

High Risk of Adult Asthma Following Severe Wheezing in Early Life

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Summary. Background: Severe wheezing in early life is associated with an increased risk of asthma during childhood and adolescence. The aim of the present follow-up was to investigate the asthma prevalence and risk factors for asthma in adulthood. Methods: We have prospectively studied asthma development in 101 children hospitalized due to severe wheezing before the age of 24 months. The cohort was re-investigated at a mean age of 27 years and tested for bronchial hyper-responsiveness and allergic sensitization. The response rate in adulthood was 81% (82/101). The results were compared with a population-based, age-matched control group ($n = 1,210$) recruited from the West Sweden Asthma Study. Results: Current doctor-diagnosed asthma was found in 37% (30/82) compared with 7% (82/1,210) in the control group. The risk of adult asthma in the cohort compared with the control group was increased 10-fold (adjusted OR 10.0, 95% CI 5.3–18.7), independently of allergic rhinitis, gender, smoking and heredity. Within the cohort, current allergy (aOR 9.6, 95% CI 3.0–31.2) and female gender (aOR 3.2, 95% CI 1.1–9.3) independently increased the risk of adult asthma. Females with current allergy had the highest risk of adult asthma (OR 29.4, 95% CI 5.0–173.3), compared with males without allergy. When separately adjusting for factors present at admission in early life within the cohort, a family history of asthma was a significant risk factor for asthma in adulthood (aOR 4.0, 95% CI 1.3–12.5). Conclusion: Subjects with severe early wheezing have a 10-fold increase in the risk of adult asthma compared to an age-matched control group, adjusted for allergic rhinitis, gender, smoking and heredity. **Pediatr Pulmonol.** © 2014 Wiley Periodicals, Inc.

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INTRODUCTION

Virus-triggered wheezing in early childhood is very common, although the problems often disappear at preschool age.¹ Nonetheless, re-investigations of children with severe wheezing in early life have demonstrated a clearly increased risk of asthma in late adolescence.^{2–4} In these studies, heredity, female gender, early tobacco exposure, and the development of allergy were found to be important risk factors for asthma at age 18–20 years.^{2,3} In addition, reduced airway function in late adolescence has been reported in subjects with severe wheezing early in life, compared with age-matched controls.⁵ This suggests that the general view of a very favorable course for early wheezing should be modified. It also underlines the importance of following available “post-bronchiolitis” cohorts beyond adolescence. However, to date, adult life re-investigation results have only been presented from one post-bronchiolitis cohort, a Finnish study by the Korppi group, reporting a fourfold increase in asthma prevalence compared with controls.^{6,7} At 27 years of age doctor-diagnosed asthma was found in 20% and self-

reported asthma in 41% in the Finnish post-bronchiolitis cohort.⁶

We have followed a cohort of children who were hospitalized for the first time before the age of 24 months due to acute severe wheezing, or “bronchiolitis,” using the US terminology.^{8,9} The children have previously been re-investigated during childhood and adolescence.^{3,10,11} At

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18 years of age, as many as 43% had current asthma.³ Knowledge of risk factors for the persistence of asthma leads to a better understanding of the underlying mechanisms and may improve preventive strategies.

The aim of the present follow-up was to investigate the asthma prevalence in adulthood in the cohort and the risk factors for current asthma. The prevalence of current doctor-diagnosed asthma was compared with an age-matched, population-based control group.

MATERIALS AND METHODS

Participants in the Cohort

One hundred and one children hospitalised for the first time due to severe wheezing, or “bronchiolitis,” using the US terminology, before the age of 24 months were included in the study and followed prospectively until adulthood. The present re-investigation was performed in 2009–2011 at a mean age of 27 years (range 25–28 years).

