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REGULAR ARTICLE

Lung function and bronchial hyper-responsiveness 11 years after hospitalization for bronchiolitis

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Abstract

Aim: Atopic infants hospitalized for wheezing not caused by respiratory syncytial virus (RSV) carry the highest risk for later asthma. In the present paper, early risk factors for later lung function abnormalities and for bronchial hyper-responsiveness (BHR) were evaluated in 81 children, hospitalized for bronchiolitis in infancy, at the median age of 12.3 years.

Methods: The basic data, including data on atopy in children and viral aetiology of bronchiolitis, had been collected on entry to the study at less than 2 years of age. Lung function was studied by flow-volume spirometry (FVS), and BHR by methacholine and exercise challenge tests 11.4 years after hospitalization during infancy.

Results: RSV aetiology of bronchiolitis was associated with reduced forced vital capacity (FVC; 93.65% of predicted ± 11.05 vs. 99.57% ± 12.59, $p = 0.009$). Early sensitization to inhalant allergens (OR 12.59, 95% CI 2.30–68.77) and maternal smoking during pregnancy (OR 4.58, 95% CI 1.28–16.39) were associated with BHR to exercise, and early atopic dermatitis (OR 3.48, 95% CI 1.09–11.10) was associated with BHR to methacholine.

Conclusions: RSV bronchiolitis was associated with a restrictive pattern of lung function. Early atopy and maternal smoking during pregnancy may play a role in the development and persistence of BHR.

INTRODUCTION

Bronchiolitis is defined as a lower respiratory infection (LRI) in infants usually caused by respiratory syncytial virus (RSV). Wheezing is common in infants and young children who suffer from LRI caused by different viruses. In population-based studies, one-third of all children have presented with wheezing before 3 years of age (1), and about 2% require hospital admission for wheezing (2).

Hospitalization for bronchiolitis in infancy has been linked with lung function abnormalities (3,4), reactive airways (4,5) and atopic asthma (4) until 10–13 years of age. In the Tucson birth cohort study, LRI caused by RSV in infancy was predictive, even in outpatients, for decreased lung function and increased airway responsiveness at the age of 11 years compared with children with non-RSV infections (6). Infants with wheezing severe enough to require hospitalization seem to have host-specific characteristics, such as atopy or eosinophilia, which modify their responses to viral infections (7). So far, risk factors for later lung function abnormalities or for the persistence of bronchial hyper-responsiveness (BHR) after wheezing in infancy have rarely been studied in prospective settings with long-term follow-ups after infantile wheeze.

Our earlier observations indicate that, among infants hospitalized for wheezing, those with atopic dermatitis, sensitisation to aeroallergens or viral aetiology other than RSV carry the highest risk for asthma continuing until teenage years (8,9). In the present paper, lung function and BHR to exercise and methacholine were studied at the age of 11–14 years in the same cohort. We aimed to elucidate whether there are any links between host-specific characteristics or viral aetiology of infantile wheeze, and subsequent lung function and/or bronchial responsiveness during teenage years.

PATIENTS AND METHODS

As described earlier in detail (10), 100 children, aged 1–23 months, were prospectively recruited into this follow-up study during 1992–1993. The enrolment criteria were the presence of wheezing and respiratory distress requiring hospital care during acute respiratory tract infection (11). Subsequently, seven study visits have been organized in order to check the respiratory status, especially the presence of asthma and symptoms presumptive for asthma, and allergic manifestations in the children (9,10,12–14).

The baseline data were collected by interviewing the parents during hospitalization for bronchiolitis in infancy (index hospitalization), using a structured questionnaire including questions on the history of wheezing and atopic dermatitis in the children, and on the family history of asthma and atopic diseases. Only the diagnoses made by a physician were recorded. In addition, information on maternal smoking during pregnancy, maternal and paternal smoking when the child was under 2 years of age, as well as exposure to tobacco smoke in day care, were registered prospectively (11).

Viral infections were studied by antigen detection in the nasopharyngeal aspirates (NPA) obtained during

hospitalization and by antibody determinations in paired sera; adeno group, influenza A and B, parainfluenza types 1, 2 and 3, and RSV were assayed (11). Later, rhinoviruses, enteroviruses and coronaviruses were studied in 81 children and RSV in 61 children by reverse transcription polymerase chain reaction (RT-PCR; 8,15) in frozen NPA samples, obtained during the index hospitalization. In all, 69 of 100 children had at least one viral finding after all viral studies were performed.

