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Preschool asthma after bronchiolitis in infancy

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ABSTRACT: Asthma risk is lower after wheezing associated with respiratory syncytial virus (RSV) than with non-RSV infection in infancy. RSV is the main wheezing-associated virus in infants aged <6 months. We evaluated the outcome of children hospitalised for bronchiolitis at <6 months of age, with special focus on viral aetiology and early risk factors.

Out of 205 infants hospitalised for bronchiolitis at <6 months of age, 127 (62%) attended a control visit at a mean age of 6.5 yrs and the parents of an additional 39 children were interviewed by telephone. Thus, follow-up data collected by identical structured questionnaires were available from 166 (81%) children. Viral aetiology of bronchiolitis, studied on admission by antigen detection or PCR, was demonstrable in 97% of cases.

Current asthma was present in 21 (12.7%) children: 8.2% in the 110 former RSV patients *versus* 24% in non-RSV patients (p=0.01). 45 (27%) children had ever had asthma. In adjusted analyses, atopic dermatitis, non-RSV bronchiolitis and maternal asthma were independently significant early-life risk factors for asthma.

The risk of asthma was lower after RSV bronchiolitis than after bronchiolitis caused by other viruses in children hospitalised at <6 months of age.

KEYWORDS: Asthma, atopy, bronchiolitis, respiratory syncytial virus, rhinovirus

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Bronchiolitis is the most common lower respiratory infection (LRI) in infancy [1]. The American Academy of Paediatrics has defined bronchiolitis as a disorder in children aged <24 months caused by viral LRI and characterised by acute inflammation, mucus production and bronchospasm of small airways [2]. In most European countries, the upper age limit used, at least in clinical practice, has been 12 months [3]. The severity of bronchiolitis and need for hospital care decrease with increasing age [4]. The viral aetiology of bronchiolitis is age-dependent; respiratory syncytial virus (RSV) is the predominant virus at <6 months and rhinovirus at >12 months of age [5]. Bronchiolitis in infancy increases the asthma risk in later life [6–8]. Studies with outcome data available beyond age 5 yrs have been performed in children aged <36 months [5, 9, 10], <24 months [11, 12] or <12 months [13, 14] on admission; however, there are no age-specific data available for children hospitalised at <6 months of age.

We prospectively followed up a group of children hospitalised for bronchiolitis at <6 months of age in 2001–2002 and 2002–2004 [15, 16]. RSV was the causative agent in 70%, rhinovirus in 7% and other viruses in 7% of the cases [15]. When the children were 5–6 yrs of age, they were invited to a clinical follow-up study in 2008–2009. The hypotheses of the study were that asthma is more common after non-RSV bronchiolitis (especially after rhinovirus bronchiolitis) than after RSV bronchiolitis, and more common after bronchiolitis at <3 months than at 3–6 months of age.

The aim of the present study was to evaluate the outcome with special focus on asthma at preschool age after hospitalisation for RSV, non-RSV and rhinovirus bronchiolitis at <6 months of age. In addition, the age at admission for bronchiolitis and other early risk factors, such as asthma and atopy in parents and atopic dermatitis in children, were analysed as predictors of childhood asthma.

MATERIALS AND METHODS

205 healthy, full-term infants aged <6 months and hospitalised for bronchiolitis at the Dept of Paediatrics, Tampere University Hospital (Tampere, Finland) were enrolled in the study between December 1, 2001 and May 31, 2002 and between October 28, 2002 and May 31, 2004. The Ethics Committee of the Tampere University Hospital District approved the study. Informed consent was obtained from parents before enrolling the children.

Bronchiolitis was characterised by LRI with rhinitis, cough and diffuse wheezes or crackles [15]. The aetiology of bronchiolitis was assessed in nasopharyngeal aspirates by immunofluorescence for

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seven viruses, including RSV, by PCR for nine viruses, including RSV and rhinoviruses, and by PCR for *Bordetella pertussis* [17].

