

REGULAR ARTICLE

Following up infant bronchiolitis patients provided new evidence for and against the united airway disease hypothesis

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Keywords

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ABSTRACT

Aim: The united airway disease (UAD) hypothesis suggests that allergic rhinitis and asthma develop together. We evaluated the evidence for and against the UAD hypothesis at five to seven years of age after hospitalisation for bronchiolitis at less than six months.

Methods: This study used prospective follow-up data for 102 children hospitalised for bronchiolitis under the age of six months. We included the presence of previous and current asthma, prolonged rhinitis and skin prick tests (SPT) to common inhaled allergens and lung function by impulse oscillometry (IOS) at five to seven years of age. Bronchial hyper-reactivity (BHR) was assessed using the exercise challenge test and bronchodilation test.

Results: Current asthma, but not previous transient asthma, was associated with prolonged rhinitis and a positive SPT. BHR, which reflected reactive airways, but not lung function, was associated with respiratory allergy, namely the combination of current asthma, prolonged rhinitis and a positive SPT.

Conclusion: This post-bronchiolitis follow-up study suggested an association between respiratory allergy and reactive airways at five to seven years of age, which supported the UAD hypothesis. However, previous transient asthma and a reduction in lung function reduction did not support the hypothesis.

INTRODUCTION

The united airway disease (UAD) hypothesis suggests that upper and lower airways share common pathogenetic mechanisms in allergic rhinitis and asthma, but the clinical manifestations differ (1,2). It also maintains that allergic rhinitis and asthma often develop one after another or even at the same time. This hypothesis is reflected in the *Allergic rhinitis and its impact on asthma* (ARIA) document, which recommends that the presence of allergic rhinitis must be considered, and treated if present, in children with asthma and vice versa (3,4).

Atopy is genetically determined, but clinical manifestations and their occurrence depend on age (5). Sensitisation to food allergens develops during infancy, and the most

common clinical manifestation is atopic dermatitis, while sensitisation to inhaled allergens starts to occur during the second or third year of life, leading to allergic rhinitis. In Finland, and similar countries such as Sweden and Germany, the incidence of allergic rhinitis in nonselected populations is 5–10% at six to seven years and 23–31% at 13 to 14 years (6). In line with this, the incidence of allergic sensitisation to inhaled allergens, assessed by a positive skin prick test (SPT), is 10–20% at five to six years and 20–40% at 11 years (7,8).

Abbreviations

BD test, Bronchodilator test; BHR, Bronchial hyper-reactivity; ECT, Exercise challenge test; FVS, Flow-volume spirometry; ICS, Inhaled corticosteroid; IOS, Impulse oscillometry; Rrs5, Respiratory system, resistance at 5 Hz; SPT, Skin prick test; UAD, United airway disease; Xrs5, Respiratory system, reactance at 5 Hz.

Key notes

- The united airway disease (UAD) hypothesis suggests that allergic rhinitis and asthma develop together, and we evaluated the evidence for the hypothesis after infant bronchiolitis at less than six months of age.
- Our findings suggested an association between respiratory allergy and reactive airways at five to seven years of age, which supported the UAD hypothesis.
- However, previous transient asthma and a reduction in lung function did not support the hypothesis.

Data previously published on this post-bronchiolitis cohort showed that 27.9% of the children had a diagnosis of asthma ever and 12.7% had current asthma at five to seven years of age (9). Lung function, as measured by impulse oscillometry (IOS), showed small airways obstruction in the baseline measurements, with 20% of these being abnormal when compared to Finnish population data. The data also showed that 16% had bronchial hyper-reactivity (BHR) (10).

This article presents a secondary analysis of the data on the 102 children and reports on the information available on asthma, prolonged rhinitis, SPT results and baseline, post-exercise and post-bronchodilator IOS results. Previous papers on this cohort have not included data on rhinitis or SPT results. We aimed to evaluate the evidence for and against the UAD hypothesis at five to seven years of age in children who had been hospitalised for bronchiolitis when they were less than six months of age. We analysed whether there were significant associations between previous or current asthma, current prolonged rhinitis, current SPT positivity, current reduced lung function as assessed by IOS and current BHR – reflecting reactive airways – based on IOS responses to exercise and, or, bronchodilation.