On admission, a venous blood sample was drawn for determination of blood eosinophils and total serum immunoglobulin E (IgE). In this study, the limits for abnormal results were $\geq$0.45 cells $\times$ 10^9/l for blood eosinophils (16) and $\geq$100 IU/mL for total serum IgE (17). Later, allergen-specific IgE antibodies (Phadiatop Combi®, Pharmacia, Uppsala, Sweden) were determined by fluoroenzyme-immunometric assay (FEIA; UniCAP™, Pharmacia, Uppsala, Sweden) in frozen serum samples, obtained during index hospitalization (18). The presence of specific IgE antibodies to a mixture of inhalant allergens was screened by the detection limit ($\geq$0.35 kU/L), and if the result was positive, analyses were continued for allergen-specific IgE antibodies by the same detection limit. Phadiatop Combi® panel for inhalant allergens includes timothy grass, birch and mugwort pollens, and cat, dog and horse epithelial dander, house dust mite *Dermatophagoides pteronyssinus*, and spores of the mould *Cladosporium herbarum*.

Eighty-one children, 60 boys and 21 girls, attended the follow-up in 2004, and they constitute the subjects of this paper. Among them, 25 of 81 had been hospitalized for RSV bronchiolitis and 19 of 66 for rhinovirus bronchiolitis in infancy. At the follow-up visit, the age of the children varied from 10.9 to 13.7 years (median 12.3), and the follow-up time from the index hospitalization varied from 10.3 to 12.3 years (median 11.4). Eighteen (22%) children were on continuous anti-inflammatory asthma medication, 17 used inhaled steroids and 1 used cromones. In addition, 11 (14%) children were advised to use inhaled steroids intermittently during pollen seasons and/or infections (9), but none of them were on anti-inflammatory medication during or prior to the study visit.

There were 19 dropouts among the original study group of 100 children. The 81 attendants and 19 dropouts were compared for early-life risk factors, including the history of wheezing and atopic dermatitis before enrolment in infancy, the family history of asthma and atopic diseases, maternal smoking during pregnancy, maternal or paternal smoking in infancy, passive smoking in infancy at home or day care, RSV or rhinovirus identification during infantile bronchiolitis, and elevated total serum IgE, blood eosinophilia and the presence of allergen-specific IgE in infancy. Maternal smoking in infancy was less common among participants than among dropouts (28% vs. 56%, $p = 0.027$). There were no other statistically significant differences between these two groups.

The follow-up study was performed from January to March 2004, during the cold season in our area. Baseline flow-volume spirometry (FVS) was examined by a pneumotachographic flow-volume spirometer (Medikro, Kuopio, Finland). Before the visit, the children were instructed not to use inhaled long-acting β2-agonists for 48–72 h, or short-acting β2-agonists for 12 h before the lung function studies. In addition, no symptoms suggestive of respiratory tract infections were allowed. First, the children were carefully instructed on how to perform the test. Thereafter, the measurements were repeated three times, and accepted if the variation in FEV_1 was less than 5% and the graphic curves were appropriate and equal in shape. The FVS was appropriately performed by 80 of 81 children.

Lung function parameters were expressed as percentages of the gender-specific height-related reference values (% of predicted) for Finnish children (19). The parameters registered were FVC (forced vital capacity), FEV_1 (forced expiratory volume in 1 sec), FEV_1/FVC, MEF_{50} (maximal expiratory flow at 50% of FVC) and MEF_{25} (maximal expiratory flow when 25% of the FVC remains to be expired). Among the acceptable FVS curves, the best FVC and FEV_1 were recorded for further analyses. The other flow-volume parameters were obtained from three technically satisfactory FVS curves by the envelope method, in which the best superimposed curves from total lung capacity were applied to form a composite maximal curve (20). The cutoff limits for abnormal results were $<$80% for FEV_1, $<$88% for FEV_1/FVC, $<$62% for MEF_{50} and $<$48% for MEF_{25} (21).

