

Wheezing in early life and asthma at school age: Predictors of symptom persistence

Csonka P, Kaila M, Laippala P, Kuusela A-L, Ashorn P. Wheezing in early life and asthma at school age: Predictors of symptom persistence. *Pediatr Allergy Immunol* 2000; 11: 225–229. © Munksgaard, 2000

Early childhood wheezing is associated with asthma later in life. However, the high spontaneous recovery rate and the lack of firm predictors for persistence of wheezing complicates the development of evidence-based guidelines for long-term management of wheezy infants and toddlers. Our aim was to define variables that could be used to identify wheezy individuals younger than 3 years of age who would continue to be symptomatic at school age. The method used was a questionnaire-based cross-sectional survey of 2027 randomly chosen, 6–13-year-old school children. Altogether 1829 (90%) questionnaires were returned. Emergency medical care had been sought for 186 (10.2%) children for wheezing during the first 3 years of life, and only 17.2% of these children had received similar emergency treatment during the 12 months preceding the survey. The total proportion of children with current asthma at school age was 11.4%. A logistic regression analysis indicated that for the early wheezers, a family history of asthma, an itchy rash or food allergy, and exposure to tobacco smoke at home before the age of 3 years, were all independently associated with symptom persistence until school age. Among all wheezy children younger than 3 years, those who have a history of food allergy, itchy rash, asthma occurrence in a sibling or parent, or are exposed to tobacco smoke during the first years of life are at highest risk for symptom persistence until school age.

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Key words: asthma; wheeze; children; risk factors; predictors

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Accepted 20 May 2000

Therapy with inhaled anti-inflammatory agents has become a cornerstone in the management of patients with asthma and asthma symptoms (1–3). As such medication can potentially prevent chronic airway obstruction, its early initiation is recommended for symptomatic individuals (4–7). Whereas the value of such an approach for adults and older children is seldom questioned, benefits for younger children, especially those under 3 years of age, are less clear (8,9). This uncertainty stems from the fact that only a minority of early wheezers remain symptomatic in adolescence or adulthood (10–12).

Despite the generally favorable outcome, there is an association between wheezing before the age of 3 years and asthma at school age (13–16). It is therefore evident that a subgroup of early wheezers have a true asthma and that these children might benefit from early anti-inflammatory medication. The identification of those at risk

for symptom persistence remains, however, problematic (10,13,15,17–20). To determine variables that could be used to identify those wheezy under-3-year-olds who continue to be symptomatic at school age, we conducted a questionnaire-based cross-sectional survey.

Subjects and methods

Study design, subjects, and the questionnaire

The study was carried out as a cross-sectional, questionnaire-based survey in Tampere, a Finnish city with 190 000 inhabitants. A list of all 40 primary schools in the area, and the respective numbers of pupils and classes in each school, were obtained from the local education department. Eleven schools, evenly distributed throughout the city, were selected and contacted for further discussions. After agreement with the

headmaster and the school nurse, a total of 96 classes were randomly selected to form the target group for the study (16 classes for each of grades 1–6).

A 12-page questionnaire was modified from the one used in the international study on asthma and allergy in childhood [ISAAC questionnaire for 6–7-year-old children (21)]. The modifications included additional questions soliciting information on a number of risk factors for wheezing, previous respiratory symptoms, and emergency room or hospital treatments for acute asthma symptoms in early childhood. The questionnaires, together with an explanatory letter, written instructions to assist completion, and a return envelope, were distributed during a normal lesson by a schoolteacher. The children took the material home to be completed by their guardian. One week later, the questionnaires were returned in sealed envelopes and collected from each school by one of the investigators.

The study was approved by the ethics committees of the Tampere University Hospital, and the Department of Social Services and Health Care of the City of Tampere.

Definitions

During the 12 months preceding the survey, the children who reported having had one or more of the following conditions were considered to have current asthma: wheezy breathing, emergency room or hospital treatment for acute asthma, or regular anti-inflammatory therapy for chronic asthma. Children with a biological parent or sibling with known asthma were considered to have a family history of asthma. Home exposure for tobacco smoke was defined as residence in a household where a parent or another permanent resident regularly smoked indoors.

Statistical analysis

The 6–13-year-old children who returned the questionnaire with appropriate age and gender information were included in the final analysis. When testing associations between various individual exposures and the probability of having current asthma, the Yates'-corrected Mantel-Haenszel test was used to examine the significance of differences between proportions.

To control for confounding and to identify predictors of current asthma from data available when the child was 3 years old, a logistic regression analysis was performed. Variables showing a statistically significant association with current asthma in a univariate analysis, or those potentially confounding the current asthma

symptoms, were entered stepwise into the model. Interactions between variables were eliminated by selecting the most relevant one if two or more variables explained the same exposure. The results were summarized using odds ratios (OR) and their 95% confidence intervals (95% CI).

