

Asthma and Lung Function 20 Years After Wheezing in Infancy

Results From a Prospective Follow-up Study

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Objective: To determine the outcome until adulthood after wheezing in infancy, compared with pneumonia in infancy and with controls.

Design: An 18- to-20-year prospective cohort study.

Setting: Pediatric department at a university hospital, providing primary hospital care for a defined population.

Patients: Fifty-four children hospitalized for bronchiolitis and 34 for pneumonia at younger than 2 years, and 45 controls with no early-life wheezing or hospitalization, were studied at median age 19 years.

Main Outcome Measures: A questionnaire on asthma symptoms and medication, physical examination, flow volume spirometry (FVS), methacholine inhalation challenge (MIC), home peak expiratory flow (PEF) monitoring, and skin prick testing (SPT) to common inhalant allergens. The 2 asthma definitions were physician-diagnosed asthma and previously diagnosed asthma with recent asthmatic symptoms (physician-diagnosed asthma included).

Results: By the 2 definitions, asthma was present in 30% (odds ratio [OR], 3.37; 95% confidence interval [CI], 1.12-10.10) and in 41% (OR 1.38; 95% CI, 0.37-5.21) in the bronchiolitis group, in 15% (OR, 5.50; 95% CI, 1.87-16.14) and in 24% (OR, 2.07; 95% CI, 0.59-7.22) in the pneumonia group, and in 11% in the control group. After bronchiolitis, the FVS values were forced vital capacity (FVC), 108% (SD, 13%) of predicted; forced expiratory volume in 1 second, 98% (SD, 12%); forced expiratory volume in 1 second divided by FVC, 91% (SD, 7.6%); midexpiratory flow at 50% of the FVC, 74% (SD, 19%); and midexpiratory flow at 25% of the FVC, 74% (SD, 22%). Bronchial reactivity by MIC was present in 25 (48%) of 52 subjects in the bronchiolitis group, in 13 (42%) of 31 in the pneumonia group, and in 14 (32%) of 44 in the control group. The prevalence of atopy (positive SPTs) was 48% to 63% in the 3 groups. In a logistic regression adjusted for atopy and smoking, infantile bronchiolitis was an independent risk factor for asthma by both definitions.

Conclusion: The increased risk for asthma persists until adulthood after bronchiolitis in infancy.

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WHEEZING IN INFANCY is a heterogeneous condition, the long-term prognosis varying from total recovery to chronic asthma and disorders in lung function.¹ Wheezing episodes decrease in frequency over time, and 15% to 20% of the wheezy infants continue to wheeze until 10 years of age.²⁻⁴

Although there are many studies on the short-term outcome of bronchiolitis or early childhood wheezing, only 1 prospective study⁵ has continued the follow-up through childhood until adulthood. In this birth cohort from the United Kingdom, early childhood wheezing was not predictive of either asthma or asthmalike symptoms at the age of 22 years, but the study was underpow-

ered for this particular purpose.^{5,6} In a recent Canadian study,⁷ the subjects with bronchiolitis in infancy were identified retrospectively from patient records of the hospitals, and bronchiolitis was associated with both clinically diagnosed asthma and lung function abnormalities between the ages of 17 to 35 years. In the Tucson Children's Respiratory Study, a birth cohort has been followed up until the age of 16 to 18 years.¹ Thus far, the results have been published to the age of 13 years. Children who started to wheeze before 3 years of age and continued to wheeze until the age of 6 years were often atopic and tended to have asthma between the ages of 11 to 13 years.^{1,8,9} Lung function of wheezing infants improved with age, but their lung function never matched those infants who had never wheezed.¹

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We have prospectively followed up a group of children hospitalized for bronchiolitis and pneumonia before the age of 2 years from 1981 to 1982 onward. The prevalence of asthma was 15% between the ages of 8 to 10 years in the original bronchiolitis group and 7% in the original pneumonia group.² In this study we evaluate asthma, atopy, bronchial reactivity, and lung function in the same cohort aged 18 to 20 years, compared with controls of the same age followed up from birth. The purpose of the study was to evaluate asthma and lung function in adolescents with early childhood hospitalization for wheezing.