The baseline pulmonary testing was followed by exercise challenge that consisted of free running outdoors for 8 min at the heart rate of 80% or more of the predicted maximum. The median outdoor temperature was −1.2°C (range from −10.0 to 16.5) and the median relative humidity was 60.0% (18.5–77.6). During running, the heart rate was monitored by telemetry (Polar Sport Tester, Polar Elektro Ltd, Kempele, Finland) at 1-min intervals. The median heart rate was 89% of the predicted maximum at 4–5 min measurements, and 91% at the end of the test. FVS was measured and the lung sounds were auscultated 5, 10 and 15 min after the exercise. The FEV_1 obtained from the baseline FVS was used in later comparisons. FEV_1 changes were calculated as follows: [(pre-exercise FEV_1 – post-exercise FEV_1)/pre-exercise FEV_1] $\times$ 100%. The exercise challenge test was regarded as positive if there was a 10% or greater fall in FEV_1 values 5, 10 or 15 min after the running (22). The exercise challenge test was appropriately performed by 78 of 81 children.

The methacholine challenge test was performed on a separate day apart from other lung function studies. The children were instructed and the baseline FVS was performed as described above. Methacholine was inhaled by Spira Electro-2 dosimeter (Spira Respiratory Care Center Ltd., Hämeenlinna, Finland) allowing the calculation of the total amount of methacholine inhaled by each subject. First, FVS was performed before and after an inhalation of physiologic saline, to obtain the baseline FEV_1. Then, methacholine was inhaled, and the numbers of breaths required to achieve a cumulative dose of 20, 80, 300, 900, 2900 and 4900 μg of methacholine were 1, 3, 11, 3, 10 and 10, respectively. The

concentration of methacholine increased from 2.5 mg/mL to 25 mg/mL after the cumulative dose of 300 μg. The baseline FEV_1 value was applied in the comparisons, with the measurements done 1.5 min after each methacholine dose. The test was continued until a 20% fall in FEV_1, or until a cumulative dose of 4900 μg of methacholine was reached. The exact cumulative dose causing a 20% fall in FEV_1 was determined by semilogarithmic interpolation and termed the provocative dose (PD_{20}) (23). The methacholine test was appropriately performed by 69 of 81 children.

One of the authors (MKH) was responsible for both the performance of lung function and exercise challenge tests and the interpretation of the results.

Asthma was defined (1) by the use of continuous or intermittent inhaled anti-inflammatory medication or (2) by repeated wheezing and positive result in the exercise challenge test (9). By this definition, asthma was present in 32 (40%) children; 29 children were on continuous maintenance and 16 were positive in the exercise challenge test (9).

The data were analyzed using SPSS 11.5 software (SPSS, Inc., Chicago, IL). Statistical significance of the differences in the continuous baseline FVS parameters and the results of the provocation tests between children with ongoing, intermittent or no anti-inflammatory medication and between non-asthmatics and asthmatics were assessed by Mann–Whitney U-test. The dichotomous data were analyzed by the Fisher's exact test with Bonferroni correction in paired comparisons. Analysis of covariance was applied to assess the significance of the differences in the continuous baseline FVS parameters (percentages of the gender-specific height-related reference values) between children with and without a risk factor present. Each risk factor was analyzed separately, with age on admission included as a covariate. In this model, age on admission acted as an effect modifier with interaction with risk factors. Similar analyses were performed between children with and without RSV or rhinovirus aetiology of wheeze. Logistic regression analysis, adjusted for age on admission, was applied to assess the differences, estimated as odds ratios (OR) and 95% confidence intervals (CI), for abnormal lung function values and bronchial responsiveness between children with and without certain risk factors present. Each risk factor was analyzed separately. Because atopic dermatitis on study entry was common among children with rhinovirus aetiology for wheezing (8), adjustment for early atopic dermatitis was added in the analyses concerning viruses and FVS or challenge test results. Adjustment for sex was included in the analyses for BHR, but not, due to the availability of gender-specific references, in the analyses for FVS.

The study was approved by Research Ethics Committee of Kuopio University and Kuopio University Hospital. Informed written consent was obtained from the parents of the children.

RESULTS

The results of the baseline FVS in the 80 study subjects are presented in Table 1. On average, all parameters were within normal limits, and even the lower limits of the 95% CIs were at a normal level when compared to gender-specific height-related references.