From 2008 to 2009, 127 (62%) children attended the study visit at 5–7 yrs of age. In addition, parents of the 39 children who did not attend the study visit were contacted and interviewed by telephone. Thus, follow-up data collected by identical structured questionnaires were available from 166 (81%) children (fig. 1). Doctor-diagnosed asthma, the age when asthma was diagnosed and the continuous or intermittent use of inhaled corticosteroids (ICS) as maintenance medication for asthma were recorded by year. Intermittent ICS medication means a pre-set, regular use during infections or respiratory symptoms. In addition, data were recorded on parent-reported wheezing episodes and episodes of other asthma-like symptoms, such as prolonged (>4 weeks) cough and night cough apart from infection. The presence of doctor-diagnosed atopic dermatitis and allergic rhinitis was recorded; only cases who were symptomatic during the preceding 12 months were included. In addition, parental doctor-diagnosed asthma and atopy (allergic rhinitis or atopic dermatitis), keeping of indoor furred pets, and parental smoking during and after pregnancy were surveyed. All data were collected separately for mothers and fathers.

Skin-prick tests (SPTs) were performed in 124 children for eight allergens: birch, timothy grass and mugwort pollens, cat and dog dander, house dust mites (*Dermatophagoides pteronyssimus* and *D. farinae*) and spores of the mould *Alternaria alternata*. Wheals with a mean diameter of $\geqslant$3 mm were regarded as positive. Children were not allowed to take any antihistamine medication for 5 days before testing.

Bronchial hyperresponsiveness (BHR) was studied by exercise challenge test (ECT), which consisted of free running outdoors for 8 min and measurements of pre- and post-exercise airway resistance by impulse oscillometry (IOS) (Master Screen IOS; Jaeger, Höchberg, Germany). Exercise was considered sufficient when heart rate, monitored using a heart rate monitor (Polar Ltd, Kempele, Finland), was $\geqslant$90% of the predicted maximum for $\geqslant$2 min. IOS was repeated until three acceptable pre-exercise and two acceptable post-exercise curves were obtained. The resistance curves had to be graphically appropriate and free from artefacts for the whole 30-s measurement time. Resistance values were measured at the 5-Hz level (total respiratory resistance at 5 Hz (R_{rs5})) and expressed as standard deviations from national height-related, sex-specific references [18]. BHR was considered to be present if the best post-exercise R_{rs5} value had increased $\geqslant$35% from the best pre-exercise value [19]. If the child had suffered from an infection during the two preceding weeks, IOS was rescheduled.

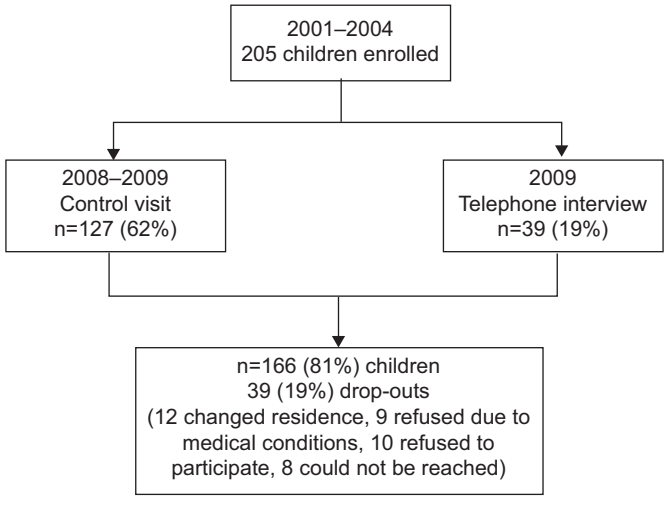

FIGURE 1. Flow chart of the study population.

Current asthma was considered to be present if the child was on continuous maintenance medication for asthma, or if the child had suffered from doctor-diagnosed wheezing or prolonged (>4 weeks) cough or night cough, apart from infection, during the preceding 12 months, and BHR was documented in ECT. Previous asthma before the control visit was defined by the use of ICS as continuous or intermittent maintenance medication for asthma. If the child had either previous or current asthma, the term ''asthma ever in life'' was used.