PATIENTS AND METHODS

DESIGN

We have prospectively followed up a group of 127 children hospitalized at the age of 1 to 24 months (median age, 10 months) for bronchiolitis (n=83) or pneumonia (n=44) in Kuopio University Hospital (Kuopio, Finland) between 1981 and 1982.^{10,11} All of the children were recruited during the hospitalization period, with a diagnosis of bronchiolitis or pneumonia confirmed by 1 of the authors (M.K.), either during hospital admission or the next morning. The diagnostic criteria for bronchiolitis were the presence of wheezing and/or prolonged expiration in association with respiratory infection, and pneumonia was diagnosed radiologically.¹⁰ Most (72%) of the children with bronchiolitis were wheezing for the first time. The follow-up visits have taken place when the subjects were between the ages of 2 to 3 years,¹¹ 4.5 to 6 years,¹² 8 to 10 years,² and in early adulthood.

The control group, consisting of 72 newborns without family history of atopy, was recruited at birth between 1979 and 1980 (for a birth cohort study on atopy), and has also been prospectively followed up.^{13,14} Follow-up revealed that none of the controls had wheezed or were hospitalized for lower respiratory tract infection before the age of 2 years.

The present study was carried out in 2000 when the participants were between 18 and 21 years (median age, 19 years). In all, 173 (87%) of the invited 199 subjects answered a written questionnaire and 133 (67%) (54 from the bronchiolitis group, 34 from the pneumonia group, and 45 controls) attended the clinical study. After physical examination, the study subjects performed baseline flow volume spirometry (FVS), methacholine inhalation challenge (MIC), skin prick tests (SPT), and after the visit, a 2-week home peak expiratory flow (PEF) monitoring. One of the authors (E.P.S.) interpreted the results, with no knowledge of the original study groups or the previous prospectively collected follow-up data. Before clinical examination, the participants filled out a written questionnaire on asthma diagnoses and lifetime medication for asthma, and on history of wheezing episodes and episodes of prolonged cough apart from infection during the preceding 12 months. In addition, smoking habits of the participants were evaluated by interview, and the average number of cigarettes smoked daily was recorded.

LUNG FUNCTION

The baseline lung function was measured in 132 of 133 participants with a flow volume pneumotachograph spirometer (Medikro, Kuopio, Finland). The indices registered were the forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), FEV₁ divided by the FVC (FEV%), midexpiratory flow at 50% of the FVC (MEF50), and midexpiratory flow at 25% of the FVC (MEF25).¹⁵ No medication was given before testing, and the use of β -agonists was not allowed during the

study day. The results were compared with the sex-specific, height-related reference values, and are given as percentages of the means (percent predicted). The cut-off limit for an abnormal result was 80% for FEV₁, 88% for FEV%, 62% for MEF50, and 48% for MEF25, representing the lower limits of 95% confidence intervals (CI) in Finnish adolescents.¹⁶ The FVS was assessed at a minimum of 3 times, and the measurements were accepted if the flow volume curve was appropriate in shape and the variation of FEV₁ in 2 curves was less than 5%.^{15,17}

BRONCHIAL REACTIVITY

Bronchial reactivity was assessed by the MIC test in 127 (95%) of 133 participants. The test was not given to 4 pregnant women. The provocative dose designates the cumulative amount of inhaled methacholine needed to produce a 20% fall (PD20) in FEV₁ compared with the baseline value. Methacholine was inhaled using a Spira Electro-2 dosimeter (Respiratory Care Center, Hämeenlinna, Finland), allowing for the calculation of the total amount inhaled by each subject. Lung function by the FVS was measured at the beginning and 1.5 minutes after each methacholine dose. The test was continued until a 20% fall in FEV₁, or until a cumulative dose of 4900 μ g of methacholine was reached.² Bronchial reactivity was classified into 4 categories: severe (PD20 $\leq$ 400), moderate (PD20 401-1600), mild (PD20 1601-4900), and no (PD20 > 4900).²