Table 1 Baseline lung function by FVS (% predicted) in 80 children hospitalized for wheezing in infancy and attending the follow-up visit during teenage years

Parameters in FVS (n = 80)	Mean (95% confidence interval)	Median (range)
FVC	97.79 (95.04–100.55)	96.98 (71.86–137.67)
FEV_1	92.23 (89.35–95.12)	90.78 (62.64–127.62)
FEV_1/FVC	94.55 (92.67–96.43)	95.22 (68.07–109.78)
MEF_{50}	81.43 (77.20–85.67)	81.88 (36.04–120.95)
MEF_{25}	71.68 (71.68–76.27)	74.40 (29.64–114.13)

FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 sec; MEF_{50} = maximal expiratory flow at 50% of FVC; MEF_{25} = maximal expiratory flow when 25% of FVC remains to be expired.
FVS = flow-volume spirometry.

Univariate analyses

As seen in Table 2, 26 (33%) children had an abnormal value in one or more of the four FVS parameters. Children with continuous, intermittent and no anti-inflammatory asthma medication differed significantly only for abnormal MEF_{25}, the group with ongoing medication having in paired comparisons higher figures than the group with no medication (Table 2).

The exercise challenge test was positive (≥10% fall in FEV_1) in 21 (26%) children, and in 18 cases the result was positive at 5 min, in 16 cases at 10 min and in 14 cases at 15 min after the exercise. In the methacholine challenge test, any responsiveness ($PD_{20} \leq 4900$ μg) was demonstrated in 40 (58%), intermediate to high responsiveness ($PD_{20} \leq 1600$ μg) in 32 (46%) and high responsiveness ($PD_{20} \leq 400$ μg) in 10 (14%) children.

Children with continuous anti-inflammatory medication had more often a positive result (≥10% fall in FEV_1) in the exercise challenge test than children with no medication (50% vs. 21%, OR 3.77, 95% CI 1.19–11.97). The group with intermittent anti-inflammatory medication did not differ from the two other groups (data not shown). Likewise, there was some evidence that the three groups might differ for responsiveness to methacholine, but in paired comparisons the differences were not significant at any PD_{20} level (data not shown).

Both methacholine and exercise challenges were appropriately performed by 66 children and 15 of them had a positive result in both tests, which is ≥10% fall in FEV_1 in exercise and $PD_{20} \leq 1600$ μg in methacholine challenge. Sixteen children were positive in the methacholine challenge alone and only 3 in the exercise challenge alone.

There were no significant differences in FVC, FEV_1, FEV_1/FVC and MEF_{50} between the 32 asthmatics and 48

Table 2 Abnormal findings in baseline FVS, in relation to anti-inflammatory medication

FVS (n = 80)	Continuous anti-inflammatory medication (n = 18)	Intermittent anti-inflammatory medication (n = 11)	No anti-inflammatory medication (n = 51)	p*
FEV_1 < 80%	5 (28%)	1 (9%)	8 (16%)	0.462
FEV_1/FVC < 88%	4 (22%)	4 (36%)	5 (10%)	0.058
MEF_{50} < 62%	4 (22%)	2 (18%)	7 (14%)	0.605
MEF_{25} < 48%	5 (28%)†	3 (27%)	3 (6%)	0.015
At least one abnormal value	7 (39%)	4 (36%)	15 (29%)	0.729

*Fisher's exact test.
†p = 0.048 vs. no anti-inflammatory medication (Fisher's exact test with Bonferroni correction).
Abbreviations are same as in Table 1.

non-asthmatics (data not shown). MEF_{25} was <48% of predicted in 8 (25%) asthmatics and in 3 (6%) non-asthmatics (OR 5.0, 95% CI 1.21–20.61).

Multivariate analyses

In analysis of covariance, family history of asthma, maternal smoking during pregnancy, maternal or paternal smoking in infancy, as well as exposure to tobacco smoke in infancy at home or in day care, elevated serum total IgE, presence of specific IgE to inhalant allergens and presence of atopic dermatitis on admission, when included separately in the model, had no significant association with any parameter in FVS (data not shown). There was a trend that elevated blood eosinophils, counted on admission, were associated with lower FEV_1 (89.54 (mean, % of predicted) ± 12.11 (SD) vs. 93.64 ± 13.48, p = 0.081), MEF_{50} (76.16 ± 18.32 vs. 83.81 ± 19.33, p = 0.059) and MEF_{25} (64.98 ± 19.08 vs. 74.72 ± 21.11, p = 0.065).

