

Asthma symptoms in early childhood – what happens then?

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Abstract

Aim: To study the outcome in early adulthood for children with early asthma symptoms and to analyse the factors associated with current asthma. **Methods:** In a prospective study, we have re-investigated 89/101 children who were hospitalized before the age of two years due to wheezing. The children were investigated using a questionnaire and allergy and bronchial hyper-responsiveness tests at the age of 17–20 years and compared with age-matched controls. **Results:** In the cohort, 43% had had asthma symptoms in the preceding 12 months compared with 15% in the control group. The strongest risk factors for asthma were current allergy, bronchial hyper-responsiveness and female gender. Female gender and passive smoking in infancy were independent infantile risk factors. In addition to female gender, two pathways led to current asthma: an allergic pathway from family atopy via the development of allergy and another pathway from early passive smoking via hyper-responsiveness and active smoking.

Conclusion: In children with early wheezing disorder, current allergy, bronchial hyper-responsiveness and female gender were the strongest risk factors for asthma in early adulthood, while female gender and passive smoking in infancy were independent infantile risk factors. The effects of early passive smoking persist longer than previously reported.

Key Words: Asthma, child, outcome, passive smoking, wheezing

Introduction

The majority of infants and toddlers with recurrent wheezing have transient conditions and the wheezing episodes are mainly related to viral infections [1]. In some infants, however, wheezing persists or relapses during childhood. Allergic sensitisation is an important factor relating to persistent asthma at school age [2–4]. An association between exposure to tobacco smoke and wheezing is seen in early childhood, but it subsequently becomes less obvious [5–7]. In addition, heredity plays a major role in asthma and other allergic diseases [8]. The heredity effects have been reported to be strongest for atopy and early wheezing [9]. While boys are over-represented in early wheezing, there is a female dominance in adult asthma [10]. An improved knowledge of the factors associated with the persistence or relapse of wheezing could result in intervention strategies to prevent asthma development, improve treatment planning for individual patients and give physicians and parents

realistic expectations in terms of the long-term outcome.

We have followed 101 children who were hospitalised before the age of two years due to acute wheezing disorder. The children have been re-investigated twice previously. At the age of four to five years, 50% had asthma [11]. The corresponding figure at 10 years was 30% [3]. We have now performed a third follow-up in early adulthood; it includes a questionnaire, tests of allergic sensitisation and tests of bronchial hyper-responsiveness. For comparison, age-matched controls were randomly selected and tested in the same way.

The aims were to study the course of wheezing and the outcome in early adulthood for these children with early asthma symptoms. Another aim was to analyse the factors associated with current asthma and the roles of allergy, family atopy, tobacco smoke, bronchial hyper-responsiveness and gender. A final aim was to develop a model describing the connection between the risk factors and adult asthma.

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Methods

Between March 1984 and November 1985, 101 consecutive children aged less than two years who were hospitalised due to wheezing bronchitis were included in a prospective study to determine the characteristics and prognosis of wheezing in early childhood. Details relating to the first hospital stay and earlier re-investigations have been published previously [3,11]. Plausible long-term risk factors such as family atopy, passive smoking and gender were registered at first admission. Family atopy was defined as asthma, allergic rhinoconjunctivitis, food allergy or atopic eczema in parents or siblings. To clarify the outcome in early adulthood, we have now re-investigated the children at the age of 17–20 years. For comparison, 401 controls from the Göteborg population matched for age were randomly sampled from the national population register. The Ethics Committee at the Faculty of Medicine, Göteborg University, approved the study.

A recent health history was obtained using a questionnaire sent by post. The answers were ascertained during a visit to the clinic or by telephone interview. In the cohort, 88% (89/101) completed the form, while 73% (294/401) did so in the control group. In the cohort, 62% (55/89) were willing to undergo specific objective testing and were tested for allergic sensitization, lung function and bronchial hyper-responsiveness. No significant differences were found in baseline characteristics between the subjects in the cohort available for follow-up and the 12 missing subjects; or between those who were tested and those who were not. In the control group, 28% were tested in a manner similar to that used in the cohort.