First Admission and Previous Re-Investigations

The earlier re-investigations were performed at age 4–5, 10, and 18 years. Details on the first hospitalization and earlier re-investigations have been published previously.^{3,10,11} At first admission, the protocol included a detailed case history concerning allergy and earlier infections, chest X-ray, nasopharyngeal culture for bacteria and blood samples for CRP, eosinophils and total IgE. In addition, viral detection was made using viral isolation from nasopharynx and feces, viral antigen in nasopharyngeal secretion, viral antibodies in sera and a complement fixation test. Diagnostic techniques were available for respiratory syncytial (RS), adeno, influenza A and B, parainfluenza 1, 2 and 3, enterovirus and rota viruses, as well as mycoplasma pneumoniae. At the time, diagnostic techniques were not available for rhinovirus and coronavirus.¹⁰

Procedures, Current Re-Investigation

After receiving written informed consent recent health history was obtained using a questionnaire sent by post. The subjects in the cohort were offered the opportunity to undergo tests for allergic sensitization, lung function, fraction of exhaled nitric oxide (FeNO) and bronchial hyper-responsiveness (BHR). The answers from the postal questionnaire were ascertained during the visit to the clinic or, when needed, by telephone interview.

The allergy tests included a skin prick test (SPT), specific IgE in serum and an eosinophil granulocyte count in the blood. The allergens in the SPT were birch, grass, mugwort, horse, dog, cat, rabbit, house dust mites (*D. pteronyssinus* and *D. farinae*), and mould (*Cladosporium*). ALK Soluprick[®] extracts were used (ALK, Copenhagen, Denmark). A weal diameter of at

least 3 mm was regarded as positive. A Phadiatop[®] test was performed for inhaled allergens and specific IgE in serum was analysed for egg white, milk, fish, wheat, peanut, and soy (Thermo Fisher Scientific, Uppsala, Sweden). The specific IgE was defined as positive when ≥ 0.35 kU/L.

FeNO was measured using the NIOX MINO[®] (Aerocrine, Solna, Sweden) and was performed once before spirometry, according to the manufacturer's protocol. An FeNO level of more than 20 ppb was regarded as elevated.

Spirometry was performed using the Medikro[®] Spirostar spirometer (Medikro Oy, Koupio, Finland) and BHR was tested using the mannitol challenge (Aridol[®], Pharmaxis Ltd., French Forest, NSW, Australia). Mannitol was inhaled according to the Aridol[®] protocol, that is, in increasing doses to a cumulative dose of 635 mg or to a positive test response. A fall in FEV₁ of $\geq 15\%$ from baseline or a fall in FEV₁ of $\geq 10\%$ between two doses was regarded as pathological, that is, a positive test response.¹² Spirometry was performed in duplicate after each inhaled dose.

Definitions

Current asthma was defined as having a doctor's diagnosis of asthma and symptoms of wheezing or asthma and/or the use of anti-asthmatic treatment (β_2 -agonists or inhaled corticosteroids) during the preceding 12 months. A doctor's diagnosis was either reported in the questionnaire or confirmed during the test procedure at the clinic.

Asthma was classified as mild or moderate to severe, according to the classification system of the Swedish Society of Paediatric Allergology (www.barnallergisektionen.se), as used in the previous re-investigations. Individuals with mild asthma had mild and infrequent asthma symptoms and symptom control with a β_2 -agonist alone. Individuals with moderate to severe asthma required both inhaled corticosteroids and β_2 -agonist treatment.

The level of asthma control was evaluated using the Asthma Control Test[™], ACT[™] (Quality Metric Incorporated, Lincoln, RI). ACT includes five different items and assesses the frequency of shortness of breath and general asthma symptoms, use of rescue medications, the effect of asthma on daily functioning and overall self-assessment of asthma control. Each item is scaled from 1 to 5 points and the total score ranges from 5 (poor control) to a maximum of 25 (complete control). An ACT score above 19 indicates well-controlled asthma. Hence, in the current study uncontrolled asthma was defined as a score of less than 20.¹³

Current allergy was defined as having reported any allergic manifestation (other than asthma, i.e., allergic rhinoconjunctivitis, atopic eczema, or food allergy) and, if tested, confirmed by a positive SPT or specific IgE.