PATIENTS AND METHODS

We prospectively followed up 166 healthy, term children who had been hospitalised for bronchiolitis before six months of age until they were five to seven years of age. Of these, 127 attended the follow-up visit, which consisted of a clinical examination by a paediatrician, data collection using a structured questionnaire and an interview, skin prick tests (SPT) to common inhaled allergens and lung function measurements, including testing for BHR (9).

Complete IOS (11) measurements, at baseline and after the exercise challenge test (ECT), and bronchodilation (BD) tests were available for 103 of these 127 children, as previously published (10). One child with no history of prolonged rhinitis or asthma refused to undergo the SPT. This meant that complete data were available for 102 children on current or previous asthma, current lung function measured using IOS, current BHR in the ECT and BD tests, current SPT results and the presence or absence of prolonged rhinitis during the last 12 months. These 102 children formed our final study population.

The IOS outcome variables of respiratory system resistance at 5 Hz (Rrs5) and respiratory system reactance at 5 Hz (Xrs5) were transformed to height-adjusted standard deviation (SD) Z-scores in order to describe the difference from the population predicted value (11–13). In the baseline IOS, the limit of pathological Rrs5 was +1.65 SD and the limit of pathological Xrs5 was –1.65 SD, representing the upper and lower 95% confidence intervals of the Z-score scale, respectively (12). BHR was considered to be present if the child presented with a rise of at least 35% in Rrs5 in the ECT test ($n = 5$) or with a decrease of at least 35% in Rrs5 in the BD test ($n = 11$), compared to baseline values (11–14).

We categorised 13 children as having current asthma because they had been on continuous or intermittent inhaled corticosteroid (ICS) medication during the last 12 months. Another two were added to the list because BHR was diagnosed at the follow-up visit, and there were asthma-presumptive symptoms during the last 12 months, such as wheezing or prolonged cough for more than four weeks or a night cough when no infection was present. The symptoms and the consumption of medicines were covered in the questionnaire and checked during the interview. Children were classified as having previous transient asthma if they had previously used ICS medication, but not during the past 12 months.

The diagnosis of current prolonged rhinitis was based on the answers given in the questionnaire and interview. The questionnaire included questions on rhinitis symptoms and their occurrence due to the season and the presence or absence of infection. Prolonged rhinitis was considered to be present if allergic rhinitis had been diagnosed by a doctor or the children had suffered from a runny, sneezing or stuffy nose during the last 12 months when they did not have an infection, in connection with seasonal pollen exposure or contact with animals.

Skin prick tests (SPT) were performed using standardised extracts (ALK, Copenhagen, Denmark) for the outdoor allergens of birch, timothy grass and mugwort pollen and spores of the mould *Alternaria alternata*, for cat and dog dander and for the house dust mites *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*. We used 10 mg/mL of histamine hydrochloride as a positive control and glycerol as a negative control. One drop of each allergen extract was applied to healthy forearm skin and punctuated with a sharp lancet, and an experienced nurse measured the reaction after 15 minutes. The test was positive if the skin wheal reached a diameter of 3 mm. Antihistamine medication had to be discontinued for five or more days before the SPTs.

Respiratory allergy was defined by combining current asthma, prolonged rhinitis and a positive SPT to provide four different definitions: (i) all three elements, (ii) current asthma plus either prolonged rhinitis or a positive SPT, (iii) current asthma on its own or rhinitis combined with a positive SPT and (iv) at least one of the three elements.

Statistics

SPSS version 21 (IBM Corp, New York, USA) was used in the statistical analyses. Pearson's chi-square test or Fisher's exact test were used, as appropriate, to analyse categorised variables. ANOVA was used to analyse continuous variables in order to compare differences in subgroups. The Bonferroni correction was used for paired comparisons, by multiplying the p-value by two, when only two of the three groups were included.

Ethics

The Ethics Committee of the Tampere University Hospital district approved the study, and written, informed consent was obtained from the parents during the hospitalisation for

bronchiolitis and at the control visit at five to seven years of age.

RESULTS

Rhinitis and asthma

Current asthma was present in 15 (14.7%) of the 102 children, and prolonged rhinitis was present in 27 (26.5%) children. We also found that eight of the 15 children (53.3%) with current asthma had prolonged rhinitis, compared with 21.8% of the 87 children without current asthma ($p = 0.016$), and that eight of the 27 children (29.6%) with prolonged rhinitis had current asthma, compared with 9.3% of the 75 children without. On the other hand, 46.7% of the children with current asthma did not have any rhinitis and 70.4% of the children with prolonged rhinitis did not have current asthma.

