level of eosinophils during bronchiolitis was not associated with atopy.[16] The reason for the divergent results is not known, but could partly relate to different study populations and age at follow-up.

The level of eosinophils was higher in infants hospitalised for non-RSV bronchiolitis compared to RSV bronchiolitis. This is in line with other studies,[17,19] and may suggest different pathophysiology with a Th2-high eosinophilic inflammation being more pronounced in non-RSV bronchiolitis.[9] Eosinophils are central effectors of allergic inflammation and are linked to atopy.[23] Correspondingly, and consistent with others, the non-RSV group in this study had more atopy than the RSV group at follow-up.[24–27] On this basis, one could suspect RSV status to impact the association between the level of eosinophils and atopy, but there was no interaction between the level of eosinophils and virus group for neither atopy nor any of the other outcomes.

This study does not support that asthma in young adulthood can be predicted based on the level of eosinophils during bronchiolitis in infancy. The result is in line with the Finnish follow-up at the same age,[17] but contrasts another recently published Finnish study which found increased blood eosinophil count during viral wheezing before 2 years of age to be an independent predictive factor for asthma in early adulthood.[28] Our finding is also contrary to post-bronchiolitis studies reporting associations between blood eosinophils and an increased risk of asthma during childhood.[15,16,19] Asthma in adult age is more heterogeneous in that Th2-low neutrophilic inflammation is

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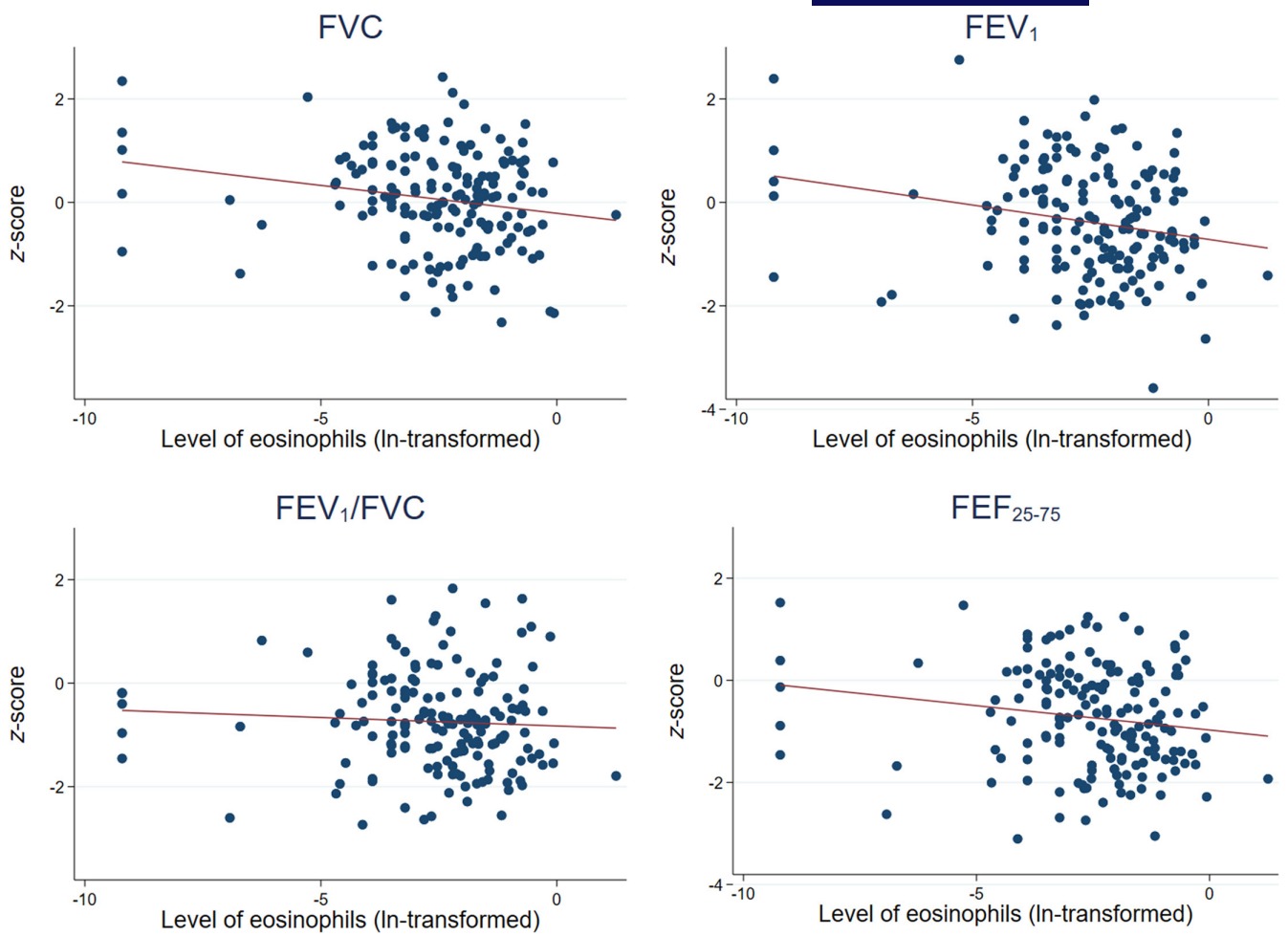