Control Group

An age-matched, population-based control group of 1,210 individuals was recruited from the West Sweden Asthma Study. Their mean age was 27 years, ranging from 25 to 28 years. The West Sweden Asthma Study is a large epidemiological study using the Swedish Obstructive Lung Disease in Northern Sweden (OLIN) and the Global Allergy and Asthma European Network (GA²LEN) respiratory and allergy-focused questionnaires.^{14–16} In all, a random sample of 18,087 subjects aged 16–75 years participated in the study after giving written informed consent. A study of non-responders has verified a good representativeness of the participants in the West Sweden Asthma Study regarding respiratory symptoms and airway diseases.¹⁷ Details relating to the questionnaire and procedures have been given elsewhere.^{18,19}

The definition of current doctor-diagnosed asthma in the control group was the same as in the cohort, that is, reporting both a doctor's diagnosis and symptoms of asthma during the last 12 months and/or the use of asthma medication. Since the control group was population-based some individuals may have been hospitalized due to severe wheezing in early childhood.

Statistical Analyses in the Cohort

The IBM SPSS Statistics version 20.0 (IBM Corp., Armonk, NY) was used for statistical calculations.

Within the Cohort

Factors predicting the presence of asthma in adulthood in the cohort were analyzed using the chi-square test and binary logistic regression (univariate analysis). To analyze potential early risk factors in the cohort, data from previous re-investigations regarding the initial admission to the hospital, severity of disease in early life and exposure to tobacco smoke in infancy were used.^{10,11} In addition, we used data on maternal smoking during pregnancy previously supplied from the Swedish Medical Birth Register.²⁰

In the multivariate analysis of factors affecting the risk of adult asthma in the cohort, adjustments were made for tentative early and current risk factors considered in the univariate analysis, see Table 1. Adjustments were made for all the early factors considered, including prenatal but not postnatal smoke exposure, as these were highly correlated. Of the current factors, adjustments were made for current allergy and current active smoking. In addition, gender was considered as both an early and a current factor. The multivariate analyses were performed in three versions: for both current and early factors together (Table 2), only for current factors and only for factors present in early life. BHR, blood eosinophils and

FeNO were not included in the multivariate analyses, as this reduced the power substantially.

Cohort Versus Control Group

Comparisons between the control group and cohort were made using the chi-square test and binary logistic regression (Tables 3 and 4).

When analyzing the risk of adult asthma in the cohort compared with the control group in the multivariate analysis (see Table 4), adjustments were made for factors present in both groups, that is, current active smoking, gender, having a family member with asthma and current allergic rhinitis (symptoms of allergic rhinitis during the past 12 months).

Ethical Approval

The study was approved by the ethics committee at the University of Gothenburg. Written informed consent was given by participants in both the cohort and the control group.

RESULTS

Cohort

Response Rate

In the cohort, the response rate was 81% (82/101). The gender distribution was 40% females and 60% males, that is, the same gender distribution as at first admission.

Current Asthma in the Cohort

Current doctor-diagnosed asthma was present in 37% (30/82) and 50% (15/30) of these had moderate or severe asthma. The use of asthma medication was reported in 83% (25/30) of the subjects with asthma, while no subject without an asthma diagnosis used asthma medication. Uncontrolled asthma according to ACT was reported in 32% (8/25) of the subjects with asthma (five subjects with asthma did not fill out the form).

The most commonly reported trigger of asthma symptoms was (cold) weather (53%), followed by pollen or furry animals (43%), airway infections (33%), and tobacco smoke (23%). Thirty-three percent reported asthma symptoms in contact with pollen and 20% with furry animals.

Univariate Associations in the Cohort

The prevalence of tentative risk factors for current asthma in the cohort is summarized in Table 1.

Of the subjects with asthma, 87% had current allergic disease. There were no significant differences in the prevalence of current allergy between males and females (54% vs. 62%, $P = 0.5$) or between males with asthma and females with asthma (85% vs. 88%, $P = 1.0$). Having a family history of asthma was significantly associated with current allergy ($P = 0.009$).