Current asthma (53.3%) and prolonged rhinitis (62.9%) were significantly associated with a positive SPT to inhaled allergens (Table 1). There were 12 children who presented with previous transient childhood asthma without current asthma at five to seven years of age. Only two (16.7%) of them had prolonged rhinitis and neither were SPT positive. In comparison, 22.7% of the 75 children with no previous or current asthma had rhinitis ($p = 0.972$) and 32.0% had a positive SPT ($p = 0.0016$).

Table 1 Skin prick test results in relation to current asthma and prolonged rhinitis in 102 former bronchiolitis patients at five to seven years of age

Skin prick test results	Current asthma n = 15	p-Value versus no current asthma	Prolonged rhinitis n = 27	p-Value versus no rhinitis
At least one inhaled allergen positive (n = 32)	8 (53.3%)	p = 0.049	17 (62.9%)	p = 0.002
Cat dander (n = 12)	6	p = 0.002	8	p = 0.002
Dog dander (n = 13)	7	p < 0.001	8	p = 0.005
Dust mites (n = 4)*	0	p = 0.542	1	p = 0.715
Birch (n = 20)	6	p = 0.042	11	p = 0.002
Timothy (n = 19)	7	p = 0.007	9	p = 0.026
Mugwort (n = 4)	2	p = 0.102	2	p = 0.285
<i>A. alternata</i> (n = 3)**	2	p = 0.056	2	p = 0.170

**Dermatophagoides farinae* in no cases, *Dermatophagoides pteronyssinus* in four cases.

***A. alternata* = *Alternaria alternata*.

Current asthma = continuous ICS or intermittent medication during the last 12 months (n = 13) or current symptoms and BHR (n = 2).
p-value < 0.05 marked in bold.

Lung function, reactive airways and asthma

The proportions of children with either increased Rrs5 or decreased Xrs5 in their baseline IOS were not significantly different in children with current asthma, previous transient asthma or no asthma (Table 2). There was a significant association between current asthma and BHR (Table 2).

We found that eight children had pathologic Rrs5 in their baseline IOS, but none of them had a pathologic 35% Rrs5 increase in their ECT. However, four (50.0%) of them had a pathological 35% decrease of Rrs5 in their BD test compared with 7.4% of the 94 children with a normal baseline Rrs5 ($p = 0.004$). Similarly, 19 children had pathologic Xrs5 in their baseline IOS and none had a pathological 35% increase in Rrs5 in their ECT. However, four (21.4%) of them had a pathologic 35% decrease of Rrs5 in their BD test compared to 16.5% of the 84 children with a normal baseline Xrs5 ($p = 0.120$).

Lung function, reactive airways and rhinitis

The IOS results in relation to the presence of prolonged rhinitis and, or, SPT positivity showed that pathologic results in the baseline IOS were not associated with prolonged rhinitis or with SPT positivity. Instead, BHR was associated with SPT positivity and with the simultaneous presence of prolonged rhinitis and SPT positivity (Table 3).

Respiratory allergy

Baseline IOS was not associated with respiratory allergy for any of the four definitions outlined in the methods section and detailed in Table 4. Reactive airways, that is BHR, was associated with the first and most strict definition and with two more lenient definitions (Table 4).

Table 2 Association of baseline impulse oscillometry and bronchial hyper-reactivity (BHR) with the presence of current asthma, previous transient asthma and no asthma

Asthma	Resistance or reactance at 5 Hz pathologic	p-Value versus no current asthma	BHR present	p-Value versus BHR absent
Current asthma	4/15 (26.7%)	0.604*	5/13** (38.5%)	0.042*
Previous transient asthma***	4/12 (33.3%)	0.358*	1/12 (8.3%)	1.00*
No asthma	13/75 (17.3%)	—	8/75 (10.9%)	—

Resistance at 5 Hz was pathological ($>+1.65$ SD) in eight cases, and reactance was pathological (<-1.65 SD) in 19 cases.

The presence of BHR was defined as a $>35\%$ increase in resistance at 5 Hz in the ECT test (n = 5) or $>35\%$ decrease in the BD test (n = 11).

*p-values were multiplied by two (Bonferroni correction).