The same early-life risk factors were included in logistic regression, and none of them were significant as a predictor of abnormal lung function, defined as one or more abnormal value in one or more FVS parameter (data not shown). The early-life factors were tested, by a similar logistic regression model, as predictors of abnormal results in exercise and methacholine challenge tests. As seen in Table 3, the presence of specific IgE to inhaled allergens on admission and maternal smoking during pregnancy were associated with BHR to exercise, and early atopic dermatitis was associated with intermediate to high responsiveness to methacholine. No other early risk factor, present during index hospitalization, was predictive of BHR at the median age of 12.3 years (data not shown). The medication status (ongoing, intermittent, no anti-inflammatory medication) had a significant association with MEF_{25} but not with any other variable in FVS and not with BHR at any level in univariate analyses. Therefore, medication was not included in the multivariate models.

Finally, the association between viral aetiology during index hospitalization and later lung function and/or BHR was studied by logistic regression. Age on admission (<12 or ≥12 months) and early atopy (atopic dermatitis at ≤24 months of age) on admission were included, but the current medication status was not included, as covariates in the model. RSV bronchiolitis was associated with a higher FEV_1/FVC and a lower FVC when compared with non-RSV aetiology (Table 4). There were no statistically significant differences in any baseline FVS parameters between 19 rhinovirus positive and 46 negative cases (data not shown). No associations were found between rhinovirus or RSV aetiology and bronchial responsiveness to exercise or methacholine (data not shown).

Table 3 Risk factors for bronchial hyper-responsiveness during teenage in 80 children hospitalized for wheezing in infancy

Risk factors for BHR* (present/tested)	BHR	OR (95% CI)†
	To exercise‡	
Specific IgE§ to inhalant allergens (n = 13/71)	10	12.586 (2.303–68.772)
Maternal smoking during pregnancy (n = 17/78)	8	4.584 (1.282–16.391)
	To methacholine¶	
Atopic dermatitis in infancy (n = 19/69)	13	3.484 (1.094–11.101)

*Only statistically significant risk factors reported.
†ORs and 95% CIs between the groups determined by logistic regression adjusted for sex and age (<12 months/≥12 months) on admission.
‡Fall in FEV_1 ≥ 10%.
§≥0.35 kU/L.
¶PD_{20} < 1600 μg methacholine.

Table 4 Findings in baseline FVS 10–12 years after hospitalization for infantile wheezing, in relation to RSV aetiology of infection

Parameter*	RSV+† (n = 24)	RSV–‡ (n = 56)	p§
FVC (% predicted)	93.65 ± 11.05	99.57 ± 12.59	0.009
FEV_1/FVC (% predicted)	98.35 ± 6.53	92.91 ± 8.70	0.033

*Only statistically significant parameters reported; FVC = forced vital capacity, FEV_1 = forced expiratory volume in 1 sec.
†RSV identified as a single viral finding or in combinations with other viruses.
‡RSV not identified.
§Analysis of covariance. Age (<12 months/≥12 months) and atopic dermatitis (present/not present) on admission were included in the model as covariates and effect modifiers.

DISCUSSION

There are three main results in the present study evaluating lung function and bronchial reactivity during teenage, in relation to early-life risk factors, in children hospitalized for bronchiolitis in infancy. First, FVS was, on average, within normal limits. However, 33% of the children had abnormal results in some individual parameters. Second, wheezing with RSV was associated with reduced FVC, suggesting a restrictive pattern of lung function. Third, BHR was rather common, presenting by the applied criteria in 26–46%. BHR to exercise was associated with early sensitization to inhalant allergens and maternal smoking during pregnancy. BHR to methacholine was associated with a history of atopic dermatitis in infancy.

Sigurs et al. followed a cohort of <12-month-old infants hospitalized for RSV bronchiolitis and a control group up to the age of 13 years, and found that FEV_1/FVC and FEF_{75} values were lower in the RSV group than in controls (4). The observations suggest persistent bronchial obstruction after RSV bronchiolitis. In contrast, in our study, 10–12 years after hospitalization for wheezing at <24 months of age, RSV bronchiolitis seemed to be associated with a restrictive pattern of lung function abnormality, documented by significantly decreased FVC values concomitantly with normal FEV_1 values and even elevated FEV_1/FVC values. In this study, children with former RSV bronchiolitis were compared with selected controls, subjects with former bronchiolitis not caused by RSV. Rhinoviruses were the most dominant viruses in this RSV-negative group, and the rhinovirus group evidently included children with their first asthma episode (8,9). To diminish this bias, age and atopy, which were associated with rhinovirus aetiology in this cohort, were included in the multivariate model, and RSV aetiology still was an independent risk factor for lower FVC. On the other hand, evidence of permanent restriction found in the present study, as well as evidence of permanent obstruction found by Sigurs et al. (4), may reflect premorbid structural changes in infants susceptible to severe RSV infection (1).