TABLE 1—Prevalence of Tentative Risk Factors Among Subjects With and Without Current Asthma in the Cohort, Together With Univariate ORs for Current Asthma

	Total prevalence % (n)	Prevalence in subjects with current asthma % (n)	Prevalence in symptom-free subjects % (n)	OR	95% CI
Early factors					
Female gender	41.5 (34/82)	56.7 (17/30)	32.7 (17/52)	2.7	1.1–6.8
Family history of asthma^a	35.4 (28/79)	55.2 (16/29)	24.0 (12/50)	3.9	1.5–10.4
Passive smoking in infancy	66.7 (54/81)	63.3 (19/30)	68.6 (35/51)	0.8	0.3–2.0
Maternal smoking during pregnancy	56.4 (44/78)	51.7 (15/30)	59.2 (29/49)	0.7	0.3–1.9
RSV infection at first admission	29.1 (23/79)	33.3 (10/30)	26.5 (13/49)	1.4	0.5–3.7
Furry pets at home in infancy	29.5 (23/78)	20.7 (6/29)	34.7 (17/49)	0.5	0.2–1.4
Start of wheezing before the age of six months	45.6 (36/79)	46.7 (14/30)	44.9 (22/49)	1.1	0.4–2.7
Intense obstructive disease as a young child ^b	21.3 (16/75)	21.4 (6/28)	21.3 (10/47)	1.0	0.3–3.2
Childhood factors					
Asthma at 5 years	43.4 (33/76)	39.3 (11/28)	45.8 (22/48)	0.8	0.3–2.0
Atopy at 5 years	28.9 (22/76)	35.7 (10/28)	25.0 (12/48)	1.7	0.6–4.6
Asthma at 10 years	29.7 (22/74)	30.8 (8/26)	29.2 (14/48)	1.1	0.4–3.1
Atopy at 10 years	46.8 (36/77)	50.0 (13/26)	45.1 (23/51)	1.2	0.5–3.1
Asthma at 18 years	43.0 (34/79)	70.0 (21/30)	26.5 (13/49)	6.5	2.4–17.7
Atopy at 18 years	59.5 (47/79)	73.3 (22/30)	51.0 (25/49)	2.6	0.99–7.1
Current factors					
Current allergy^c	57.3 (47/82)	86.7 (26/30)	40.4 (21/52)	9.6	2.9–31.5
Doctor-diagnosed allergic rhinoconjunctivitis	42.0 (34/81)	56.7 (17/30)	33.3 (17/51)	2.6	1.03–6.6
Doctor-diagnosed food allergy	13.6 (11/81)	23.3 (7/30)	7.8 (4/51)	3.6	0.95–13.5
Doctor-diagnosed atopic eczema	12.3 (10/81)	16.7 (5/30)	9.8 (5/51)	1.8	0.5–7.0
Atopic eczema last 12 months	11.1 (9/81)	20.0 (6/30)	5.9 (3/51)	4.0	0.92–17.4
Active smoking	29.6 (24/81)	30.0 (9/30)	29.4 (15/51)	1.0	0.4–2.8
Allergic sensitisation	61.9 (26/42)	68.2 (15/22)	55.0 (11/20)	1.8	0.5–6.2
Bronchial hyper-responsiveness ^d	17.5 (7/40)	28.6 (6/21)	5.3 (1/19)	7.2	0.8–66.6
FeNO > 20 ppb	35.7 (15/42)	45.5 (10/22)	25.0 (5/20)	2.5	0.7–9.3
Blood eosinophils > 0.4 × 10 ⁹ /L ^e	7.1 (3/42)	13.6 (3/22)	0 (0/20)	—	—

Factors with significant ORs are in bold.

^aFamily member (parent or siblings) with asthma.

^bDaily asthma medication for at least six continuous months during the first years of life.

^cCurrent allergic sensitisation, allergic rhinoconjunctivitis, food allergy, or atopic eczema.

^dFall in FEV₁ ≥ 15% after mannitol challenge.

^eNo OR could be calculated due to no cases among symptom-free subjects.