Statistics

The data were analysed using SPSS 18.0 (IBM, Helsinki, Finland). The statistical significances of differences between the groups were calculated with the unpaired t-test, Chi-squared test and Fisher's exact test. Logistic regression was used to analyse the associations between risk factors and asthma, first by univariate analyses and then by multivariate analyses adjusted for age on admission (<3 *versus* >3 months), sex and characteristics which were significant in univariate analyses. Odds ratios with 95% confidence intervals are reported from both univariate (OR) and multivariate adjusted (aOR) analyses.

RESULTS

The mean$\pm$SD age of the 166 children attending the study was 6.5$\pm$0.57 yrs and 86 (52%) were male. Current asthma was present in 21 (12.7%) children: in 14 males (16.3% of males; p=0.05 *versus* females) and in seven females (8.8% of females). In addition, there were 24 children with no current asthma who had been previously, but not during the preceding 12 months, taking ICS as maintenance medication for asthma. Thus, the number of children with asthma ever in life before or during the study was 45 (27%). The age-specific prevalence and cumulative incidence of asthma, defined by the use of continuous or intermittent ICS, are presented in figure 2. The highest prevalence, 26.9%, was seen at 2–3 yrs of age.

18 children with current asthma had used ICS during the preceding 12 months. 12 children were on continuous and six on intermittent ICS, and two of them also used leukotriene antagonists. Five (24%) children were symptomatic and six (29%) hyperresponsive in ECT despite maintenance medication. Three additional children had symptoms consistent with asthma and were hyperresponsive in ECT, and they were defined to have asthma. BHR was documented in five other children, but none of them reported doctor-diagnosed wheezing or prolonged or night cough. Six (4%) of the nonasthmatic children had suffered from repeated parent-reported wheezing, but none of them reported doctor-diagnosed wheezing, prolonged or night cough, or had BHR in ECT.

RSV had caused 117 (70.5%) and rhinovirus 21 (12.7%) of the 166 bronchiolitis cases (table 1). *B. pertussis* was involved in 10 (6%)

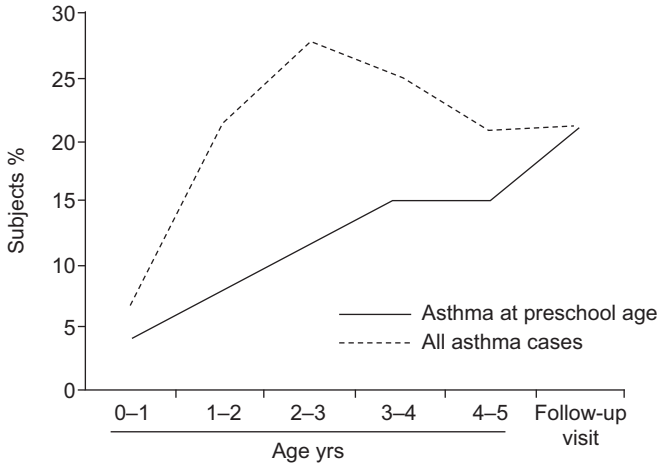

FIGURE 2. The age-specific prevalence and cumulative incidence of asthma, defined by the use of inhaled corticosteroids, in the 166 study subjects.

cases, but all were mixed infections with viruses. Current asthma at 6.5 yrs of age was present in nine (7.7%) of former RSV bronchiolitis patients (*versus* 24.4% of former non-RSV patients; p=0.01), in three (14.3%) former rhinovirus bronchiolitis patients and in one (10%) former *B. pertussis*-positive patients.

Age on admission as a continuous variable (but not categorised into <3 and >3 months), atopic dermatitis at <12 months of age (71.4% *versus* 23.4%; p<0.001) and asthma in mothers (38.1% *versus* 11.0%; p=0.001) but not in fathers were significantly associated with current asthma (table 1). Conversely, maternal smoking, paternal smoking and keeping furred pets at home during infancy had no association with later asthma (table 1).