HOME PEF MONITORING

A 2-week home PEF monitoring (Spira PEF meter; Respiratory Care Center, Hämeenlinna, Finland) was carried out by 110 (83%) of 133 study subjects. Among them, 64 (58%) had suffered from wheezing (n=40) or cough (n=45) during the preceding 12 months, or had an ongoing maintenance medication for asthma (n=10). Among the 23 study subjects with home PEF monitoring data not available, the respective figure was 13 (57%), and none of them were receiving maintenance medication for asthma. Three consecutive measurements were recorded twice a day, and the best value of each session was recorded for the analyses. The measurements were accepted if 2 best results were within 20 L/min. Daily variability was considered significant if PEF values (the difference between the best morning and the best evening value divided by the mean of these values) varied by more than 20% in 2 or more days during the 2-week surveillance time.^{18,19} Further, bronchial obstruction was estimated during the second week of the follow-up by measuring PEF values before and 15 minutes after inhaled β -agonist inhalation (0.5 mg of terbutalin with Turbuhaler; Astra, Södertälje, Sweden) twice a day.²⁰ The limit for significant improvement in PEF was 15% demonstrated at least twice during the 1-week follow-up.^{18,19} The PEF monitoring was accepted if the test was performed appropriately for 10 days during the 14-day follow-up period, or if the criteria of pathological monitoring were fulfilled in a shorter time.

SKIN PRICK TESTING

Atopy in adulthood was defined by a positive SPT reaction to 1 or more of the 8 common inhalant allergens (ALK, Copenhagen, Denmark); tests for birch, timothy grass and mugwort pollens, cat and dog dander, house dust mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), and spores of *Cladosporium herbarum* were performed for 128 (96%) of 133 participants. The concentration of each allergen extract was 3 histamine-equivalent pricks. The reaction was considered positive if the average diameter of the wheal was 3 mm or larger, and at least half of that produced by the positive control (histamine hydrochloride, 10 mg/mL).²¹ In addition, if the shape

Table 1. Asthma in 88 Young Adults Who Were Hospitalized for Bronchiolitis or Pneumonia in Infancy and in 45 Controls*

	Bronchiolitis Group (n = 54)	Pneumonia Group (n = 34)	Control Group (n = 45)	P Value†
Definition of asthma				
Current physician-diagnosed asthma	16 (30)	5 (15)	5 (11)	.04
OR (95% CI)‡	3.37 (1.12-10.10)	1.38 (0.37-5.21)	1.00	
Maintenance therapy§	7	1	2	
Previous asthma and wheezing or prolonged cough within 12 mo	22 (41)	7 (21)	5 (11)	.003
OR (95% CI)‡	5.50 (1.87-16.14)	2.07 (0.59-7.22)	1.00	

Abbreviations: CI, confidence interval; OR, odds ratio.

*See the "Definition of Asthma" subsection of the "Patients and Methods" section for the 2 definitions of asthma used in this study. Data are given as number (percentage) unless otherwise indicated.

†Analysis of variance and χ^2 test.

‡Measured using logistic regression.

§Represents number of subjects with physician-diagnosed asthma who had ongoing maintenance therapy when entering the 20-year follow-up study.

||Current physician-diagnosed asthma included.

of the wheal was irregular with pseudobodies, the reaction was regarded as positive. No reaction against a standardized quality negative control solution (Soluprick, ALK) was accepted.

DEFINITION OF ASTHMA

Bronchial asthma was defined in 2 different ways, reflecting the degree of certainty of the diagnosis. One way was current physician-diagnosed asthma, with the patient either taking ongoing maintenance medication for asthma or a symptomatic participant receiving home PEF monitoring. The second way was previously diagnosed asthma and self-reported wheezing or prolonged cough during the preceding 12 months, current physician-diagnosed asthma included.

STATISTICS

The data were analyzed using SPSS 9.0 and 11.0 (SPSS Inc, Chicago, Ill). The χ^2 test was used for categorical variables, and the 1-way analysis of variance, after ensuring the normality of the data, was used for continuous variables. In the multivariate analyses, the risks for asthma (separately by both definitions), bronchial reactivity, and abnormal lung function were estimated as odd ratios (ORs) by logistic regression after adjustment for current smoking and atopy (defined by positive SPT results).

ETHICS

This follow-up study was approved by the joint ethics committee for human research at Kuopio University and Kuopio University Hospital. A written informed consent was obtained from all study subjects and from at least 1 parent.

RESULTS

Current physician-diagnosed asthma was, at the median age of 19 years, present in 30% of the participants who had bronchiolitis in infancy (OR, 3.37; 95% CI, 1.12-10.10), compared with 15% in those with pneumonia in infancy and with 11% in controls (**Table 1**). By the less strict asthma criteria, there were 6 additional asthma cases in the bronchiolitis group (OR, 5.50; 95% CI, 1.87-16.14), and 2 in the pneumonia group, whereas the asthma rate in the controls remained the same.