**The asthma diagnosis was partially based on BHR documented by IOS in two cases, and these cases are not included in the analyses between BHR and asthma.

***Children with current asthma not included.

p-Value < 0.05 marked in bold.

Table 3 Baseline impulse oscillometry and bronchial hyper-reactivity in relation to prolonged rhinitis and, or, skin prick test (SPT) positivity to inhaled allergens

Prolonged rhinitis and/or SPT positivity	Resistance or reactance at 5 Hz pathologic (n = 21)	p-value versus resistance and reactance at 5 Hz normal	Bronchial hyper-reactivity present (n = 16)	p-value versus bronchial hyper-reactivity absent
Prolonged rhinitis (n = 27)	5 (23.8%)	p = 0.498	7 (43.8%)	p = 0.084
Positive SPT (n = 32)	6 (28.6%)	p = 0.756	9 (56.3%)	p = 0.020
Prolonged rhinitis and positive SPT (n = 15)	3 (14.3%)	p = 0.629	5 (31.3%)	p = 0.057
Prolonged rhinitis or positive SPT (n = 44)	8 (38.1%)	p = 0.601	11 (68.8%)	p = 0.024

Resistance at 5 Hz was pathological ($>+1.65$ SD) in eight cases, and reactance was pathological (<-1.65 SD) in 19 cases.

Bronchial hyper-reactivity was defined as $>35\%$ increase in resistance at 5 Hz in the ECT (n = 5) or $>35\%$ decrease in the BD test (n = 11).

p-Value < 0.05 marked in bold.

Table 4 Baseline impulse oscillometry and bronchial hyper-reactivity in the groups constructed on the basis of respiratory allergy and current asthma

Respiratory allergy	Resistance or reactance at 5 Hz pathologic (n = 20)*	Resistance and reactance at 5 Hz normal (n = 80)*	Bronchial hyper-reactivity present** (n = 14)*	Bronchial hyper-reactivity absent** (n = 86)*
Current asthma and (prolonged rhinitis and positive SPT) (n = 6)	1 (5.0%) p = 0.833	5 (6.3%)	3 (21.4%) p = 0.034	3 (3.5%)
Current asthma and (prolonged rhinitis or positive SPT) (n = 8)	2 (10.0%) p = 0.712	6 (7.5%)	3 (21.4%) p = 0.081	5 (5.8%)
Current asthma or (prolonged rhinitis and positive SPT) (n = 21)	5 (25.0%) p = 0.623	16 (20.0%)	6 (42.9%) p = 0.041	15 (17.4%)
Current asthma or (prolonged rhinitis or positive SPT) (n = 48)	9 (45.0%) p = 0.764	39 (48.8%)	12 (85.7%) p = 0.002	36 (41.9%)

*The current asthma diagnosis was partially based on BHR documented by IOS in two cases, and these cases are not included in the analyses (n = 100).

**See methods section for details of diagnosis.

p-Value < 0.05 marked in bold.

DISCUSSION

Three main results emerged from this study that provided evidence for or against the UAD hypothesis, based on infants who were hospitalised for bronchiolitis under the age of six months and then followed up at five to seven years of age. Firstly, current asthma was associated with prolonged rhinitis and skin test positivity, but previous asthma was not. Secondly, baseline lung function, measured by IOS, showed no significant association with prolonged rhinitis, a positive SPT or respiratory allergy, which combined prolonged rhinitis and a positive SPT with current asthma. Thirdly, BHR, which was established by the ECT or BD test, was associated with prolonged rhinitis, a positive SPT and respiratory allergy.

In this cohort, asthma at five to seven years of age was strongly associated with prolonged rhinitis and, or, SPT positivity to inhaled allergens, in line with the UAD hypothesis (1,2). On the other hand, nearly half of the children with current asthma did not have prolonged rhinitis or a positive SPT, which does not support the UAD hypothesis. Although five to seven years old is an appropriate age at which to study allergy and allergic sensitisation to inhaled allergens, new allergies also develop after that age and new UAD cases can be diagnosed at a later age. Another study showed that a positive SPT was present in 15% of children at the age of five, but that this prevalence had increased to 39% at 11 years of age. In

addition, new sensitivities emerged in 23% of the children over those six years (8).