Current asthma was defined as wheezing or asthma and/or the need for anti-asthmatic treatment (β_2 -agonists or inhaled corticosteroids) during the preceding 12 months. Asthma was classified as mild, moderate or severe, according to the classification system of the Swedish Society of Paediatric Allergology (www.barnallergisektionen.se). Children with mild asthma had mild and infrequent asthma symptoms and symptom control with a β_2 -agonist alone. Individuals with moderate asthma had symptoms >twice a week and needed inhaled corticosteroids ≤ 400 $\mu\text{g/day}$ plus a β_2 -agonist or leukotriene antagonist. Severe asthma required inhaled corticosteroids >400 $\mu\text{g/day}$, plus a long-acting β_2 -agonist and/or leukotriene antagonist.

The allergy tests included a skin prick test (SPT), specific IgE in serum and an eosinophil count in the blood. The allergens included in the SPT were birch, grass, mugwort, horse, dog, cat, rabbit, house dust mites (*D. pteronyssinus* and *D. farinae*) and moulds (*Alternaria* and *Cladosporium*). The ALK Soluprick®

extracts were used (ALK, Copenhagen, Denmark). Saline was used as a negative control and 10 mg/ml of histamine dihydrochloride was used as a positive control. A weal diameter of at least 3 mm was regarded as positive. A Phadiatop® test was performed for inhalant allergens (Pharmacia Diagnostics, Uppsala, Sweden). The allergens included in the Phadiatop® test were birch, grass (timothy), mugwort, horse, dog, cat, house dust mite (*D. farinae*) and mould (*Cladosporium*). Detection limit for each allergen was ≥ 0.35 kU/L. Allergic sensitization was defined as positive SPT or Phadiatop®. The presence of current allergic sensitization, allergic rhinoconjunctivitis or atopic eczema was denoted as current allergy.

Bronchial hyper-responsiveness was tested using a dry, cold air hyperventilation challenge, a method that is regarded as more specific for asthma than pharmacological challenges [12]. Inhaled long-acting β_2 -agonists or anti-leukotrienes were withheld for 24 h, while short-acting β_2 -agonists, inhaled corticosteroids or sodium cromoglycate were withheld for six hours before testing. Three maximum forced expirations were performed. The largest forced expiratory volume in one second (FEV₁) was noted. A dry, cold (-20°C) air mixture containing 5% CO₂ was hyperventilated over four minutes using a respiratory heat exchange system (Jaeger RHES®, Erich Jaeger AG, Würzburg, Germany). Spirometry was performed in duplicate, two, five and 10 minutes after challenge. The highest FEV₁ values at each time point were noted and the maximum post-challenge percentage fall in FEV₁ from resting was calculated. A fall in FEV₁ of $\geq 10\%$ was regarded as pathological [13].

For statistics, SPSS 12.0 for Windows was used. Factors predicting the presence of asthma were analysed using the chi-square test, independent samples *t*-test and binary logistic regression. Unavailable data were coded as missing.

Results

At 17–20 years, 43% (38/89) of the subjects in the cohort had had asthma symptoms in the preceding 12 months; 27% (24/89) were classified as mild and 16% (14/89) as moderate or severe asthma. In the control group, 15% (44/294) reported asthma symptoms with wheezing in the preceding 12 months; 10% (29/294) were classified as mild and 5% (15/294) as moderate or severe asthma (Figure 1). The risk of having asthma was four times higher in the cohort (OR 4.2, 95% CI 2.5–7.2). Among the girls, the asthma prevalence was 65% in the cohort compared with 18% in the control group (OR 8.4, 3.8–18.6).

A small percentage of the cohort, 12%, reported persistent asthma since they were admitted to the study (Figure 2). At an early age, 29% had lost their asthma symptoms and had been symptom-