In the FVS, the mean values (percent predicted) were normal, and even the lower limits of the 95% CIs were normal in all groups (**Table 2**). However, all 4 variables (FEV₁, FEV%, MEF50, and MEF25) were significantly lower after infantile bronchiolitis than in the controls. Likewise, at least 1 abnormal value in the FVS was observed more often in the bronchiolitis (36%) than in the control group (11%) (OR, 4.47; 95% CI, 1.51-13.24). The difference between the groups was most obvious in the proportions of decreased MEF50 values: 30% in the bronchiolitis, and less than 15% in the 2 other groups (**Table 2**).

In the MIC, measurable bronchial reactivity (PD20 $\leq$ 4900) was demonstrated in 52 participants (41%) (**Table 3**). Severe hyperreactivity (PD20 $\leq$ 400) was observed in only 3 cases, all belonging to the bronchiolitis group. There were no significant differences between the 3 groups at any level of bronchial reactivity (**Table 3**).

Atopy, defined as SPT reactivity, was present in about half of the participants (**Table 4**). The participants of the bronchiolitis group were significantly more often reactive to dog and cat dander than the controls. Reactions to seasonal pollens were similar in all 3 groups and reactions to house dust mites and molds were rare (<15%). As seen in **Table 5**, asthma (by both definitions) and bronchial reactivity were significantly associated with atopy, but lung function abnormalities were not.

The association of bronchiolitis or pneumonia in infancy with asthma (by both definitions), bronchial reactivity, abnormal lung function, and atopy in adulthood was also analyzed by a logistic regression model adjusted for current smoking and current atopy (**Table 6**). Current smoking, defined by smoking at least 1 cigarette daily, was present in 34 (26%) of 133 participants. Current atopy, defined by SPT results, was present in 71 (56%) of 128 participants. In this model, bronchiolitis in infancy was an independent risk factor for asthma and lung function abnormalities in early adulthood, but was not associated with bronchial reactivity. However, bronchiolitis was not significantly associated with any individual parameter in the FVS. Pneumonia in infancy was not related to any later outcome parameters.

Seventy-five (56%) of 133 participants, including 7 of 10 participants on maintenance medication for asthma,

Table 2. Lung Function Results in Flow Volume Spirometry in 87 Young Adults Who Were Hospitalized for Bronchiolitis or Pneumonia in Infancy and in 45 Controls*

Parameter in Spirometry	Bronchiolitis Group (n = 53)	Pneumonia Group (n = 34)	Control Group (n = 45)	P Value†
FEV ₁				
Mean (95% CI)	98 (94-101)	100 (96-104)	104 (100-108)	.05
Abnormal findings‡	4 (8)	1 (3)	1 (2)	.4
FEV%				
Mean (95% CI)	91 (89-94)	96 (93-99)	96 (94-98)	.003
Abnormal findings‡	14 (26)	7 (21)	5 (11)	.16
MEF50				
Mean (95% CI)	74 (69-79)	84 (77-90)	87 (81-92)	.004
Abnormal findings‡	16 (30)	5 (15)	4 (9)	.02
MEF25				
Mean (95% CI)	74 (68-80)	85 (76-93)	89 (80-98)	.01
Abnormal findings‡	5 (9)	0	3 (7)	.19
At least 1 lung function abnormality	19 (36%)	9 (27%)	5 (11%)	.02
OR (95% CI)§	4.47 (1.51-13.24)	2.88 (0.87-9.58)	1.00	

Abbreviations: CI, confidence interval; FEV₁, forced expiratory volume in 1 second; FEV%, FEV₁ divided by forced vital capacity; MEF50, midexpiratory flow at 50% of forced vital capacity; MEF25, midexpiratory flow at 25% of forced vital capacity; OR, odds ratio.

*Data are given as number (percentage) unless otherwise indicated.

†Analysis of variance and χ^2 test.

‡The cut-off limit was 80% of predicted for FEV₁, 88% for FEV%, 62% for MEF50, and 48% for MEF25.

§Measured using logistic regression.