48 (29%) study children had suffered from symptoms presumptive for allergic rhinitis during the preceding 12 months and 13 (27%) of them had current asthma (*versus* 6.8% in those 118 with no allergic rhinitis; p<0.001). Correspondingly, 61.9% of the 21 children with and 24.1% of those 145 without asthma had allergic rhinitis. SPTs were performed in 124 children; eight (53.3%) out of 15 children with asthma were SPT-positive (*versus* 6.4% of those 109 with no asthma; p=0.07). Birch pollen (22.8%), timothy grass pollen (19.2%), dog dander (12.7%) and cat dander (11.7%) were common, and mugwort pollen (1.0%), house dust mites (1.0%) and spores of moulds (0%) were rare allergens.

Maternal history of asthma was a significant risk factor for asthma in children (table 1). However, 21 (87.5%) out of the 24 mothers with asthma (p=<0.001 *versus* 52 mothers with no asthma) and six (60%) out of the 10 fathers with asthma (p=0.06 *versus* 34 fathers with no asthma) also had doctor-diagnosed allergic rhinitis or atopic dermatitis. The association between parental asthma and atopy was so strong that their independent associations with asthma in children could not be studied, and we included only maternal asthma in the multivariate analyses.

As seen in table 2, non-RSV bronchiolitis was an independent risk factor for preschool asthma in multivariate analyses adjusted for age on admission, sex, atopic dermatitis in infancy and maternal asthma (aOR 3.74, 95% CI 1.28–10.99). Atopic dermatitis in infancy and maternal asthma were other significant risk factors for current asthma in adjusted analyses (table 2).

TABLE 1 Baseline data in 166 children hospitalised for bronchiolitis at <6 months of age, presented in relation to asthma at preschool age

	Current asthma	No asthma	p-value
Subjects n	21	145	
Age at admission days	113 (63–147)	77 (38–118)	0.027
Age at admission months			0.06
<3	9 (42.9)	93 (64.1)	
>3	12 (57.1)	52 (35.9)	
Males	14 (66.7)	72 (49.7)	0.145
RSV bronchiolitis	9 (42.9)	108 (74.5)	0.015
Non-RSV bronchiolitis#	12 (57.1)	37 (25.5)	0.01
Atopic dermatitis at <12 months of age	15 (71.4)	34 (23.4)	<0.001
Maternal smoking during pregnancy	1 (4.8)	28 (19.3)	0.129¶
Maternal history of asthma	8 (38.1)	16 (11.0)	0.001
Paternal history of asthma	0 (0.0)	10 (6.8)	0.231¶
Maternal history of atopy	13 (61.9)	60 (41.4)	0.077
Paternal history of atopy	8 (38.1)	32 (22.1)	0.109
Maternal smoking in infancy	5 (23.8)	42 (29.0)	0.624
Paternal smoking in infancy	9 (42.9)	61 (42.1)	0.946
Furred pet at home in infancy	5 (23.8)	46 (31.7)	0.462

Data are presented as median (interquartile range) or n (%), unless otherwise stated. The t-test was used for continuous variables and Pearson's Chi-squared test was used for categorised variables, unless otherwise stated. RSV: respiratory syncytial virus. #: rhinovirus in three cases, influenza A virus in three cases, parainfluenza type 3 virus in three cases, adenovirus in one case and human metapneumovirus in one case, and two cases with no viral aetiology; ¶: Fisher's exact test.

The analyses were repeated in the subgroup of 124 children with SPT results available by including SPT positivity in the model. SPT positivity was associated with an increased asthma risk in univariate analyses (OR 3.60, 95% CI 1.19–10.9) but not in multivariate analyses (aOR 2.81, 95% CI 0.72–10.9). In these analyses, atopic dermatitis in infancy, non-RSV bronchiolitis and maternal asthma lost statistical significance as risk factors of current asthma (data not shown).