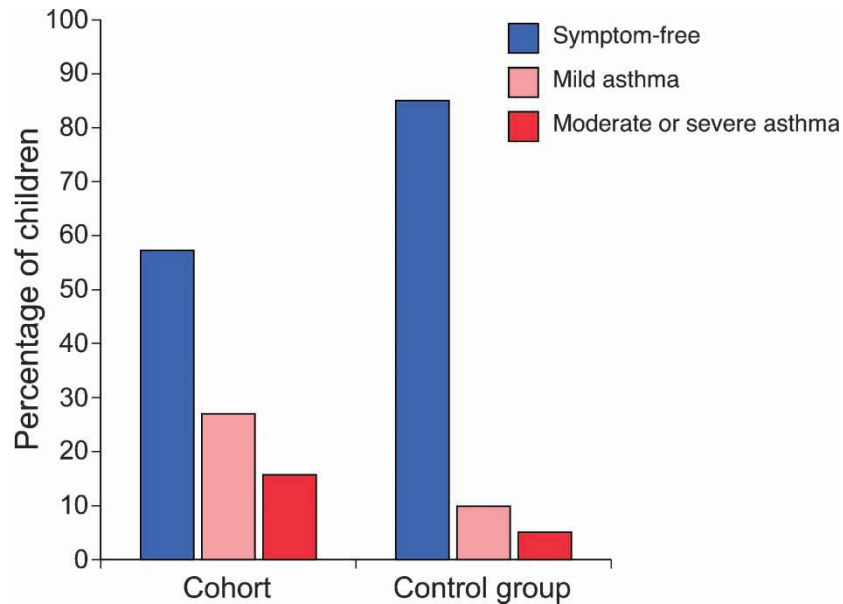


Figure 1. Percentage of asthma at follow-up at age 17–20 years in the cohort compared with the control group.

free from age four to five years (transient wheezing). The remaining part of the cohort had either become symptom-free later in adolescence (wheezing in remission) or was symptom-free at pre-school/school age but had experienced a relapse of wheezing (Figure 2).

Univariate analyses in the cohort

Current allergy and family atopy

Allergic manifestations, and in particular current allergy where allergic manifestations and sensitisation were combined, were strongly associated with current asthma (Table I). The more severe the asthma, the more frequent the presence of current allergy, χ^2 for trend $P < 0.001$ (Figure 3). Subjects with moderate or severe asthma were all allergic. Family atopy showed an association with current allergy (OR 2.8, 1.1–6.9) and a borderline association with current asthma ($P = 0.050$, Table I).



Figure 2. Course of wheezing from early childhood to age 17–20 years in the cohort. Red bars indicate presence of wheezing.

Passive smoking in infancy

There was an association between passive smoking in infancy and current asthma ($P = 0.049$, Table I). This relationship was also more obvious the more severe the asthma ($P = 0.017$, Figure 3). A lower risk of current asthma was seen if the parents had given up smoking compared with subjects who were exposed to passive smoking throughout their childhood (Table II). In addition, there was a significant association between passive smoking in infancy and current active smoking (OR 8.0, 1.7–37.1) and between current smoking and asthma (Table I). There was no correlation between early passive smoking and current allergic sensitisation (OR 0.4, 0.1–1.3). However, subjects with both early passive smoking and current allergy ran a high risk of asthma in early adulthood (OR 13.0, 3.6–47.6). Furthermore, the combination of own smoking and current allergy also carried a high risk of asthma (OR 28.0, 2.4–326.7).

Hyper-responsiveness

There was a significant association between bronchial hyper-responsiveness and asthma (Table I). The more severe the asthma, the higher the percentage of subjects displaying bronchial hyper-responsiveness ($P = 0.001$, Figure 3). Hyper-responsiveness was associated with passive smoking in infancy (OR 4.8, 1.0–24.2).

Gender

When first admitted to hospital in early childhood, the cohort consisted of 61% boys and 39% girls. There has now been a shift to 63% girls and 37% boys in the

Table I. Prevalence of tentative risk factors among subjects with and without asthma in the cohort, together with univariate odds ratios for current asthma.