There was also a strong association between BHR, prolonged rhinitis and SPT positivity for inhaled allergens, in line with the UAD hypothesis (1,2). This observation means that the development of allergies to inhaled allergens after infant bronchiolitis happened jointly with continuing or emerging airway reactivity, in line with the UAD hypothesis (1,2). On the other hand, one-third of the BHR cases were not associated with prolonged rhinitis or SPT positivity, at least by the age of five to seven. The nine children who had BHR, but not asthma, formed an interesting group: seven (78%) of them had either prolonged rhinitis or were sensitised to inhaled allergens, and it is very probable that they would have become asthmatic at a later age (15).

Reactive airways, assessed in this study by BHR, has been closely associated with rhinitis in childhood, with a BHR prevalence of 50% in children with allergic rhinitis and 25% in nonallergic rhinitis (16). In a study of children aged three to five years, the severity of rhinitis was strongly associated with wheezing (17) and a review concluded that many allergic rhinitis patients had subclinical BHR and that allergic rhinitis often preceded the development of asthma (15). In line with these findings, our current study revealed that prolonged rhinitis, a positive SPT and respiratory allergy, which combined current asthma, rhinitis and a

positive SPT, were significantly associated with reactive airways in former bronchiolitis patients.

We did not find any significant associations between baseline lung function and prolonged rhinitis, SPT positivity or respiratory allergy. This means that baseline lung function disorder does not belong to the UAD entity, in contrast to BHR, or possibly that this connection emerges later than at five to seven years of age. However, this is unlikely as the Tucson and Denmark birth cohorts both showed that lung function disorders developed by the age of six to seven years (18,19).

Flow-volume spirometry is better established than IOS for examining lung function in children, including tests for BHR (11,13), but may be unreliable at the age of five to seven years because of the need for long forced expiratory blows (13,20). IOS has been shown to be applicable in children from two to three years of age onwards (21,22), and this method may be even superior in detecting reversible obstruction compared to flow-volume spirometry in children (23). A Finnish study showed that IOS in 158 wheezing children at the age of 2–7 years accurately predicted flow-volume spirometry results at 12–18 years of age (24). Increased baseline Rrs5 in IOS in that study was also related to a sixfold risk of pathologic post-BD forced expiratory volume in one-second in later flow-volume spirometry (24).

In our study, the 12 children with previous asthma who wheezed and used ICS but stopped wheezing by five to seven years of age, provided strong but indirect evidence for the UAD hypothesis. Only 16.7% reported prolonged rhinitis, none were sensitised to inhaled allergens and none were shown to have BHR by the ECT or BD tests. The most likely explanation is that they stopped wheezing because their respiratory allergy and subsequent airway reactivity did not develop. However, 33.3% of them presented with decreased lung function, in particular low baseline reactance, reflecting small airways obstruction and, or, diminished lung elastic properties. This was in line with the theory that an early infection with RSV, which was the main causative agent of bronchiolitis in our cohort, was more strongly associated with a restrictive than obstructive pattern of later lung function (25). In the Tucson birth cohort, the nonatopic transient wheezing phenotype was associated with low lung function at the age of six (18).

Previous RSV bronchiolitis cohorts have shown somewhat higher current asthma prevalence, at 21–23% versus the 15% in our study, and higher cumulative asthma prevalence at 30–39% versus our figure of 27% at the age of 6–7 years. They also showed a slightly lower or similar prevalence of allergic, SPT positive, rhinitis at 5.7–15% versus our finding of 17% and SPT positivity and atopy at 20–30% versus our level of 31% (26,27). The age criterion for bronchiolitis in these studies was less than 12 months. Our patients were hospitalised at less than six months of age and RSV caused 70% of all the cases in infancy (28) and 60% of those who completed the follow-up period (10). Thus, former non-RSV bronchiolitis patients were more likely to take part in our study than former RSV bronchiolitis

patients, and that might have been reflected in our high numbers of allergic rhinitis and atopy. Non-RSV aetiology of bronchiolitis was strongly associated with preschool asthma (9), which is supported by previous studies (29,30). Another post-bronchiolitis follow-up study from Finland compared the prevalence of asthma at a median age of 7.2 years in relation to the viral aetiology of bronchiolitis (29). RSV was the predominant causative agent at less than 12 months of age, and the prevalence of asthma was 7.4%. Rhinoviruses were the predominant causative agents at 12–24 months of age, and the prevalence of asthma was 56%. In the Childhood Origins of Asthma cohort study of high-risk children, rhinovirus-induced wheezing during the first three years life increased the average asthma risk at the age of six years to 9.8-fold and RSV-induced wheezing to 2.8-fold (30). Thus, the age at which a child has bronchiolitis and inherited atopic predisposition are the most important factors when it comes to predicting long-term outcomes after viral bronchiolitis.

