

Severe Respiratory Syncytial Virus Bronchiolitis in Infancy and Asthma and Allergy at Age 13

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We have prospectively studied wheezing disorder and allergy in 47 children hospitalized with respiratory syncytial virus (RSV) bronchiolitis in infancy and 93 matched control subjects. Subjects with at least three episodes of wheezing were defined as recurrent wheezers and as having asthma if the episodes were doctor verified. Here we report the outcome at age 13 years in 46/47 children with RSV and 92/93 control subjects. Wheezing disorder and clinical allergy were estimated using a questionnaire. Skin prick tests were performed and serum IgE antibodies measured. Spirometry was undertaken at rest, after dry air challenge, and after β_2 -agonist inhalation. The occurrence of symptoms over the previous 12 months was significantly higher in the RSV group than among the control subjects, 43% versus 8% for asthma/recurrent wheezing and 39% versus 15% for allergic rhinoconjunctivitis. Sensitization to common inhaled allergens was more frequent in the RSV group than in the control subjects, judged by skin prick tests (50% versus 28%; $p = 0.022$), or by serum IgE antibodies (45% versus 26%; $p = 0.038$). Compared with the control subjects, the RSV group showed mild airway obstruction both at rest and after bronchodilation, and had slightly more reactive airways. RSV bronchiolitis in infancy severe enough to cause hospitalization is a risk factor for allergic asthma in early adolescence.

Keywords: airway obstruction; atopic hypersensitivity; children; respiratory syncytial virus

Most children are infected by respiratory syncytial virus (RSV) before age 2 (1, 2). In some children only an upper respiratory tract infection is noted, but many infants develop symptoms from the lower airways (1, 2). One to two percent of previously healthy infants are admitted to the hospital with RSV bronchiolitis (1). Both mild and severe RSV bronchiolitis may be followed by recurrent wheezing for several years (3–6). It has been debated whether the recurrent wheezing is mainly a nonallergic condition with a good long-term prognosis or an early onset of IgE-associated asthma (3, 7–9). Wheezing disorder after mild RSV bronchiolitis in early childhood, i.e., not requiring hospitalization, seems to be a self-limiting disease with symptoms up to age 11 but not to age 13 (3). So far, there have been no reported controlled prospective studies of the outcome up to early adolescence in subjects hospitalized with RSV bronchiolitis in the first year of life.

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We have followed prospectively a cohort of 47 children hospitalized with RSV bronchiolitis in infancy and 93 control subjects recruited at the same time and matched regarding sex, age, and residential area (5, 6). Wheezing disorder, clinical allergy, and allergic sensitization were more frequent up to age 7 in the RSV bronchiolitis group (6). In the present study we hypothesized that these differences would persist even at age 13, supporting the view that severe RSV bronchiolitis in infancy is a strong risk factor for IgE-mediated asthma. Some of the results of this study have been previously reported in the form of an abstract (10).

METHODS

Forty-seven children (21 boys) hospitalized with RSV bronchiolitis in infancy (mean age 116 days, 43 ± 6 months) and a control group of 93 infants were followed prospectively (5, 6). At the present follow-up (median age in both groups 13.4 years, range 13.0–14.0), data on clinical symptoms and environmental factors were obtained using structured questionnaires in 46 of 47 subjects with RSV (20 boys) and 92 of 93 control subjects (41 boys). A clinical examination was performed in 45 children with RSV and in 89 control subjects. Initial bronchiolitis was defined according to Court (11), and Ruuskanen and Ogra (1). Asthma was defined as three or more episodes of physician-verified wheezing, "recurrent wheezing" as three or more episodes not verified by a physician (5, 6). The combined rates of asthma and recurrent wheezing are also tabulated. Allergic rhinoconjunctivitis and atopic dermatitis were defined as previously (5, 6, 12). Current disorder means symptoms during the last year. Heredity for atopy and asthma was defined as previously and based on a doctor's diagnosis.

Skin prick tests were done in 42 subjects with RSV and 87 control subjects to inhalant allergens (dog, horse, cat; birch, timothy, mugwort; Der. pteronyssinus, Der. farinae, and molds), using the same techniques as previously (5, 6). Serum IgE antibodies to inhaled allergens were measured in 44 subjects with RSV and 86 control subjects using a screening test (Phadiatop; Pharmacia Upjohn Diagnostics AB, Uppsala, Sweden) (5, 6, 13). Subjects with a positive Phadiatop were investigated for specific antibodies (Pharmacia CAP system) (14).