Fifty-one percent (42/82) of the responders agreed to be tested for allergic sensitization, BHR, FeNO, blood eosinophils and lung function. In subjects with current asthma (22/42), allergic sensitization, BHR, high FeNO

TABLE 2—Multivariate Analysis of the Risk of Adult Asthma in the Cohort

	OR	95% CI
Female gender	2.6	0.8–8.9
Current allergy	7.5	1.9–29.5
Active smoking	1.1	0.3–4.0
Maternal smoking during pregnancy	0.5	0.2–1.9
Family history of asthma	1.9	0.5–7.1
RSV infection at first admission	1.6	0.4–5.9
Furry pets at home in infancy	1.2	0.3–7.5
Start of wheezing before the age of six months	1.4	0.3–5.8
Intense obstructive disease as a young child ^a	1.6	0.3–7.5

Adjustments are made for both current factors and factors present in early life. Independent significant risk factors are in bold.

^aDaily asthma medication for at least six continuous months during the first years of life.

and high blood eosinophils were more common, but the difference did not reach statistical significance (Table 1). Among those who were tested, asthma (52.4% vs. 20.0%, $P=0.003$) and current allergy (64.3% vs. 42.5%, $P=0.076$) were over-represented compared with non-tested subjects. Two subjects were not tested for BHR due to vascular disease in one case and pregnancy in the other.

Current asthma at age 27 was associated with asthma at the previous re-investigation at age 18 years, while current asthma was not significantly associated with asthma or allergy at the re-investigations at early ages (Table 1). Of the subjects identified as symptom free at re-investigations at 5, 10, and 18 years, 26% (7/27) had asthma at the current re-investigation at a mean age of 27 years. On the other hand, 55% (5/9) of the subjects with asthma at 5, 10, and 18 years were now symptom free.

Multivariate Analyses in the Cohort

When adjusting for all (both current and early) factors in the same model in a multivariate analysis in the cohort, only current allergy remained significant (Table 2).

TABLE 3—Characteristics of the Cohort (n = 82) and the Controls (n = 1,210), Together With the Univariate Odds Ratios for the Cohort Versus the Controls

Factor	Cohort % (n)	Controls % (n)	OR	95% CI
Female gender	41.5 (34)	57.8 (699)	0.5	0.3–0.8
Current doctor-diagnosed asthma	36.6 (30)	6.8 (82)	7.9	4.8–13.1
Asthma medication	30.5 (25)	8.0 (97)	5.0	3.0–8.4
Current allergic rhinitis	42.0 (34)	33.0 (399)	1.5	0.93–2.3
Family member with asthma	35.4 (28)	22.4 (264)	1.9	1.2–3.1
Active smoking	29.6 (24)	16.0 (190)	2.2	1.3–3.6

Significant ORs and 95% CI are in bold.

However, when considering only the current factors (female gender, current allergy, and active smoking), female gender and current allergy increased the risk of adult asthma (adjusted OR 3.2, 95% CI 1.1–9.3 and aOR 9.6, 95% CI 3.0–31.2, respectively). Among the factors already present in early life, a family history of asthma was an independent risk factor for current asthma (aOR 4.0, 95% CI 1.3–12.5). The early factors considered were female gender, family history of asthma, maternal smoking during pregnancy, RSV infection at first admission, furry pets at home in infancy, start of wheezing before the age of 6 months and intense obstructive disease as a young child. No significant interaction was seen between gender and a family history of asthma ($P = 0.8$).

Stratified Analysis in the Cohort

In a logistic regression analysis stratified for gender and current allergic status, females with current allergy had the highest risk of adult asthma (OR 29.4, 95% CI 5.0–173.3), compared with males without allergy. The corresponding OR for males with allergy was 8.3 (1.6–43.0). This is further illustrated in the survival plot in Figure 1, where females with current allergy had the lowest chance of recovery. However, there was no significant interaction between gender and allergy ($P = 0.7$).

Cohort Versus Control Group

Univariate Analysis

Characteristics of the cohort compared with the control group are summarized in Table 3. Current doctor-

diagnosed asthma was clearly more prevalent in the cohort compared with the control group and this was also obvious for the use of asthma medication and heredity for asthma. In addition, active smoking was over-represented in the cohort. The difference regarding current allergic rhinitis did not reach significance.