The small number of patients was a clear weakness of the study, as it increased the chance of type two errors, and the lack of a control group was also a weakness as it lessened the generalisability of our results. This means that our results need to be interpreted with caution, as it is clear that our conclusions cannot be simply applied to a nonselected population. We used the term bronchial hyper-reactivity (BHR) to include either exercise-induced bronchoconstriction or bronchodilator responsiveness. To be precise, both reflect a risk of asthma.

The strengths of our study were the prospective design, the long follow-up period and the careful data collection during and after bronchiolitis in early childhood and at the age of five to seven years. The lung function results were based on highly professional analysis of the IOS findings and were compared to population-based, age-specific, height-adjusted reference values (12). In addition, the definition of allergy was not just based on symptoms, but also on objective evidence of sensitisation to inhaled allergens in the SPTs. The history of prolonged rhinitis was based on parental reports, but it was obtained from structured questionnaires and confirmed by clinical interviews.

CONCLUSION

This study found a significant association between allergic sensitisation, prolonged rhinitis, BHR reflecting reactive airways and asthma in five- to seven-year-old children who were hospitalised for bronchiolitis when they were less than six months of age. This means that we were able to document new evidence for the UAD hypothesis, based on former bronchiolitis patients. However, there were no significant associations between any of the above parameters and a decline in baseline lung function, as measured by IOS. This suggests that lung function disorder, in contrast to BHR, may not be a part of the UAD entity or will be established at later than preschool age in a post-bronchiolitis cohort.

FINANCE STATEMENT

The authors have not received specific funding for this work.

CONFLICT OF INTERESTS

The authors have no conflict of interests to declare.