Although FVC values were lower in RSV-positive than in RSV-negative cases, the values were within normal limits in both groups, which make the clinical significance of the finding unclear. In the Childhood Asthma Management Program (CAMP) study, FVC growth velocities were higher among children with asthma than among children without asthma until 14 years for boys and 12 years for girls (24). In the present cohort, asthma was more common after RSV-negative than after RSV-positive bronchiolitis (9), and FVC growth velocity pattern comparable to the subjects in the CAMP study could explain our findings. On the other hand, we have recently found that asthma and bronchial hyperreactivity, after many nonsymptomatic years, have a tendency to recur in early adulthood (25). Therefore, minor changes in lung function or in bronchial reactivity, though clinically nonsignificant, may be useful predictors of subsequent morbidity.

In the study of Wennergren et al., 37% of <24-month-old children hospitalized for bronchiolitis had abnormal results in histamine challenge at the age of 10 years (5), the figure being in between our BHR figures by two approaches, 26% in the exercise and 46% in the methacholine challenge, at an average of 12.3 years of age. Wennergren et al. did not find any association between early atopy and asthma or BHR at the age of 10 years (5). In the present cohort, instead, the presence of atopic dermatitis or specific IgE in inhalant allergens in early life were significant predictors of asthma at teenage (9) and were also independent risk factors for BHR, as seen in the present paper. Our findings are in accordance with a recent birth cohort study from Germany (26), in which BHR at school age was significantly associated with sensitization to perennial allergens in early life, particularly in those children who suffered from current wheezing.

In a meta-analysis including 22 studies, maternal smoking was associated with small but statistically significant deficits in lung function in school-aged children (27). In the present study, there was no significant association between passive smoking in infancy and abnormal lung function at late school age. The results were similar when maternal and paternal smoking were analyzed separately. In contrast, maternal smoking during pregnancy was an independent risk factor for BHR to exercise, even after adjustment with passive smoking in infancy. Although there is some evidence that in utero exposure to tobacco smoke may increase bronchial responsiveness continuing through childhood (28), many factors, such early-life passive smoking and later active smoking, complicate the interpretation of the results (28,29). In the present study, tobacco smoke exposure in infancy was rather common, presenting in 46% of the cases (9), but none of the children smoked at the time of the study visit. A recent Swedish long-term follow-up after bronchiolitis in infancy stressed the link between early-life tobacco smoke exposure, later BHR and later asthma (30). Early passive smoking was an independent risk factor for BHR and for active smoking at young adult age, and both of them were associated with chronic asthma (30).

The strengths of the present study are the long-term prospective follow-up time, careful collection of data in infancy, extensive viral studies with advanced methods and a good, more than 80% attendance to the study more than 10 years later. FVS was studied twice 2 weeks apart, with nearly identical results, and bronchial responsiveness was studied by two methods, reflecting different mechanisms of BHR. In addition, our patients represented a certain child population, and covered the whole spectrum of hospital-treated bronchiolitis, because our university hospital is the only one providing inpatient care for children in this area. Thus, we regard our results concerning both lung function and bronchial responsiveness trustworthy and representative for school children with early-life hospitalization for wheezing. The main shortcoming of the study was the absence of a control group. On the other hand, population-based gender-specific height-related reference values were available for lung function studies. Because lung function abnormalities were rather rare, and bronchial hyper-reactivity was rare in the subgroups constructed on the basis of early risk factors, some differences were probably missed due to insufficient power of the study. Because of the lack of a

control group, and of an obvious underpowering for stratified analyses, the conclusions from the present results should be drawn carefully.