Table 3. Results of the Methacholine Inhalation Challenge in 83 Young Adults Hospitalized for Bronchiolitis or Pneumonia in Infancy and 44 Controls*

Degree of Bronchial Reactivity	Bronchiolitis Group (n = 52)	Pneumonia Group (n = 31)	Control Group (n = 44)	P Value†
Severe (PD20 < 400)	3 (6)	0	0	.11
Moderate (PD20 400-1600)	7 (13)	3 (10)	5 (11)	.87
Mild (PD20 1600-4900)	15 (28)	10 (33)	9 (21)	.57
Bronchial reactivity present	25 (48)	13 (42)	14 (32)	.27
OR (95% CI)	1.98 (0.86-4.58)	1.55 (0.60-4.30)	1.00	NA

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio; PD20, cumulative dose of methacholine (in micrograms) producing a 20% fall in forced expiratory volume in 1 second.

*Data are given as number (percentage) unless otherwise indicated.

†Measured using χ^2 test.

had suffered from wheezing or prolonged cough during the preceding 12 months. Wheezing was equally common after infantile bronchiolitis (24/54; 44%) and pneumonia (13/34; 38%), being present in 22% (10/45) of the controls ($P = .07$). The prevalence of prolonged cough in the 3 groups was 48% (26/54), 47% (16/34), and 29% (13/45) ($P = .11$), respectively.

Questionnaire data were available for 40 (61%) of 66 of the subjects not attending the clinical study. Among them, wheezing was present in 4 subjects (10%), compared with 35% of the attendants ($P = .004$), and prolonged cough was present in 12 (30%), compared with 41% of the attendants ($P = .26$). The prevalence of previously diagnosed asthma was rather similar in these 2 groups (18% vs 20%).

COMMENT

There are 3 main results in the present prospective study on the long-term outcome of wheezing in infancy until

adulthood. First, the increased risk for bronchial asthma continued until the age of 18 to 20 years. In logistic regression, bronchiolitis in infancy was a significant risk factor for asthma independently from atopy or smoking. Second, lung function parameters by FVS were, on average, within normal limits. However, abnormal values in spirometry were more common in the bronchiolitis group than in the controls. Third, asthma and bronchial reactivity were significantly associated with the development of atopy, but lung function abnormalities were not.

In the present study, at the age of 18 to 20 years, 30% to 40% of subjects with bronchiolitis in infancy had asthma in young adulthood. Our result is rather similar to the findings of a recent study from Canada.⁷ In that study, asthma was diagnosed clinically at the age of 17 to 35 years, but the study subjects were identified and the data on early-life wheezing were collected retrospectively from the patient records of 2 hospitals. The prevalence of asthma was 38% after hospitalization for bronchiolitis before the age of 18 months, significantly higher than in

Table 4. Skin Prick Test Reactions to 8 Common Inhalant Allergens in the 84 Index Subjects and in 44 Controls*

	Bronchiolitis Group (n = 51)	Pneumonia Group (n = 33)	Control Group (n = 44)	P Value†
Allergen				
Birch pollen	19 (37)	8 (24)	11 (25)	.4
Timothy pollen	25 (49)	8 (24)	15 (34)	.06
Mugwort pollen	3 (6)	4 (12)	6 (14)	.44
Cat dander	23 (45)	7 (21)	8 (18)	.008
Dog dander	23 (45)	14 (42)	7 (16)	.006
<i>Dermatophagoides farinae</i>	4 (11)	2 (7)	1 (3)	.36
<i>Dermatophagoides pteronyssinus</i>	7 (14)	5 (16)	4 (9)	.67
<i>Cladosporium herbarum</i> spores	0	2 (8)	0	.55
At least 1 positive test result	32 (63)	17 (51)	22 (50)	.31
OR (95% CI)‡	1.68 (0.74-3.82)	1.06 (0.43-2.02)	1.00	NA

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.

*Data are given as number (percentage) unless otherwise indicated.

†Measured using χ^2 test.

‡Measured by logistic regression.

Table 5. Presence of Asthma, Bronchial Reactivity, and Abnormal Lung Function in Relation to Atopy in Adulthood*

	Atopy Present† (n = 71)	Atopy Not Present (n = 57)	OR (95% CI)‡
Current physician-diagnosed asthma	18 (2)	6 (11)	2.89 (1.06-7.85)
Previous asthma and wheezing or prolonged cough within 12 mo§	25 (35)	7 (12)	3.88 (1.53-9.8)
Bronchial reactivity	36 (51)	16 (30)	2.51 (1.19-5.32)
Abnormal lung function¶	22 (31)	9 (16)	2.34 (0.98-5.61)

Abbreviations: CI, confidence interval; OR, odds ratio.