References

- Rimmer J, Ruhno JW. Rhinitis and asthma: united airway disease. *Med J Aust* 2006; 185: 565–71.
- Garcia-Marcos L, Rubi Ruiz T, Garcia-Hernandez G, Suarez-Varela MM, Valverde-Molina J, Sanchez-Solis M. Asthma and rhinoconjunctivitis comorbidity: united airway disease or inherited target organs? *Pediatr Allergy Immunol* 2010; 21: e142–8.
- Bousquet J, Van Cauwenberge P, Khaltaev N, Aria Workshop Group, World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001; 108: S147–334.
- Bousquet J, Schunemann HJ, Samolinski B, Demoly P, Baena-Cagnani CE, Bachert C, et al. Allergic rhinitis and its impact on asthma (ARIA): achievements in 10 years and future needs. *J Allergy Clin Immunol* 2012; 130: 1049–62.
- Shaker M. New insights into the allergic march. *Curr Opin Pediatr* 2014; 26: 516–20.
- Strachan D, Sibbald B, Weiland S, Ait-Khaled N, Anabwani G, Anderson HR, et al. Worldwide variations in prevalence of symptoms of allergic rhinoconjunctivitis in children: the international study of asthma and allergies in childhood (ISAAC). *Pediatr Allergy Immunol* 1997; 8: 161–76.
- Kulig M, Bergmann R, Klettke U, Wahn V, Tacke U, Wahn U. Natural course of sensitization to food and inhalant allergens during the first 6 years of life. *J Allergy Clin Immunol* 1999; 103: 1173–9.
- Pesonen M, Kallio MJ, Siimes MA, Ranki A. Allergen skin prick testing in early childhood: reproducibility and prediction of allergic symptoms into early adulthood. *J Pediatr* 2015; 166: 401–406.e1.
- Koponen P, Helminen M, Paasilta M, Luukkaala T, Korppi M. Preschool asthma after bronchiolitis in infancy. *Eur Respir J* 2012; 39: 76–80.
- Lauhkonen E, Koponen P, Nuolivirta K, Paasilta M, Toikka J, Korppi M. Lung function by impulse oscillometry at age 5–7 years after bronchiolitis at age 0–6 months. *Pediatr Pulmonol* 2015; 50: 389–95.
- Oostveen E, MacLeod D, Lorino H, Farre R, Hantos Z, Desager K, et al. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. *Eur Respir J* 2003; 22: 1026–41.
- Malmberg LP, Pelkonen A, Poussa T, Pohjanpalo A, Haahtela T, Turpeinen M. Determinants of respiratory system input impedance and bronchodilator response in healthy finnish preschool children. *Clin Physiol Funct Imaging* 2002; 22: 64–71.
- Beydon N, Davis SD, Lombardi E, Allen JL, Arets HG, Aurora P, et al. An official american thoracic society/european respiratory society statement: pulmonary function testing in preschool children. *Am J Respir Crit Care Med* 2007; 175: 1304–45.
- Malmberg LP, Makela MJ, Mattila PS, Hammaren-Malmi S, Pelkonen AS. Exercise-induced changes in respiratory impedance in young wheezy children and nonatopic controls. *Pediatr Pulmonol* 2008; 43: 538–44.
- Cruz AA, Popov T, Pawankar R, Annesi-Maesano I, Fokkens W, Kemp J, et al. Common characteristics of upper and lower airways in rhinitis and asthma: ARIA update, in collaboration with GA(2)LEN. *Allergy* 2007; 62(Suppl 84): 1–41.
- Kim SW, Han DH, Lee SJ, Lee CH, Rhee CS. Bronchial hyperresponsiveness in pediatric rhinitis patients: the difference between allergic and nonallergic rhinitis. *Am J Rhinol Allergy* 2013; 27: e63–8.
- Pereira AM, Morais-Almeida M, Santos N, Nunes C, Bousquet J, Fonseca JA. Severity of rhinitis and wheezing is strongly associated in preschoolers: a population-based study. *Pediatr Allergy Immunol* 2015; 26: 618–27.
- Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. the group health medical associates. *N Engl J Med* 1995; 332: 133–8.
- Bisgaard H, Jensen SM, Bonnelykke K. Interaction between asthma and lung function growth in early life. *Am J Respir Crit Care Med* 2012; 185: 1183–9.
- Arets HG, Brackel HJ, van der Ent CK. Forced expiratory manoeuvres in children: do they meet ATS and ERS criteria for spirometry? *Eur Respir J* 2001; 18: 655–60.
- Delacourt C, Lorino H, Herve-Guillot M, Reinert P, Harf A, Housset B. Use of the forced oscillation technique to assess airway obstruction and reversibility in children. *Am J Respir Crit Care Med* 2000; 161: 730–6.
- Marotta A, Klinnert MD, Price MR, Larsen GL, Liu AH. Impulse oscillometry provides an effective measure of lung dysfunction in 4-year-old children at risk for persistent asthma. *J Allergy Clin Immunol* 2003; 112: 317–22.
- Komarow HD, Skinner J, Young M, Gaskins D, Nelson C, Gergen PJ, et al. A study of the use of impulse oscillometry in the evaluation of children with asthma: analysis of lung parameters, order effect, and utility compared with spirometry. *Pediatr Pulmonol* 2012; 47: 18–26.
- Knihtila H, Kotaniemi-Syrjanen A, Makela MJ, Bondestam J, Pelkonen AS, Malmberg LP. Preschool oscillometry and lung function at adolescence in asthmatic children. *Pediatr Pulmonol* 2015; 50: 1205–13.
- Hyvarinen MK, Kotaniemi-Syrjanen A, Reijonen TM, Korhonen K, Korppi MO. Lung function and bronchial hyperresponsiveness 11 years after hospitalization for bronchiolitis. *Acta Paediatr* 2007; 96: 1464–9.
- Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. *Am J Respir Crit Care Med* 2000; 161: 1501–7.
- Zomer-Kooijker K, van der Ent CK, Ermers MJ, Uiterwaal CS, Rovers MM, Bont LJ, et al. Increased risk of wheeze and decreased lung function after respiratory syncytial virus infection. *PLoS ONE* 2014; 9: e87162.
- Helminen M, Nuolivirta K, Virta M, Halkosalo A, Korppi M, Vesikari T, et al. IL-10 gene polymorphism at -1082 A/G is associated with severe rhinovirus bronchiolitis in infants. *Pediatr Pulmonol* 2008; 43: 391–5.
- 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.
- Jackson DJ, Gangnon RE, Evans MD, Roberg KA, Anderson EL, Pappas TE, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med* 2008; 178: 667–72.