Multivariate Analysis

The multivariate analysis showed a 10-fold increase in the risk of adult asthma among subjects in the cohort (early severe wheezing) compared with the controls (Table 4).

DISCUSSION

The main finding in this study is the high prevalence of adult asthma, 37%, following severe wheezing in early life. In actual fact, the prevalence of asthma in the cohort was five times that of the age-matched, population-based control group. Likewise, the use of asthma medication was four times as common in the cohort compared with the control group. In the multivariate analysis, an

TABLE 4—Multivariate Analysis of the Risk of Adult Asthma in the Cohort Compared With the Control Group

	Doctor-diagnosed asthma	
	OR	95% CI
Female gender	1.0	0.6–1.6
Current allergic rhinitis	10.7	6.2–18.3
Active smoking	0.8	0.4–1.4
Family history of asthma	2.5	1.6–4.0
Belonging to the cohort with early severe wheezing	10.0	5.3–18.7

Independent significant risk factors are in bold.

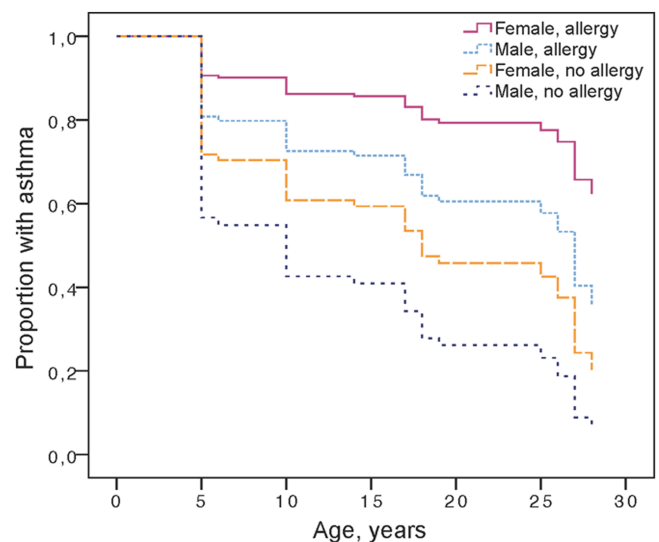


Fig. 1. Stratified analysis of the cumulative recovery rate among females and males, with and without current allergy, in the cohort. The diagram shows the proportion of subjects with asthma within each group.

independent 10-fold increase in the risk of adult asthma was seen in the cohort compared with the population-based control group.

The high prevalence of adult asthma in our cohort fits nicely with that seen in the corresponding Finnish long-term follow-up of early bronchiolitis by the Korppi group. They report a prevalence of 20% for doctor-diagnosed asthma and 41% for self-reported asthma at age 27 and 31% and 35% at age 30.^{6,7} In addition, older studies of children with a history of asthma or wheezy bronchitis at school age report a prevalence of 30% for adult asthma.²¹

In the present study, the multivariate analysis showed a 10-fold increase in the risk of adult asthma in the cohort compared with the control group. This indicates that children with early severe wheezing constitute a specific group with a long-term high risk of asthma. The increased risk of asthma was seen even though the comparison was made with a population-based control group (probably including some subjects with severe early wheezing). This indicates an even larger “true” difference in the risk of asthma if the comparison had been made with subjects with no early wheezing at all. Furthermore, the increased risk of asthma in the cohort compared with the controls, that is, following severe early wheezing, was independent of current allergic rhinitis, gender, active smoking, or heredity. This fits well with the corresponding Finnish long-term follow-up, where bronchiolitis before 24 months was an independent risk factor for adult asthma.⁶ The results of the present study, and the corresponding Finnish one, call for a modification of the often promoted, generalized view that early wheezing has a very favorable prognosis.