Forced expiratory maneuvers were performed using a turbine spirometer before and after β_2 -agonist inhalation according to ATS recommendations (15), in 44 subjects with RSV and 86 control subjects. FVC, FEV₁, and the maximal expiratory flow at 75% of FVC (FEF₇₅) were recorded. Results were related to Swedish normative data (16). Inhaled long-acting β_2 -agonists were withheld for 24 hours and short-acting ones or cromoglycates for 6 hours before testing. Inhaled corticosteroid use was continued. Hyperventilation challenge was performed after baseline spirometry in 43 children with RSV and in 86 control subjects (17). Dry air containing 5% CO₂ was hyperventilated at a rate corresponding to resting FEV₁ $\times$ 26 (L $\cdot$ minutes⁻¹) over 4 minutes. FEV₁ was measured in duplicates at 2, 5, and 10 minutes after challenge and the highest value at each point in time was noted. Maximum fall in FEV₁ from resting was calculated. Ten minutes after challenge, 400 μ g of salbutamol was inhaled via a dry powder inhaler (800 μ g if fall in FEV₁ was $\geq 10\%$), followed by spirometry 15 minutes later.

Statistics

Fisher's two-tailed exact test was used for univariate comparisons. A multivariate forward stepwise logistic regression analysis was performed to establish which risk factors were independently related to wheezing disorders or sensitization using the SAS logistic procedure. The two-tailed

Student's *t* test was used for evaluation of differences between groups in spirometry findings. *p* Values < 0.05 were regarded as significant.

Ethics

Parents and children gave their oral consent after receiving oral and written information. The study was approved by the Human Research Committee of the Medical Faculty of Gothenburg University.

RESULTS

Demographic data and background factors were similar in the RSV and control groups at age 13 (Table 1). Menarche had started in 67% of the RSV girls and in 65% of the control subjects.

The rates of asthma, asthma/recurrent wheezing, or allergic rhinoconjunctivitis during the year before the follow-up were higher in the RSV group than in the control group, whereas the rates of atopic dermatitis were similar (Table 2). Nine of the 13 children with current asthma in the RSV group used inhaled corticosteroids regularly, in 5 cases combined with long-acting β_2 -agonists, and another child used sodium cromoglycate. The three children with current asthma in the control group were prescribed only inhaled short-acting β_2 -stimulants for symptom relief. Among the children with recurrent wheezing, one of the seven children with RSV used β_2 -agonists occasionally, whereas none of the four control subjects took any medication.

Positive skin prick tests or serum IgE tests were more frequent in the RSV group than in the control group (Table 3). Sensitization to animal dander, judged by either skin prick test or serum IgE antibodies, was more common in the RSV group than in the control group (Table 3). Of the 20 children with RSV with current asthma/recurrent wheezing, 16 (80%) had at least one positive allergy test, compared with 3 of 7 (43%) in the control group (*p* = 0.144).

In the combined RSV and control groups, severe RSV infection in infancy and several possible hereditary and environmental risk factors for asthma, asthma/recurrent wheezing, or allergic sensitization at age 13 years were evaluated using a univariate test (outcome for asthma/recurrent wheezing and allergic sensitization, Table 4). For asthma/recurrent wheezing at age 13 and for sensitization to animal dander, two risk factors reached statistical significance: severe RSV bronchiolitis in infancy and asthma in one or both parents.

Risk factors with *p* values < 0.10 in the univariate analyses were included in a multivariate analysis which showed that severe RSV bronchiolitis in infancy was an independent risk factor for both current asthma (odds ratio [OR] 10.1, 95% confidence interval [95% CI] 3.4–29.8, *p* < 0.001) and current asthma/recurrent wheezing (OR 9.3, 95% CI 3.6–24.5, *p* = 0.026). For current

TABLE 2. ASTHMA, RECURRENT WHEEZING, ALLERGIC RHINOCONJUNCTIVITIS, AND ATOPIC DERMATITIS IN THE RESPIRATORY SYNCYTIAL VIRUS AND CONTROL GROUPS AT AGE 13