*See the "Definition of Asthma" subsection of the "Patients and Methods" section for the 2 definitions of asthma used in this study; data are given as number (percentage) unless otherwise indicated.

†Atopy means 1 or more positive skin prick test responses to 8 common inhaled allergens.

‡Measured by logistic regression.

§Cases with current physician-diagnosed asthma included.

||The provocative dose that designated the cumulative amount of inhaled methacholine needed to produce a 20% fall was less than 4900 μ g in the methacholine-inhalation challenge test.

¶At least 1 abnormal result in flow volume spirometry.

Table 6. Association of Asthma, Bronchial Reactivity, and Abnormal Lung Function With Bronchiolitis or Pneumonia in Infancy, Analyzed in a Logistic Regression Model Adjusted for Current Atopy and Current Smoking*

	Bronchiolitis Group	Pneumonia Group	Control Group
Current physician-diagnosed asthma			
Crude OR (95% CI)†	3.37 (1.12-10.10)	1.38 (0.37-5.21)	1.00
Adjusted OR (95% CI)‡	2.97 (0.96-9.18)	1.06 (0.26-4.37)	1.00
Previous asthma and wheezing or prolonged cough within 12 mo			
Crude OR (95% CI)†	5.50 (1.87-16.14)	2.07 (0.59-7.22)	1.00
Adjusted OR (95% CI)‡	5.07 (1.66-15.50)	1.74 (0.47-6.50)	1.00
Bronchial reactivity			
Crude OR (95% CI)†	1.98 (0.86-4.58)	1.55 (0.60-4.03)	1.00
Adjusted OR (95% CI)‡	2.03 (0.85-4.83)	1.56 (0.59-4.13)	1.00
Abnormal lung function			
Crude OR (95% CI)†	4.47 (1.51-13.24)	2.88 (0.87-9.58)	1.00
Adjusted OR (95% CI)‡	4.13 (1.36-12.51)	2.52 (0.73-8.68)	1.00

Abbreviations: CI, confidence interval; OR, odds ratio.

*For the definitions of current physician-diagnosed asthma, previous asthma with wheezing or prolonged cough within 12 months (current physician-diagnosed asthma included), bronchial reactivity, and abnormal lung function, see the text. Atopy means the presence of 1 or more positive skin prick test reactions to 8 common inhaled allergens.

†Logistic regression with no adjustments.

‡Logistic regression adjusted for current atopy (positive skin prick test results) and smoking of the participants.

controls with no such history. In a birth cohort from England, wheezing in infancy was not associated with asthma in adulthood. In that study, data on wheezing were collected prospectively, but the number of infants with wheezing was too low to allow any proper risk estimation. If the children started to wheeze between 2 and 5 years of age, they were likely to wheeze also as adults.^{5,6}

In the Tucson Children's Respiratory Study, follow-up data have been collected until participants were 16 to 18 years of age,^{1,3} but published only until they were 11 to 13 years of age. In that birth cohort, 60% of the children had wheezed during their first 3 years of life, and 10% of them still suffered from recurrent wheezing at the age of 13 years.³ Wheezing infants with atopy were at a particular risk to have permanent asthma in adolescence.^{1,22} In the present study, asthma at the age of 18 to

20 years was associated with current atopy in the subjects. Despite this, bronchiolitis in infancy was a significant risk factor for asthma in early adulthood, independently from the development of atopy, and carried a 3- to 5.5-fold risk for asthma in young adults.