Thus, children with early severe wheeze constitute a group with a high risk of asthma throughout childhood into adult life.^{3,4,6,11} The viral infection itself has been suggested as a causal factor of subsequent asthma by direct effects in the airway or by immunological mechanisms. However, premorbid factors may explain the long-term high risk of asthma seen in children with early severe wheezing. Immunological factors and a change in lung function already at birth have been associated with an increased risk of subsequent recurrent wheezing and allergic disease. A premorbid reduced lung function and bronchial hyper-responsiveness appears to precede acute severe bronchiolitis in infants.^{22,23} However, children who suffer severe wheeze in early life without a predisposition for asthma seem to have a favorable prognosis, while others appear to be predisposed both to severe wheeze with viral infection and the development of asthma, due to genetic alterations in airway and/or immune response.^{24,25} For example, genetic factors with different polymorphisms affecting the susceptibility for asthma development have been identified.²⁶ In addition an atopic predisposition appears to be of great importance for the risk of asthma development, where viral infection

might give rise to an atopy dependent immunoinflammatory response in the airways.^{25,27} Moreover, a dysregulation of the innate immune airway response have been reported in children at risk of developing wheezing and asthma, with different cytokine profiles during the first months of life and altered interferon production in mononuclear cells in infants.^{28,29} A complex interaction between a predisposed, vulnerable host exposed to severe viral infection could possibly explain the long-term asthma risk seen in children with severe early wheeze.^{25,30} In short, we do not regard the early viral infection as a causal factor for adult asthma, but rather the early wheezing with viral infection as a marker of a predisposed host. The most noticeable factors that could explain the increased risk of adult asthma seen in our cohort following severe early wheeze are the atopic predisposition and perhaps also the pre- and postnatal smoke exposure.

A high risk of asthma in adulthood in the cohort was seen, irrespective of which virus was detected at first admission. In other words, adult asthma was as common among those with RSV infection as among those where another virus was detected at admission. Similar results were found in the Finnish follow-up in adulthood.⁶ However, in adolescence, they found a higher risk of asthma with non-RSV bronchiolitis, primarily caused by a rhinovirus infection,^{2,31} and other studies have also reported an increased risk of childhood asthma after non-RSV bronchiolitis, particularly wheezing illness with rhinovirus.^{27,32} In the Swedish follow-up study of RSV-bronchiolitis by Sigurs et al.⁴ an increased risk of asthma, compared with healthy individuals, up to the age of 18 has been reported. Taken together, our results confirm a long-term risk of asthma following severe wheezing disorder in early life, not attributable to which virus was detected at first admission.

Within the cohort, that is, only among the subjects with early severe wheezing, the most evident risk factors for adult asthma were the heredity of asthma, female gender and the development of other allergic manifestations. These risk factors are also evident in cross-sectional studies of adult populations.¹⁸ Other long-term studies of wheezy bronchitis into adolescence and early adulthood have confirmed the subjects' own allergic disease and parental asthma as risk factors for asthma persistence.^{2-4,33} Since allergy and asthma were overrepresented among subjects that underwent testing in our cohort, it could be speculated that this might affect the calculated relationship between allergy and asthma. Therefore, we included all subjects of the cohort in the analysis, tested as well as non-tested, where the questionnaire-based response on allergy was used for non-tested subjects. Our findings of a close link between allergy and asthma are supported by the findings in the Finnish 27-year follow-up, where allergy in terms of current rhinitis was a significant risk factor for asthma.⁶ In our study, almost 90% of the subjects with

asthma had current allergy and 57% reported doctor-diagnosed rhinoconjunctivitis.

Asthma phenotypes following early severe wheezing appear not to be stable entities. Subjects in the cohort had a markedly increased risk of adult asthma compared with the population-based control group. However, within the cohort, the majority of subjects had both episodes of asthma and symptom-free periods from childhood into adulthood. In fact, within the cohort asthma and allergy at preschool and school age did not predict adult asthma. On the other hand, asthma in adolescence was associated with adult asthma, but both remissions and relapses occurred between the ages of 18 and 27. We observed remissions of asthma present at age 18, as well as relapses of asthma in subjects who had transient wheezing in early childhood. In the well-known Dunedin asthma study, one third of the study members with asthma in remission at 18 years of age relapsed by 21 years or 26 years of age.³⁴ Taken together, the presence of asthma symptoms during childhood fails to predict the long-term prognosis among subjects with early severe wheezing.