	Total prevalence % (n)	Prevalence in subjects with current asthma % (n)	Prevalence in symptom-free subjects % (n)	OR	95% CI
Infantile factors					
Female gender	42 (37/89)	63 (24/38)	25 (13/51)	5.0	2.0–12.5
Family atopy	63 (54/86)	75 (27/36)	54 (27/50)	2.6	1.0–6.5
Passive smoking in infancy	67 (60/89)	79 (30/38)	59 (30/51)	2.6	1.0–6.9
RSV infection at first admission	28 (25/89)	32 (12/38)	25 (13/51)	1.3	0.5–3.4
Furry pets at home in infancy	30 (26/87)	25 (9/36)	33 (17/51)	0.7	0.3–1.7
Start of wheezing before the age of six months	48 (43/89)	53 (20/38)	45 (23/51)	1.3	0.6–3.1
Intense obstructive disease as a young child ^a	21 (18/85)	23 (8/35)	20 (10/50)	1.2	0.4–3.4
Current factors					
Current allergy ^b	60 (53/89)	87 (33/38)	39 (20/51)	10.2	3.4–30.6
Allergic rhinoconjunctivitis	48 (42/88)	70 (26/37)	31 (16/51)	5.2	2.1–13.0
Allergic sensitisation ^c	60 (33/55)	73 (19/26)	48 (14/29)	2.9	0.9–9.0
Atopic eczema	30 (26/87)	50 (18/36)	16 (8/51)	5.4	2.0–14.6
Bronchial hyper-responsiveness ^d	27 (15/55)	46 (12/26)	10 (3/29)	7.4	1.8–30.8
Active smoking	27 (24/88)	41 (15/37)	18 (9/51)	3.2	1.2–8.4
Blood eosinophils					
>0.4 × 10 ⁹ /L	9 (5/55)	8 (2/26)	10 (3/29)	0.7	0.1–4.7

^aDaily asthma medication for at least six continuous months during the first years of life [11].

^bCurrent allergic sensitisation, allergic rhinoconjunctivitis or atopic eczema.

^cPositive SPT and Phadiatop[®] in 30 subjects, positive SPT alone in 2 subjects and positive Phadiatop[®] alone in 1 subject.

^dFall in FEV₁ ≥10% after dry, cold air hyperventilation challenge.

group with asthma ($P=0.010$). Female gender was a significant risk factor for current asthma (Table I). The asthma prevalence among females in the cohort has increased from 32% at 10 years of age to 60% in early adulthood. Since the first admission, 21% of the females have had persistent asthma; as many as 39%

experienced a recurrence of their asthma after a symptom-free period. Among the boys in the cohort, asthma has decreased from 40% at age four to five years and 33% at 10 years to 27% now. Only 8% of the boys have had persistent asthma and as many as 40% have had transient wheezing.