In this cohort the prevalence of physician-diagnosed asthma after wheezing in infancy was 15% and 7% after

pneumonia in infancy at the age of 8 to 10 years.² The prevalence of asthma at school age is 4% to 5% in our population.^{23,24} The figure after infantile wheezing correlates with similar studies; wheezing has continued until 10 or more years in 15% to 20% of the subjects.^{3,4} In the birth cohort from Tucson, children with pneumonia (not associated with wheezing) in infancy had an increased risk for asthma by the age of 11 years.¹ Compared with our earlier follow-up data, the asthma figures were higher, up to 30% for the bronchiolitis group and 15% for the pneumonia group, in the present study in early adulthood. This observation is consistent with the earlier finding from the United Kingdom that subjects who have grown out of childhood wheezing at puberty may become symptomatic again in adulthood.⁴

In the present study, all parameters in spirometry, although normal on average, were lower after infantile bronchiolitis than in the controls. This finding correlates with the results of the Tucson Children's Respiratory Study.^{1,3} By the age of 11 years, infantile wheezers did not regain the lung function of infants who never wheezed, even though they often outgrew their symptoms. In accordance, wheezing before age 18 months resulted in lowered FEV₁ and FEV% values in adulthood in the Canadian study.⁷ In 2 follow-up studies^{25,26} from the United Kingdom and New Zealand, deteriorated lung function in adulthood was associated with preschool-age wheezing and/or asthma, but only in those with symptoms continuing in adulthood. In an Australian follow-up study, children with asthma or repeated wheezing before school age had subnormal lung function in adulthood.²⁷ In the present study in young adults, hospitalization for wheezing at younger than 2 years carried a 3- to 4-fold risk for lung function abnormalities.

Skin prick test reactivity was used for objective definition of atopy in adulthood. A positive test reaction to at least 1 of 8 common inhalant allergens was demonstrated in more than half of the participants. The figure was 48% in controls, though they were from nonatopic families. Reactions to cat and dog danders, as the only specific allergens, showed an association with the history of infantile wheezing. In the Tucson Children's Respiratory Study, more than 50% of all subjects had a positive test result in SPTs at the age of 11 years, and no association was found with history of early childhood wheezing.^{3,28} The only allergen that associated significantly with asthma was the mold *Alternaria alternata*. In the study from New Zealand, like in many other studies, skin reactivity to house dust mites in childhood predicted asthma in adulthood.²⁶ In the present study, reactions to house dust mites and molds were rare, as they have been in other studies from northern climates.²⁹⁻³²

The shortcomings of the present study are the low number of study subjects with asthma and/or lung function abnormalities, and the selected control group recruited from nonatopic families. However, the controls had been followed up from birth with no need for retrospective data collection. Also, nearly half of them were atopic in adulthood, which offers a proper comparison with the other 2 groups. The proportion of subjects who dropped out was 33%, and they had, based on questionnaire data available, less wheezing during the preceding

What This Study Adds

Early childhood wheezing predisposes to asthma in later childhood, but the outcome in adulthood is poorly known, owing to a lack of sufficiently long follow-up studies. The present, 18- to 20-year cohort study is the longest prospective study that has been published on the outcome of early life wheezing. The main result was that there was an increased risk for asthma and impaired lung function, independently from the development of atopy, in young adults who had been hospitalized for wheezing before the age of 24 months.

12 months. Comparably, no differences were seen in asthma medication or cough symptoms, and in addition, the proportions of the dropouts were similar in the 3 study groups. Our conclusion is that the confounding effect caused by dropouts is not significant in terms of the main results: there is an increased risk for asthma after early childhood wheezing, and asthma symptoms may begin again in adults who have grown out of wheezing in childhood.

The main strength of the present study is the long follow-up time of participants from infancy to young adulthood (>18 years). To date, this study is the longest prospective so far published after bronchiolitis in infancy. The basic data were registered before 2 years of age, and the follow-up data included careful clinical, allergological, and lung function studies. The study was prospective, controlled, and also blinded, since the clinical examination and diagnostic decisions were made without any knowledge of the earlier data. The definitions of asthma were rather strict, based on continuous maintenance medication for asthma, recent wheezing and/or cough symptoms, and pathological results in the PEF home monitoring.

Atopic constitution, as well as passive and active smoking, are factors significantly predisposing to both early-life wheezing and later asthma.^{27,32,33} Therefore, current atopy and smoking were included as confounding factors in the logistic regression model, which did not change the results remarkably. Wheezing in infancy proved to be a significant risk factor for asthma and lung function abnormalities in early adulthood, independently from atopy and smoking.

In conclusion, we found that wheezing in early childhood was a significant predictor of asthma, and also seemed to predict lung function abnormalities in early adulthood. Thus, early wheezing may have pulmonary consequences persisting until adulthood, and although the outcome of children with early wheezing is good at school age,^{2,12} they may become symptomatic again as adults.

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