In the present study, female gender increased the risk of adult asthma among the subjects with early severe wheezing, that is, within the cohort. As seen in Figure 1, females with current allergy clearly had the lowest chance of recovery. However, no significant interaction between gender and allergy could be verified. In the present re-investigation in adulthood, the gender distribution between the subjects with asthma was comparable to that in late adolescence, where a gender shift in female dominance had become obvious and female gender appeared as a strong risk factor for asthma. The increased prevalence of asthma among women in adolescence and adulthood appears to be at least partly attributable to hormonal factors; oestrogen appears to shuttle adaptive immunity toward the TH2 phenotype and to have pro-inflammatory properties.^{35,36} Furthermore, our observation of a male dominance among asthmatics during childhood and that boys have a greater chance of recovery from asthma during adolescence compared with girls also contributes to the gender shift.^{3,10,11,21,37}

Active smoking in adulthood was common in the cohort, almost double that in the population-based control group. In the study by the Korppi group, current smoking was also clearly over-represented among subjects with early bronchiolitis compared with controls and it did in fact increase the risk of adult asthma.⁶ It may seem surprising that active smoking was so common in the cohort in the present study, given the high prevalence of asthma. However, a higher prevalence of active smoking among teenagers with asthma than without asthma has been previously shown.³⁸ In our study, this most probably reflects the high risk of becoming a smoker when growing up in a smoking environment.^{19,20,38,39} As described earlier for our cohort, the prevalence of passive smoke

exposure during pregnancy, infancy, and childhood was high among the subjects with early wheezing.²⁰ For example, prenatal smoke exposure was reported in 55% compared with 34% in the average population at that time.²⁰ Looking back, only a few (16%) members of the cohort had not been exposed to tobacco smoke until adulthood, that is, exposure pre- or postnatally, in childhood or as own smoking in adolescence or adulthood.

Smoking habits in our cohort varied over time, with 23% changing their smoking habits from adolescence to adulthood. As a result, the impact of smoke exposure can be somewhat difficult to assess in such a highly exposed group. In fact, active smoking did not significantly increase the risk of adult asthma among the subjects in the cohort in the present follow-up in adulthood. Furthermore, sensitivity to tobacco smoke may vary in the population and individuals who associate asthma symptoms with tobacco smoke might change their smoking habits accordingly. In actual fact, studies have shown a greater asthma risk in ex-smokers than in active smokers.¹⁸ In addition, we were not able to confirm the association between pre- or postnatal smoke exposure with asthma and bronchial hyper-responsiveness that we saw in adolescence. It is difficult to say whether this reflects the fact that the early effect of smoke exposure has now vanished or is overshadowed by other factors, or whether the lack of a significant association was simply due to low power.

When considering potential risk factors already present in early life among the subjects with severe early wheezing, that is, the cohort, only a family history of asthma was independently associated with adult asthma. The age at first admission and the intensity of disease during early life did not significantly affect the risk of adult asthma. The effect of early life factors might be weakened by the influence of other modifying factors during childhood and adolescence. In addition, the cohort is small, which gives low statistical power.

The major strengths of this study are the long follow-up of more than 25 years and the high response rate, with more than 80% still in the study. Another strength is the large, population-based control group. The control group came from the large, questionnaire-based West Sweden Asthma study, using validated, well-known questionnaires.^{17,18} Furthermore, recruitment was made from the same part of Sweden as the original cohort of severe wheezers. We therefore believe that the results from the cohort have been compared with valid population-based data and we regard the observed difference in asthma prevalence as trustworthy. Although the questionnaires were not identical, we carefully assessed the questions used when comparing the cohort with the control group and we used only questions with high concordance. The limitations of the study are the fairly small size of the cohort and the small number of tested subjects. However,

despite the somewhat small cohort, we were able to demonstrate significant associations within the cohort and clear differences between the cohort and the control group.

CONCLUSIONS

In conclusion, the prevalence of current doctor-diagnosed asthma in adulthood was as high as 37% in subjects with severe early wheezing, compared with 7% in an age-matched control group. In a multivariate analysis, the risk of asthma in the cohort was increased 10-fold compared with controls.

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