There were no significant differences in baseline characteristics, such as sex, age on admission and viral aetiology of bronchiolitis, between the 166 attendees and the 39 drop-outs (data not shown). Likewise, there were no significant differences in baseline or questionnaire-based characteristics, such as atopy, asthma and smoking in parents, or atopic dermatitis in infancy and allergic rhinitis at preschool age in study children, between those 39 interviewed by telephone and those 127 attending the study visit (data not shown).

DISCUSSION

There are four main results in the present prospective follow-up study at preschool age after hospitalisation for bronchiolitis at <6 months of age. First, asthma prevalence was only 12.7% at a mean age of 6.5 yrs. This figure is lower than the previously reported prevalence figures up to 48% after bronchiolitis in infancy [11–14, 20]. Secondly, atopic dermatitis in infancy was a

TABLE 2 Logistic regression: risk factors for asthma at a mean age of 6.5 yrs

	Subjects	Crude	Multivariate
Age ⩾3 months at admission	64	2.31 (0.91–5.85)	2.04 (0.69–6.04)
Male sex	86	2.03 (0.77–5.32)	2.01 (0.64–6.29)
Atopic dermatitis at <12 months of age	49	8.16 (2.94–22.7)	7.45 (2.45–22.89)
Non-RSV bronchiolitis	50	4.04 (1.57–10.36)	3.74 (1.28–10.99)
Maternal history of asthma	24	4.96 (1.78–13.79)	3.39 (1.03–11.24)

Data are presented as n or odds ratio (95% confidence interval). n=166. Multivariate analyses were performed and adjusted for age on admission, sex, atopic dermatitis in infancy, viral aetiology of bronchiolitis and maternal asthma. RSV: respiratory syncytial virus.

significant risk factor for asthma, in line with earlier post-bronchiolitis studies [12, 21, 22]. Thirdly, asthma in mothers, but not in fathers, was a significant risk factor for asthma. Asthma in mothers was associated more than asthma in other family members with asthma risk in children in birth cohorts [10]. Finally, confirming the study hypothesis, asthma at preschool age was more common after non-RSV bronchiolitis (24%) than after RSV bronchiolitis (8%) in infancy. This observation is in line with previous studies after early-life wheezing from Finland and Wisconsin, USA [9, 20, 23], but we were not able to confirm the specific role of rhinovirus aetiology of bronchiolitis as an asthma predictive factor.

The prevalence of preschool asthma has varied from 15% to 48% in previous post-bronchiolitis studies [11–14, 20], which means a four- to 10-fold increase in asthma prevalence compared with nonselected populations [24]. In earlier post-bronchiolitis studies from Finland and Sweden, the prevalence of asthma was 30% when the infants were hospitalised at <12 months of age [13] and 25–47% when hospitalised at <24 months of age [11, 12, 20]. In birth cohort studies, the prevalence figures have been higher (30–60%) after wheezing in early life, reflecting the inclusion of mild, parent-reported wheezing cases treated at home [9, 10]. In the present study, after hospitalisation for bronchiolitis at <6 months of age, asthma prevalence at preschool age was low (12.7%), and even lower (only 8.9%) after hospitalisation at <3 months of age. In a recent study from Missouri, USA, the cumulative prevalence of parent-reported, doctor-diagnosed asthma by age 6 yrs was as high as 48% after RSV bronchiolitis at age <12 months [14]. The cumulative prevalence in the present study, called asthma ever in life, was not higher than 27% when only cases treated with ICS were included.

Atopic dermatitis in infancy, parental atopy, parental asthma (especially asthma in mothers) and passive smoking (especially smoking mothers) have been linked with an increased risk for later asthma [13, 20, 21, 25]. In this study, one-third of children with atopic dermatitis presenting during the first year of life had asthma at preschool age. The figure is higher than in earlier post-bronchiolitis studies after hospitalisation at <24 months of age, which evidently included children with less severe atopy not presenting in early infancy [12, 20, 22]. Thus, atopy in infancy is an important risk factor for asthma in later life, and invasive RSV infections in infancy may increase, in addition to the risk of asthma, the risk of allergy at early school age [13, 14].