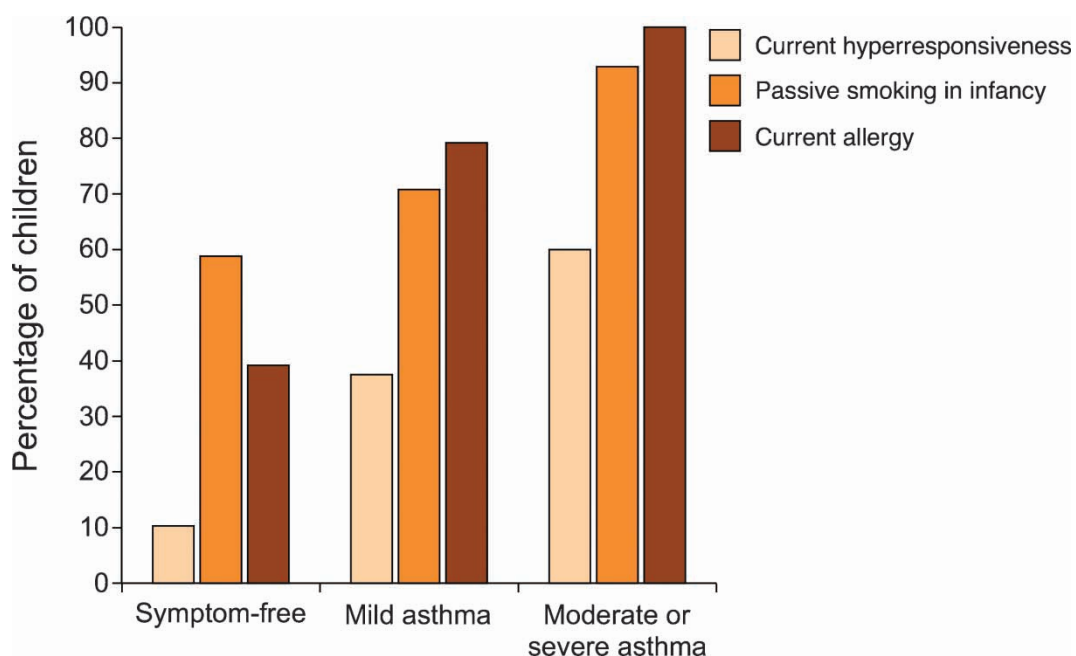


Figure 3. Presence of current hyper-responsiveness, passive smoking in infancy and current allergy in the cohort in symptom-free subjects and subjects with mild and moderate or severe asthma.

Table II. Smoke exposure and risk for current asthma in the cohort.

Smoke exposure	Subjects with asthma	Subjects without asthma	OR	95% CI
Nil	5	15	1.0	Ref.
Passive smoking discontinued during childhood	11	12	2.8	0.8–10.1
Continuous passive smoking	15	11	4.1	1.1–14.7

χ^2 for trend $P=0.031$.

The prevalence of current allergy among females has increased steadily, from 37% at four to five years of age to 56% at 10 years and as much as 81% now. Among the boys, the corresponding prevalence has remained at approximately 40% and it is now 44%.

Eosinophils, RSV, disease start and early disease intensity

Current blood eosinophils of $>0.4 \times 10^9/L$ did not reach a significant association with asthma, hyper-responsiveness or allergic sensitisation. The children with no respiratory syncytial virus (RSV) infection had a percentage of current asthma similar to that of the children with RSV infection diagnosed at first admission, 41% and 48% ($P=0.53$). Furry pets at home during infancy did not predict asthma in early adulthood. The early start of wheezing during infancy or intense obstructive disease as a young child did not remain as risk factors (Table I).

In addition to the risk factors listed in Table I, asthma at age four to five years and at 10 years was significantly associated with an increased risk of current asthma (OR 3.0, 1.2–7.4 and 3.1, 1.2–7.9 respectively).

Multivariate analyses in the cohort

In a multivariate model with the current factors of current allergy, bronchial hyper-responsiveness, current smoking and gender, we found that current allergy and hyper-responsiveness were significant risk factors (OR 7.2, 1.5–34.9, and 8.3, 1.6–42.0 respectively), while female gender and smoking were not

(OR 2.8, 0.8–10.6 and 1.8, 0.3–9.1 respectively). Similarly, in a multivariate model containing all the significant univariate variables, hyper-responsiveness and current allergy remained as independent risk factors for adult asthma.

However, when planning the final multivariate analysis (Table III), we noted the previously mentioned significant associations between family atopy and current allergy and between early passive smoking and hyper-responsiveness. In the second step, we found significant associations between both current allergy and current asthma and between hyper-responsiveness and asthma. Similar associations were found between early passive smoking and current smoking and between current smoking and asthma. We concluded that current allergy and hyper-responsiveness could be regarded as intermediate variables between family atopy, passive smoking in infancy and current asthma. The multivariate analysis, therefore, was performed according to these considerations and the model contained the infantile risk factors of gender, family atopy and early passive smoking. In this analysis, gender and early passive smoking were independent risk factors for adult asthma, while family atopy did not reach significance ($P=0.06$).

Pathogenetic asthma model

The pathogenetic model in Figure 4 has been constructed from the associations seen in the cohort. In this model, three pathways lead to current asthma: a pathway from female gender, one allergic pathway from family atopy via the development of allergy and another pathway from early passive smoking via hyper-responsiveness and active smoking.

Comparison of the cohort and the controls

A comparison between the cohort and the controls is shown in Table IV. We especially noted the higher prevalence of asthma, current passive smoking and current furry pets in the cohort (Table IVa). When comparing the asthmatic subjects in the groups, there was a striking preponderance of current passive smoking in the cohort (Table IVb).

Table III. Multivariate analysis of infantile risk factors in the cohort. Significant risk factors in the univariate analysis (family atopy, passive smoking in infancy and female gender) are included in the model.