	RSV Group (<i>n</i> = 46)	Control Group (<i>n</i> = 92)	RR (95% CI)	<i>p</i> Value
Asthma				
Current	13 (28%)	3 (3.3%)	8.7 (2.6–28.9)	< 0.001
Cumulative	17 (37%)	5 (5.4%)	6.8 (2.7–17.3)	< 0.001
Recurrent wheezing				
Current	7 (15%)	4 (4.3%)	3.5 (1.1–11.4)	0.065
Cumulative	14 (30%)	15 (16.3%)	1.9 (1.0–3.5)	0.093
Asthma/ recurrent wheezing				
Current	20 (43%)	7 (7.6%)	5.7 (2.6–12.5)	< 0.001
Cumulative	31 (67%)	20 (21.7%)	3.1 (2.0–4.8)	< 0.001
ARC				
Current	18 (39%)	14 (15%)	2.6 (1.4–4.7)	0.004
Cumulative	18 (39%)	14 (15%)	2.6 (1.4–4.7)	0.004
AD				
Current	5 (11%)	7 (8%)	1.4 (0.5–4.3)	0.729
Cumulative	14 (30%)	22 (24%)	1.3 (0.7–2.3)	0.533

Definition of abbreviations: AD = atopic dermatitis; AR = allergic rhinoconjunctivitis; RR = relative risk; RSV = respiratory syncytial virus.

Number (percent) with symptoms.

asthma, parental asthma was also an independent risk factor (OR 4.7, 95% CI 1.6–13.9, *p* = 0.016). Only two independent risk factors for sensitization at age 13 were found: severe RSV bronchiolitis for sensitization to animal dander (OR 5.6, 95% CI 2.2–14.4, *p* < 0.001), and a history of parental asthma for sensitization to any tested allergen (OR 2.5, 95% CI 1.1–5.3, *p* = 0.019).

Table 5 shows that the RSV group had lower FEV₁/FVC ratios and lower FEF₇₅ values than the control group, both at rest and after β_2 -agonist inhalation. In addition, the RSV group showed a statistically greater fall in FEV₁ than the control group after dry air challenge. The 27 subjects with current asthma or recurrent wheezing in both groups together had on average lower resting FEV₁/FVC values than the remaining 103 subjects (83.3% versus 87.7%; *p* < 0.001), and also lower FEF₇₅ results (66.3% predicted versus 81.1% predicted; *p* < 0.001). After β_2 -agonist inhalation, FEV₁/FVC values remained lower (86.7% versus 89.1%; *p* = 0.011). These 27 subjects also showed a greater fall

TABLE 1. DEMOGRAPHIC AND BACKGROUND DATA IN THE RESPIRATORY SYNCYTIAL VIRUS GROUP AND THE CONTROL GROUP AT AGE 13

Variable	Respiratory Syncytial Virus Group (<i>n</i> = 46)	Control Group (<i>n</i> = 92)	<i>p</i> Value
Weight, kg	52.2 (10.6)	52.9 (11.2)	0.70
Height, cm	160.3 (8.8)	162.3 (8.3)	0.19
Heredity atopy, total	34 (74%)	68 (74%)	1.00
Heredity atopy, parent(s)	28 (61%)	50 (54%)	0.59
Heredity asthma, total	23 (50%)	32 (35%)	0.13
Heredity asthma, parent(s)	17 (37%)	25 (27%)	0.33
Smoking in family, current	16 (35%)	39 (42%)	0.50
Indoor furred pets, current	29 (63%)	68 (74%)	0.26
Number of siblings	2.0 (0.95)	1.8 (0.99)	0.31

Mean values (SD) or numbers (percent) of subjects are given.

TABLE 3. COMPARISON OF ALLERGIC SENSITIZATION IN RESPIRATORY SYNCYTIAL VIRUS AND CONTROL GROUPS AT AGE 13

Allergy test	RSV Group (<i>n</i> = 46)	Control Group (<i>n</i> = 92)	RR (95% CI)	<i>p</i> Value
SPT				
Any positive SPT	21/42 (50%)	24/87 (28%)	1.8 (1.1–2.9)	0.022
Dander	13/42 (31%)	6/87 (7%)	4.6 (1.9–11.2)	0.001
Pollens	11/42 (26%)	17/87 (20%)	1.3 (0.7–2.6)	0.523
Mites	7/42 (17%)	10/87 (11%)	1.5 (0.6–3.5)	0.581
Serum IgE antibodies				
Phadiatop	20/44 (45%)	22/86 (26%)	1.8 (1.1–2.9)	0.038
Dander	15/44 (34%)	7/86 (8%)	4.2 (1.8–9.5)	0.001
Pollens	14/44 (32%)	11/86 (13%)	2.5 (1.2–5.0)	0.020
Mites	9/44 (20%)	11/86 (13%)	1.6 (0.7–3.6)	0.372
Any positive test	22/44 (50%)	27/87 (31%)	1.6 (1.1–2.5)	0.055

Definition of abbreviations: RR = relative risk; RSV = respiratory syncytial virus; SPT = skin prick test.