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References

1. Taussig LM, Wright AL, Holberg CJ, Halonen M, Morgan WJ, Martinez FD. Tucson children's respiratory study: 1980 to present. *J Allergy Clin Immunol* 2003; 111: 661–75.
2. Korppi M, Halonen P, Kleemola M, Launiala K. Viral findings in children under the age of two years with expiratory difficulties. *Acta Paediatr Scand* 1986; 75: 457–64.
3. Noble V, Murray M, Webb MS, Alexander J, Swarbrick AS, Milner AD. Respiratory status and allergy nine to 10 years after acute bronchiolitis. *Arch Dis Child* 1997; 76: 315–9.
4. Sigurs N, Gustafsson PM, Bjarnason R, Lundberg F, Schmidt S, Sigurbergsson F, et al. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. *Am J Respir Crit Care Med* 2005; 17: 137–41.
5. 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: 351–5.
6. Stein RT, Sherrill D, Morgan WJ, Holberg CJ, Halonen M, Taussig LM. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999; 354: 541–5.
7. Martinez FD. Heterogeneity of the association between lower respiratory illness in infancy and subsequent asthma. *Proc Am Thorac Soc* 2005; 2: 157–61.
8. 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.
9. 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: 316–23.
10. Reijonen T, Korppi M, Kuikka L, Remes K. Anti-inflammatory therapy reduces wheezing after bronchiolitis. *Arch Pediatr Adolesc Med* 1996; 150: 512–7.
11. Reijonen T, Korppi M, Pitkäkangas S, Tenhola S, Remes K. The clinical efficacy of nebulized racemic epinephrine and albuterol in acute bronchiolitis. *Arch Pediatr Adolesc Med* 1995; 149: 686–2.
12. Reionen 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: 113–9.
13. Reijonen TM, Kotaniemi-Syrjänen A, Korhonen K, Korppi M. Predictors of asthma three years after hospital admission for wheezing in infancy. *Pediatrics* 2000; 106: 1406–12.
14. 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: 418–25.
15. Kotaniemi-Syrjanen A, Laatikainen A, Waris M, Reijonen TM, Vainionpaa R, Korppi M. Respiratory syncytial virus infection in children hospitalized for wheezing: virus-specific studies from infancy to preschool years. *Acta Paediatr* 2005; 94: 159–65.
16. Eisen AH. Eosinophilia. In: Bierman CW, Pearlman DS, editors. *Allergic diseases in infancy, childhood and adolescence*. Philadelphia, PA: W.B. Saunders, 1980: 761–2.
17. Lindberg RE, Arroyave C. Levels of IgE in serum from normal children and allergic children as measured by enzyme immunoassay. *J Allergy Clin Immunol* 1986; 78: 614–8.
18. Paganelli R, Ansotegui IJ, Sastre J, Lange CE, Roovens MH, de Groot H, et al. Specific IgE antibodies in the diagnosis of atopic disease. Clinical evaluation of a new in vitro test system, UniCAP, in six European allergy clinics. *Allergy* 1998; 53: 763–8.
19. Salorinne Y. Reference values for flow-spirometry in children (abstract). *Clin Physiol* 1990; 10: 303–2.
20. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report of Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 1993; 16: 5–40.
21. Viljanen A. Reference values for spirometric, pulmonary diffusing capacity and body plethysmographic studies. *Scand J Clin Lab Invest* 1982; 42 Suppl 159: 1–50.
22. Godfrey S. Bronchial hyper-responsiveness in children. *Paediatr Respir Rev* 2000; 1: 148–55.
23. Korppi M, Kuikka L, Reijonen T, Remes K, Juntunen-Backman K, Launiala K. Bronchial asthma and hyperreactivity after early childhood bronchiolitis or pneumonia. An 8-year follow-up study. *Arch Pediatr Adolesc Med* 1994; 148: 1079–84.
24. Strunk RC, Weiss ST, Yates KP, Tonascia J, Zeiger RS, Szefler SJ. Mild to moderate asthma affects lung growth in children and adolescents. *J Allergy Clin Immunol* 2006; 118: 1040–7.
25. 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: 1070–6.
26. Illi S, Von Mutius E, Lau S, Niggemann B, Gruber C, Wahn U. Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study. *Lancet* 2006; 368: 763–70.
27. Cook DG, Strachan DP, Carey IM. Health effects of passive smoking. 9. Parental smoking and spirometric indices in children. *Thorax* 1998; 53: 884–93.
28. Cook DG, Strachan DP. Parental smoking, bronchial reactivity and peak flow variability in children. *Thorax* 1998; 53: 295–301.
29. Lodrup Carlsen KC, Carlsen KH. Effects of maternal and early tobacco exposure on the development of asthma and airway hyperreactivity. *Curr Opin Allergy Clin Immunol* 2001; 1: 139–43.
30. Goksör E, Åmark M, Alm B, Gustafsson PM, Wennergren G. Asthma symptoms in early childhood–what happens then? *Acta Paediatr* 2006; 95: 471–8.