Computation was carried out using spss/win and epiinfo 6.04b on a PC and bmdp statistical software on a UNIX/SUN mainframe

Results

Response rate and study population

Of the 2027 questionnaires that were distributed, 1829 (90%) were returned. Thirteen children were excluded either owing to incomplete data on age or gender or because they were older than 13 years. Therefore, 1816 children (915 boys and 901 girls) were included in the final analysis. The ages of the children ranged from 6.1 to 12.9 years and the mean $\pm$ SD age was 9.7 ± 1.8 years for boys and girls alike. Four per cent of the respondents had had doctor-diagnosed asthma, and 14% reported a family history of it. Other pertinent background characteristics are shown in Table 1.

Frequency of emergency care for acute asthma symptoms at various ages

The proportion of children who had required emergency medical treatment for acute wheezing during the first 3 years of life, between the ages of 3 and 6 years, and in the 12 months preceding the survey, were 10.2%, 9.1%, and 4.6%, respectively. In the under 3-years age-group, emergency medical care was more common among boys,

Table 1. Background characteristics of the study population

Variable	%	95% CI
Premature birth (<37 gestational weeks)	6.0	5.0–7.2
Birth weight under 2500 g	4.7	3.7–5.7
History of asthma	4.0	3.1–5.0
History of hay fever	17.5	15.8–19.4
History of itchy rash	23.7	21.8–25.7
History of eczema	28.7	26.5–31.0
History of food allergy	24.2	22.3–26.3
Anti-inflammatory medication ever	4.8	3.4–5.9
Anti-inflammatory medication before 3 years of age	1.1	0.7–1.7
Family history of asthma	14.1	12.5–15.8
Atopy of mother or father	26.2	24.0–28.3
Atopy of sibling	25.7	23.6–27.9
Passive smoking in the past year	6.9	5.8–8.2
Passive smoking before 3 years of age	6.3	5.2–7.5
Maternal smoking during pregnancy	14.4	12.8–16.1
Furry pets at home in the past year	49.2	46.9–51.6

95% CI, 95% confidence interval.

but the gender difference became smaller with increasing age (Table 2).

Of the 186 children who had been treated for acute wheezing when younger than 3 years, 102 (54.8%) had required at least one emergency treatment when aged between 3 and 6 years, and 32 (17.2%) had required at least one emergency treatment in the 12 months preceding the survey.

Prevalence of current allergic symptoms and asthma

Table 3 summarizes the prevalence of various allergic symptoms during the 12 months preceding the survey. Rhinitis was slightly more common amongst boys than girls (36.5% vs. 29.1%), but otherwise there were no gender differences in the symptom prevalence.

Anti-inflammatory asthma medication had been used by 3.6% (95% CI 2.8–4.5) of the respondents during the previous year. The proportion of children who during this period had used anti-inflammatory asthma medication, had experienced wheezing or needed emergency care for asthma symptoms, was 11.4% (95% CI 10.0–13.0). Of these 207 children considered to have current asthma, 62 (30.0%) had required hospital treatment for wheezing when younger than 3 years of age.

Risk factors for current asthma

Table 4 shows univariate association between various background characteristics and current asthma. To summarize, a history of food allergy, itchy rash or eczema, having a first-degree relative with asthma, and home exposure to tobacco smoke before the age of 3 years, were all significant risk factors for current asthma. A history of emergency room or hospital treatment for wheezing before the age of 3 years predicted current asthma, but not as strongly as similar treatment at the age of 3–6 years (Table 4).

To identify factors that would facilitate the recognition of wheezy children under 3 years of age who would continue to have asthma symptoms at school age, a logistic regression analysis was performed. For this purpose, all variables describing data that were available when the

Table 3. Symptoms in the year preceding the survey

Variable	%	95% CI
URTI	70.6	68.5–72.7
Any wheeze	9.6	8.3–11.1
Wheeze in the morning	6.1	5.0–7.3
Exercise-induced wheeze	3.9	3.0–4.9
Severe wheeze, limiting speech	1.8	1.3–2.6
Rhinitis apart from URTI	32.8	30.6–35.1
Conjunctivitis apart from URTI	18.4	16.6–20.3
Itchy rash	16.8	15.1–18.6

URTI, upper respiratory tract infections.