Number of subjects tested (percent) with a positive skin prick test (SPT) and/or positive serum IgE antibody tests to common inhaled allergens.

TABLE 4. UNIVARIATE TESTS OF VARIOUS POSSIBLE RISK FACTORS FOR CURRENT ASTHMA/RECURRENT WHEEZING AND SENSITIZATION TO DANDER OR POLLENS AT AGE 13 IN THE COMPILED RESPIRATORY SYNCYTIAL VIRUS AND CONTROL GROUPS

Risk Factor	Asthma/Recurrent Wheezing			Sensitization to Dander			Sensitization to pollens		
	OR	(95% CI)	p Value	OR	(95% CI)	p Value	OR	(95% CI)	p Value
RSV bronchiolitis	9.3	(3.6–24.6)	< 0.001	5.6	(2.2–14.4)	< 0.001	1.8	(0.8–4.1)	0.227
Heredity atopy, total	1.3	(0.5–3.5)	0.810	1.1	(0.4–3.0)	1.00	1.3	(0.5–3.4)	0.710
Heredity atopy, parent(s)	2.6	(1.0–6.7)	0.063	1.7	(0.7–4.2)	0.382	2.0	(0.8–4.5)	0.163
Heredity asthma, total	2.2	(0.9–5.2)	0.103	2.5	(1.0–6.1)	0.073	1.2	(0.6–2.7)	0.754
Heredity asthma, parent(s)	2.6	(1.1–6.2)	0.050	2.8	(1.1–6.9)	0.045	1.5	(0.7–3.5)	0.437
Indoor furred pets at age 1	0.6	(0.2–1.5)	0.397	0.9	(0.4–2.3)	1.0	1.0	(0.4–2.2)	1.0
Smoking in family up to age 3	0.6	(0.2–1.4)	0.293	0.6	(0.2–1.5)	0.341	0.8	(0.4–1.8)	0.797
Male sex	1.2	(0.5–2.8)	0.801	1.6	(0.7–3.9)	0.392	1.0	(0.4–2.2)	1.000

Definition of abbreviation: OR = odds ratio.

in FEV₁ after challenge (7.5% versus 4.5%; $p < 0.001$), and greater response to β_2 -agonist inhalation (4.8% versus 3.05%; $p = 0.002$) than the remainders. Twenty-four subjects with RSV and 79 control subjects did not have current asthma or recurrent wheezing. This RSV subgroup had a lower resting FEV₁/FVC ratio than the 79 nonsymptomatic control subjects (85.9% versus 88.3%, $p = 0.035$), and showed a greater fall in FEV₁ after dry air challenge (5.9% versus 4.1%; $p = 0.021$). In addition, FEF₇₅ after β_2 -agonist inhalation tended to be lower in these 24 RSV subjects than in the nonsymptomatic control subjects (82.9% versus 93.3%; $p = 0.054$).

DISCUSSION

This prospective study with matched control subjects and high attendance rates shows that there remains a strong association between severe RSV bronchiolitis in the first year of life and asthma, clinical allergy, and allergic sensitization up to early adolescence. Our findings differ from those in the three previously reported controlled studies, in which wheezing and allergic sensitization were assessed at age 10 or more after verified RSV lower respiratory tract infection (3, 4, 18). The first of these studies compared 130 out of 180 children hospitalized with RSV lower respiratory tract infection before age 1 with 111 control

subjects (4). The children with RSV had more wheezing episodes during the first years of life, but not at age 10, and a lower frequency of positive skin prick tests (4). The second report concerns a subgroup of subjects from the Tucson Children's Respiratory Study (3). RSV lower respiratory tract infection before age 3, not requiring hospitalization, was a risk factor for wheezing episodes up to age 11 but not at age 13. At age 11, the rates of positive skin prick tests (59%) were similar in index children and control subjects (3). The third study found no differences in the rates of asthma or allergic sensitization after 18–20 years in 36/51 subjects hospitalized with RSV lower respiratory tract infection before age 2, compared with 45/72 control subjects from nonatopic families originally assembled for a diet intervention study (18).