FIGURE 4 Scatter plots depicting lung function at follow-up versus ln-transformed levels of blood eosinophils during bronchiolitis. The y-axes depict lung function variables in z-scores, and the x-axes depict levels of blood eosinophils during bronchiolitis transformed using the natural logarithm after adding 0.1 to all values. Fitted values are represented by the red line. FEF_{25-75}, forced expiratory flow between 25% and 75% of the forced vital capacity; FEV_1, forced expiratory volume in first second; FVC, forced vital capacity.

more common than in childhood asthma.[12,13] This means that the proportion of subjects with late-onset Th2-low neutrophilic asthma will be higher in adults with a previous history of bronchiolitis compared to children with the same history, and may partly explain why eosinophils measured during bronchiolitis are not associated with subsequent asthma in young adult age.

There was a negative association between the level of eosinophils during bronchiolitis and non-atopic asthma. However, as bronchiolitis in general increases the risk of subsequent asthma, the interpretation should not be that eosinophilia during bronchiolitis protects against subsequent asthma. Rather, if an infant with a high level of eosinophils during bronchiolitis presents with asthma in early adult life, the asthma phenotype is more likely to be atopic than non-atopic.

The level of eosinophils during bronchiolitis was associated with lower lung function in young adult age both for FVC and FEV_1, but not the FEV_1/FVC ratio, suggesting a tendency towards a more restrictive than obstructive lung function pattern. A negative association with FEV_1 was found also in our previous follow-up at 11 years.[16] In the Finnish cohort, a high level of eosinophils during bronchiolitis was associated with irreversible airway obstruction at 28–31 years of age.[14] These differences may partly be explained by different ages both at the hospitalisation for bronchiolitis and at follow-up. The Finnish study included children with bronchiolitis up to 24 months of age, contrasting our cut-off at 12 months.[14] Inclusion of older subjects with bronchopulmonary obstruction during the second year of life may increase the heterogeneity of the post-bronchiolitis group, by potentially including more subjects in whom the bronchiolitis represents early onset asthma with a subsequent higher risk of long-term obstructive lung function.

Our study emphasises clinical and pathophysiological differences between RSV bronchiolitis and non-RSV bronchiolitis. Children with RSV bronchiolitis tend to be younger at hospitalisation. They have impaired lung function,[6] which might either be present prior to the respiratory insult of bronchiolitis, or a result of the acute infection, but with a normal inflammatory response with suppressed eosinophils during bronchiolitis. This may further result in persistently impaired lung function with increasing clinical relevance after the peak of lung function is passed in early adulthood,[29] but is neither associated with subsequent atopy nor eosinophilic inflammation. On

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the other hand, children with non-RSV bronchiolitis tend to be older at hospitalisation, have higher levels of eosinophils and more atopy in young adult age.

The main strengths of this study were the high number of subjects with clinical data on lung function and atopy, and the inclusion of children hospitalised for both RSV bronchiolitis and non-RSV bronchiolitis, allowing us to study differences between virus groups. Only children hospitalised during their first year of life were included, facilitating a more homogeneous study population.[30] A main weakness was the modest participation rate potentially increasing the risk of selection bias. In addition, the lack of specific viral aetiologies in the non-RSV group disallowed further studies of subsets of this group. Missing data represent a limitation, but this was handled by multiple imputation to achieve higher statistical power and less skewness in the estimates than analyses limited to subjects with complete data would provide.

5 | CONCLUSIONS

The level of eosinophils during bronchiolitis in infancy was negatively associated with lung function in young adult age, but we found no associations with atopy or asthma. These associations were not different after RSV bronchiolitis compared to non-RSV bronchiolitis.

ACKNOWLEDGEMENTS

We are grateful to all children, young adults, and parents who have taken part in this study. Our special thanks are also extended to the nurses at the Paediatric Clinical Trial Unit at Haukeland University Hospital and the study nurses in Stavanger for executing the clinical examinations.

FUNDING INFORMATION

The manuscript was financed with support from Stavanger University Hospital, the Western Norway Regional Health Authority (grant number F-12502), The Kloster Foundation, The Norwegian Allergology and Immunopathology Association and The Norwegian Asthma and Allergy Association.

CONFLICT OF INTEREST

The authors declare that they have no potential conflict of interest related to the manuscript content.

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How to cite this article: Sørensen KG, Øymar K, Dalen I, Halvorsen T, Bruun Mikalsen I. Blood eosinophils during bronchiolitis: Associations with atopy, asthma and lung function in young adults. Acta Paediatr. 2023;112:820–829. https://doi.org/10.1111/apa.16666

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