Risk factor	Total prevalence % (n)	Prevalence in subjects with current asthma % (n)	Prevalence in symptom-free subjects % (n)	OR	95% CI	P
Female gender	42 (37/89)	63 (24/38)	26 (13/51)	4.7	1.8–12.6	0.002
Passive smoking in infancy	67 (60/89)	79 (30/38)	59 (30/51)	3.1	1.0–9.2	0.044
Family atopy	63 (54/86)	75 (27/36)	54 (27/50)	2.7	0.9–7.5	0.06

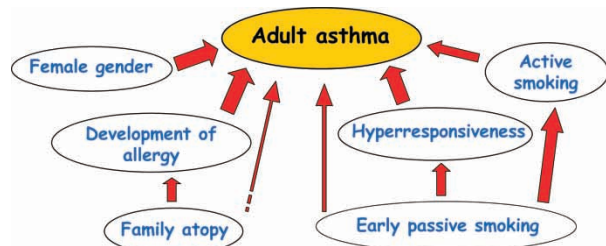


Figure 4. Pathogenetic model based on the risk factors for the presence of asthma in early adulthood. Statistically significant associations in the cohort in the univariate analysis are shown with arrows (for ORs, see Table I and Results).

Discussion

Current asthma symptoms in 43% of the cohort may seem high. However, in a similar Finnish 18- to 20-year follow-up of children who were hospitalised before the age of two years, the asthma prevalence was 30 to 41%, depending on the asthma definition used, compared with 11% in a control group [14]. Our prevalence of asthmatic symptoms corresponds fairly well with these figures.

The recurrence of asthma is well known. In studies from Australia, the UK and New Zealand, symptoms tended to recur in adulthood after a period of remission during late teenage years [10,15–17]. However, we appear to see an earlier relapse than that mentioned in these studies. A similar pattern was seen in the Finnish cohort [14]. The subjects who experienced a recurrence of their asthma symptoms in our cohort were primarily girls with allergy. Current allergy was strongly correlated to asthma in both the cohort and the control group. This demonstrates the important relationship between allergy and asthma [10,18–21].

The correlation between passive smoking in infancy and current asthma contrasts partly to what has been reported. It has been suggested that the connection is seen in early childhood but is less obvious later [5–7]. The correlation does not appear to be due to allergic

sensitization but it is instead mediated via increased hyper-responsiveness [22]. The significant trend with different durations of passive smoking emphasises the benefits of smoking cessation when it comes to decreasing the risk for persistent asthma. In the cohort, smoke exposure at home as a young child predicted own smoking later. This demonstrates the parental influences on the subject's own smoking pattern [23]. The association between parental smoking and asthma and between own smoking and asthma is important to note, since smoking is a preventable factor.

Female dominance in asthma in adulthood is well known [10]. Looking back, there was a constant decrease in the frequency of boys with asthmatic symptoms since early childhood, while many girls experienced a recurrence of their asthma after having a symptom-free period. The reversal in gender distribution is seen somewhere between the age of 10 years and late adolescence [24].

The pathogenetic model presented here was constructed based on the associations seen while working on the multivariate analysis. Current allergy, hyper-responsiveness and current smoking were regarded as intermediate steps between family atopy, early passive smoking and current asthma. In the multivariate model that contained the infantile factors of female gender, family atopy and early passive smoking, we found female gender and early passive smoking to be independent risk factors for current asthma. In addition to female gender, we see two different pathways leading to current asthma in early adulthood: the allergic pathway from family atopy through current allergy and the hyper-responsive pathway from early passive smoking through hyper-responsiveness and own smoking. Allergy is a strong risk factor not only for persistent asthma in childhood but also for asthma persisting into adulthood [13,18–21,25,26]. However, there does not appear to be a direct relationship between allergy and bronchial

Table IV. (a) Characteristics of the cohort ($n=89$) and the controls ($n=294$).