There are three published follow-up studies with control groups to ages between 10 and 13 after bronchiolitis of various etiology (19–22). In the first of these studies, 61 of 101 children hospitalized with bronchiolitis in infancy and 47 of 73 control subjects were followed up at age 10 years (19, 20). Thirty-nine percent in the postbronchiolitic group and 13% among the control subjects had current asthma. The rates of positive skin prick tests were similar at age 10 (19) but higher in the index group at age 6 (20). In the second study, mild bronchiolitis before age 2 was found to be a risk factor for wheezing at age 8 but not at age 13 (21). In the third study, asthma or allergy was not more common among the 16 11-year-olds with a history of bronchiolitis (two hospitalized) before age 2 than in 178 control subjects (22). Controlled follow-up studies into early childhood after unspecified or verified RSV bronchiolitis in infancy have produced various outcomes regarding wheezing disorder and sensitization (23–26). In the most recent of these studies, children hospitalized with RSV bronchiolitis and matched control subjects were followed up at age 1, at which time allergic sensitization measured by serum IgE antibodies was significantly increased in the RSV bronchiolitis group (26).

The two spirometry variables reflecting airway obstruction, FEV₁/FVC ratio and FEF₇₅, were significantly lower in the RSV group than in control subjects, both at rest and after bronchodilator therapy. These results support the clinical findings of a greater proportion of subjects with obstructive airway disorder in the RSV group than in the control group. Airway function, airway reactivity, and bronchodilator response were all significantly greater among the 27 subjects with current asthma or recurrent wheezing from both groups compared with those without such a history, giving objective support to the clinical classification. It is interesting to note that the 24 asymptomatic subjects with RSV showed some evidence of airway obstruction and had slightly more reactive airways compared with the 79 asymptomatic control

TABLE 5. SPIROMETRY FINDINGS AT REST, AFTER β_2 -AGONIST THERAPY, MAXIMUM RELATIVE FALL IN FEV₁ AFTER DRY AIR HYPERVENTILATION CHALLENGE, AND CHANGE IN FEV₁ AFTER β_2 -AGONIST THERAPY (REVERSIBILITY), IN SUBJECTS WITH RESPIRATORY SYNCYTIAL VIRUS AND IN CONTROL SUBJECTS

Spirometry	RSV Group (n = 44)	Control Group (n = 86)	95% CI	p Value
Resting				
FEV ₁ (% pred)	90.8 (10.3)	93.2 (10.3)	(−6.2 to 1.4)	0.211
FEV ₁ /FVC (%)	84.8 (4.8)	87.8 (4.95)	(−4.8 to −1.2)	0.001
FEF ₇₅ (% pred)	71.3 (18.8)	81.5 (19.4)	(−17.3 to −3.2)	0.005
After β_2 therapy				
FEV ₁ (% pred)	94.0 (10.5)	95.8 (10.6)	(−5.6 to 2.1)	0.370
FEV ₁ /FVC (%)	87.5 (4.6)	89.2 (4.2)	(−3.2 to −0.1)	0.043
FEF ₇₅ (% pred)	80.6 (21.7)	92.5 (23.2)	(−20.3 to −3.6)	0.005
Challenge				
Fall in FEV ₁ (%)	6.1 (4.3)	4.6 (3.8)	(−3.0 to −0.1)	0.047
Reversibility				
Rise in FEV ₁ (%)	3.8 (2.3)	3.1 (2.9)	(−0.3 to 1.7)	0.153

Definition of abbreviations: % pred = percentage of predicted values (16); FEF₇₅ = maximal expiratory flow at 75% of FVC; RSV = respiratory syncytial virus.

Mean (SD), 95% confidence intervals, and p values are given.

subjects. More sensitive measures of peripheral airway function, such as ventilation distribution studies (17, 27), could possibly have disclosed further evidence of airway function abnormalities after RSV bronchiolitis. Our findings agree with those from other studies showing increased bronchial lability or decreased airway function in school children or young adults who had bronchiolitis in early childhood (3, 4, 18).