A recent post-bronchiolitis study from Sweden stressed the differences in the harmful effects of maternal and paternal smoking [25]. Maternal smoking led to BHR and reduced lung function, whereas paternal smoking increased the risk of active smoking at teen age. Many studies, like the present study, have not been able to confirm the increased asthma risk after *in utero* or early-life tobacco smoke exposure [13, 21, 23, 26]. A selection bias might have occurred since passive smoking in infancy is a risk factor of bronchiolitis [27]. In the present study, ~30% of mothers and ~40% of fathers smoked, which is more than reported in young Finnish females (20%) and males (30%) [28].

RSV has been shown to be the predominant virus in bronchiolitis in infants aged <6 months and rhinovirus in infants aged >12 months [5]. Asthma risk at preschool age after rhinovirus bronchiolitis has been two- to four-fold compared with RSV bronchiolitis [9, 29]. Consistent with this, only 8.2% of the former RSV bronchiolitis patients in our study had asthma at preschool age; in fact, the figure was close to 4–6% asthma prevalence in a nonselected, age-specific population in Finland [24]. Accordingly, non-RSV bronchiolitis was a significant risk factor for preschool asthma, even after adjustment with potential confounding factors. However, no single virus was predominant in the former non-RSV group with current asthma. The mechanisms behind the link from bronchiolitis in infancy to asthma in childhood are not known. Non-RSV bronchiolitis most probably reveals susceptible infants rather than directly causes later asthma [9, 21, 29]. The role of rhinoviruses as an asthma-predicting factor may be age dependent (not seen in bronchiolitis patients aged <6 months).

The study of SIGURS *et al*. [13] is the only post-bronchiolitis follow-up comparable with the present study. In that study, 47 former RSV bronchiolitis patients hospitalised at <12 months of age attended the control visit at the median age of 7.5 yrs, and 23% of them had asthma, compared with 3% in controls. In the present study, asthma prevalence at the mean age of 6.5 yrs was substantially lower, only 8.2% among 117 children hospitalised for RSV bronchiolitis at <6 months of age. In addition, SIGURS *et al*. [13] reported that 20% of former RSV bronchiolitis patients were sensitised to inhaled allergens documented by SPTs, compared with 6% in controls. In our study, former RSV and non-RSV patients had the same SPT positivity rate (29%). In the Swedish study, parental asthma was present in 45% of the infants with bronchiolitis, compared with 20% in our patients, which may partly explain the differences in outcome at preschool age.

The main strengths of the present post-bronchiolitis study are the prospective design, and large number and homogeneity of the enrolled patients; all were <6 months of age, all needed hospital care and 166 children were followed up over 5 yrs. When bronchiolitis is defined as viral LRI with wheezing at <24 months of age, which has been the practice in most earlier studies, the study population is more heterogeneous, consisting of patients with bronchiolitis, reactive airway disease and early-onset asthma.

The main shortcoming of the present study is that population-based controls were not enrolled. However, the age-specific prevalence of asthma in Finnish children is well known, being 4–6% at preschool age [24]. In addition, many subgroups were rather small and thus, the study was underpowered to find many obvious associations. Data on atopic dermatitis and family history of asthma and atopy were carefully collected, but no tests were available for allergen-specific immunoglobulin E, eosinophils or eosinophilic markers, which are well-known risk factors of childhood asthma after bronchiolitis [21, 30]. However, later asthma was so rare and atopic dermatitis in infancy was such a strong predictive factor that any additional data on risk factors would not have changed the main conclusions of the study.

In conclusion, asthma prevalence was low (only 12.7%) at the mean age of 6.5 yrs after hospitalisation for bronchiolitis at <6 months of age. In agreement with the study hypothesis, non-RSV aetiology of bronchiolitis was an independently significant risk factor of asthma in adjusted analyses, but in disagreement with the study hypothesis, age >3 months compared with age <3 months was not.

SUPPORT STATEMENT

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STATEMENT OF INTEREST

None declared.

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