Factor	Cohort % (n)	Controls % (n)	OR	95% CI
Female gender	42 (37)	53 (156)	0.7	0.4–1.0
Asthma last five years	54 (48)	19 (55)	5.1	3.1–8.5
Current asthma	43 (38)	15 (44)	4.2	2.5–7.2
Mild	27 (24)	10 (29)	3.4	1.8–6.2
Moderate or severe	16 (14)	5 (15)	3.5	1.6–7.5
Asthma medication	34 (30)	12 (35)	3.8	2.1–6.6
Only β_2 -agonists	18 (16)	7 (19)	3.2	1.6–6.5
Inhaled corticosteroids + β_2 -agonists	16 (14)	5 (16)	3.2	1.5–6.9
Current allergy	60 (53)	55 (159)	1.2	0.7–1.9
Current furry pets	51 (45)	38 (109)	1.7	1.1–2.8
Active smoking	27 (24)	21 (60)	1.4	0.8–2.5
Current passive smoking	49 (43)	29 (84)	2.3	1.4–3.8

Table IV. (b) Characteristics of asthmatic subjects in the cohort ($n=38$) and among the controls ($n=44$).

Factor	Cohort with asthma % (n)	Controls with asthma % (n)	OR	95% CI
Female gender	63 (24)	64 (28)	1.0	0.4–2.4
Current asthma				
Mild	63 (24)	66 (29)	0.9	0.4–2.2
Moderate or severe	37 (14)	34 (15)	1.1	0.5–2.8
Asthma medication	79 (30)	73 (32)	1.4	0.5–3.9
Only β_2 -agonists	42 (16)	36 (16)	1.3	0.5–3.1
Inhaled corticosteroids + β_2 -agonists	37 (14)	36 (16)	1.0	0.4–2.5
Current allergy	87 (33)	86 (37)	1.1	0.3–3.8
Current furry pets	51 (19)	32 (14)	2.3	0.9–5.6
Active smoking	41 (15)	27 (12)	1.8	0.7–4.6
Current passive smoking	51 (19)	25 (11)	3.2	1.2–8.1

hyper-responsiveness but rather an association between both these factors and asthma [18].

Irrespective of whether or not RSV was detected in the cohort at first admission, a high risk of asthma was seen. Korppi et al. actually found a reduced risk in the RSV group compared with children in whom rhinovirus could be detected [27]. In the Swedish study by Sigurs et al., an elevated risk of asthma was found in subjects with a primary RSV infection, but this was compared with healthy control individuals, not with infants with bronchiolitis due to other viral agents [28]. Our findings are therefore not at variance with those in the Sigurs study. Young children who react with obstructive disease with viral infections obviously run an increased risk of future asthma. Interestingly, it has recently been shown that not only RSV but also other airway viruses can induce a Th2-biased response in the very young [29].

The poor differentiation in the concentration of eosinophils between symptom-free subjects and subjects with asthma was unexpected. In our re-investigation at 10 years, both the start of wheezing before the age of six months and an intense obstructive disease in early childhood predicted the persistence of asthma. This effect had now been lost.

The cohort and the controls clearly stand apart in terms of asthma prevalence and children who are hospitalised with early wheezing constitute a group that runs a high risk of persistent asthma. The higher prevalence of hyper-responsiveness among the subjects with asthma in the cohort could reflect the higher prevalence of current passive smoking compared with the controls with asthma.

The long observation period and the good consistency of the cohort with a response rate of 88% are strengths of this study, while the relatively small sample size gives low power in some analyses. Furthermore, a questionnaire at the first admission with more detailed information about family atopy and smoking would have been desirable. Our primary data did not differentiate between the mother's smoking during pregnancy and smoke exposure dur-

ing infancy. The mother's smoking during pregnancy appears to be more important than passive smoking in infancy [7]. Exposure to tobacco smoke in utero leads to reduced lung function in the infant [30]. Alternatively, it could be argued that smoking during and after pregnancy are intimately linked.

In conclusion, the strongest risk factors for asthma in early adulthood in children with early wheezing were current allergy, bronchial hyper-responsiveness and female gender. Female gender and passive smoking in infancy were independent infantile risk factors. In addition to female gender, two pathways led to current asthma: an allergic pathway from family atopy via current allergy and another pathway from early passive smoking via hyper-responsiveness and current smoking. The effects of early passive smoking persist longer than previously presumed.

Acknowledgements

The study was supported by the Faculty of Medicine, Göteborg University, the Swedish Asthma and Allergy Association and the Swedish Foundation for Health Care Sciences and Allergy Research.

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