In our previous reports, only physician-verified episodes of wheezing were regarded as true asthma due to the fact that respiratory symptoms in preschool children may be misinterpreted by the parents (5, 6). In the present study, physician-verified wheezing as well as recurrent wheezing not verified by a physician is regarded as asthma based on the higher age of the participants at the current follow-up. The frequency of 43% of asthma/recurrent wheezing in the RSV group is markedly higher than the rate of 8.5% reported in a recent Swedish questionnaire study of 12- to 13-year-old children (28), but the latter rate is similar to the frequency of asthma/recurrent wheezing (8%) in our control subjects. Furthermore, the rates of allergic rhinoconjunctivitis (15%) and positive skin prick tests (28%) among our control subjects agree with those in a recent Swedish study (17% and 32%, respectively) of 12- to 13-year-olds tested with extracts from the same manufacturer (29).

Important features of the present study are that the index children had verified RSV bronchiolitis severe enough to require hospitalization in the first year of life (43 of 47 $\leq$ 6 months old), that the control group was recruited at the same time in infancy during the same winter season, that the two groups were followed up prospectively on four occasions regarding symptoms of bronchial obstruction, clinical allergies, and sensitization, and that attendance rates were 98 to 100%. Furthermore, in all follow-up investigations, the possibly relevant demographic and environmental factors were similar and no differences in the family history of atopy/asthma were found (5, 6). We have previously reported that RSV IgG or IgA antibodies were found in 100% of the subjects with RSV at age 1 versus 42% of the control subjects ($p < 0.001$) (30). The higher rates of such antibodies to RSV in the RSV group compared with the controls at age 1, support the conclusion that a severe RSV infection was an important difference between the groups (30). The control group might not be a true reference population; however, because a selection bias may have occurred when recruiting control subjects not suffering from severe RSV bronchiolitis in the same residential areas at the time of an RSV epidemic (8). Such subjects might have been less prone to develop severe bronchiolitis and future allergy and asthma, but the fact that the frequency of atopic dermatitis and the family histories of atopy/asthma were similar in the two groups at all follow-ups would suggest that they do not differ genetically with regard to atopy or asthma.

There are several reasons why the findings in our 13-year follow-up after RSV bronchiolitis differ from those in the follow-up study by Stein and coworkers (3). The children in our study were hospitalized and all of them were less than 1 year old (91% $\leq$ 6 months old), suggesting a more severe disease. Other dissimilarities may include differences in populations, climatic factors, and also allergen load, as only 28% of our control subjects had positive skin prick test compared with 59% in the study by Stein and colleagues (3). Our results also differ from the follow-up at age 18 to 20 by Korppi and coworkers (18). One important difference between our report and the latter study is the separate ages at the time of the RSV infection, as the children in the study by Korppi and colleagues were up to age 2 at the time of the hospital admission (18). We regard our results as valid and representative for subjects hospitalized during early infancy with RSV bronchiolitis. However, our investigation is a comparatively small descriptive study and cannot solve the issue

whether RSV by itself contributes to the postbronchiolitic symptoms and the increased frequency of allergic sensitization and clinical allergy in the children with RSV, or if additional risk factors are required.

Several mechanisms may contribute to recurrent wheezing after RSV bronchiolitis and to various extents in different subgroups of children (5–9, 31). Lower airway function before any viral infection could contribute to the occurrence of both RSV bronchiolitis and subsequent wheezing disorder (32, 33), and changes in the airways due to RSV infection may result in later wheezing (31). Animal experiments suggest that disturbed neuroimmune mechanisms after RSV infection may contribute to postbronchiolitic symptoms (34). Animal studies have also shown that sensitization to inhaled allergens is enhanced by RSV infection, but there is no proof for this in humans (31). Based on results from *in vitro* analyses of peripheral blood mononuclear cells from children in the present report, it can be speculated that RSV bronchiolitis in infancy may increase the risk of allergic sensitization by providing a local interleukin (IL)-4-rich environment in which inhaled allergens are first encountered (35). Alternatively, a recent study proposed that severe RSV disease might be related to increased Th2 response, which might be mediated by overexpression of IL-4, providing preliminary evidence for a genetic link between severe RSV disease and subsequent wheezing (36). It has also been suggested that a genetic defect associated with delayed postnatal maturation of helper T cell type 1 (Th1) function may underlie susceptibility to both allergic sensitization and the development of severe viral infections (37).

The present study provides evidence that severe RSV bronchiolitis in early infancy is a strong risk factor for the occurrence of allergic asthma in early adolescence. Population-based controlled randomized studies on the effects of preventing RSV bronchiolitis in infancy are required to answer the question of causation versus association between RSV bronchiolitis and subsequent asthma and allergy.

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