95% CI=95% confidence interval.

children were 3 years old and that showed a statistically significant association with current asthma in a univariate analysis, were entered stepwise into the regression model. Those variables (gender, birth weight, use of inhaled anti-inflammatory asthma medication before the age of 3 years, passive smoking in the past year) that did not demonstrate an independent effect ($p>0.05$) were excluded from the model based

Table 4. Univariate analysis: variables associated with increased risk for current asthma among 1816 school children in Tampere

Variable	OR	95% CI	p-value
Male gender	1.2	0.9–1.6	0.360
Birth weight under 2500 g	1.2	0.6–2.2	0.769
Prematurity	1.3	0.7–2.3	0.482
Hospital contact for wheezing			
Between 3 and 6 years of age	10.7	7.5–15.2	0.000
Under 3 and between 3 and 6 years of age, combined	8.9	5.8–13.6	0.000
Between 3 and 6 years of age, but not before	7.9	4.7–13.4	0.000
Under 6 years of age	7.1	5.2–9.8	0.000
Under 3 years of age	4.9	3.5–7.0	0.000
Only under 3 years of age	1.3	0.7–2.5	0.463
Factors in the past year			
Rhinitis apart from URTI	5.8	4.3–8.0	0.000
Conjunctivitis	4.5	3.3–6.2	0.000
Itchy rash	2.9	2.1–4.1	0.000
Passive smoking	1.6	1.0–2.6	0.100
Furry pets at home	0.7	0.5–0.9	0.014
Other factors			
Hay fever ever	4.1	3.0–5.6	0.000
Itchy rash ever	2.9	2.1–3.9	0.000
Food allergy ever	2.8	2.1–3.8	0.000
Family history of asthma	2.5	1.8–3.5	0.000
Passive smoking <3 years of age	2.2	1.3–3.5	0.002
Maternal asthma	2.2	1.3–3.6	0.005
Eczema ever	2.1	1.5–2.8	0.000
Maternal smoking during pregnancy	1.7	1.2–2.4	0.009
Atopy of mother or father	1.7	1.2–2.3	0.003
Atopy of sibling	1.1	0.8–1.5	0.703
Regular anti-inflammatory medication when <3 years of age	10.0	4.1–24.5	0.000

OR, odds ratio; 95% CI, 95% confidence interval; URTI, upper respiratory tract infections.

Table 2. Proportion of children treated for acute wheezing in an emergency room or hospital ward at different age periods

Age period of hospital contact	%	95% CI	Proportion of boys (%)
Under 3 years of age	10.2	8.9–11.8	62.4
Between 3 and 6 years	9.1	7.8–10.5	64.0
In the past year	4.6	3.7–5.6	55.4

95% CI, 95% confidence interval.

on likelihood ratio testing. According to the final model, exposure to tobacco smoke at home before the age of 3 years, a history of itchy rash or food allergy, and a family history of asthma, were all independently associated with current asthma (Table 5).

Furry pets at home during the past year demonstrated a protective effect (OR 0.70, 95% CI 0.50–0.97) in one model. This variable was excluded from the analysis as the lack of pets was more likely be a consequence than a cause of current asthma. Its removal did not affect the strength of associations of the other variables in the model.

Discussion

This cross-sectional survey, utilizing a modified ISAAC questionnaire, characterized the frequency and predictors of symptom persistence after emergency treatment for wheezy breathing among children under 3 years old. The proportion of children who had required emergency treatment for wheezy breathing before the age of 3 years was 10%. At 6–12 years of age, the prevalence of wheezy breathing ($\approx 10\%$), itchy rash (17%), allergic rhinitis (33%), and conjunctivitis (18%), were similar to those reported previously in Finland (22,23). This, together with the large sample size (2027) and high response rate (90%), gives credibility to the results. A cautionary note is needed, however, as the assessment of risk factors was performed retrospectively and the accuracy of the guardians' recollections on emergency medical contacts was not ascertained from individual patient files.

In agreement with results from previous studies, there was a direct association between early wheezing and subsequent asthma symptoms (13–16). However, of those children who needed emergency treatment for wheezy breathing before

the age of 3 years, only 50% continued to need such treatment at 3–6 years of age and less than 20% at school age. This confirms earlier findings that the majority of early wheezers outgrow their problem during childhood (10,11,15,19). However, the proportion of symptomatic individuals per age-group does not decrease accordingly, as other children start wheezing after the age of 3 years (15). In fact, in our study, only 30% of those with current asthma at school age had needed emergency treatment for wheezing during the first 3 years of life.

The association between early childhood wheezing and later asthma, together with the high spontaneous recovery rate, complicates the development of evidence-based guidelines for long-term management of wheezy infants and toddlers. With the present evidence, universal anti-inflammatory medication can hardly be justified for all early wheezers. In contrast, those with persisting symptoms would probably benefit from such therapy (24). It is therefore important to identify factors that would help to detect children at highest risk for symptom persistence (20).

In our study, independent predictors of symptom persistence among wheezy children under 3 years of age were a history of food allergy, itchy rash, family history of asthma, and exposure to tobacco smoke at home before the age of 3 years. Previous studies have also associated persistent symptoms with the child's own atopy or with a family history of asthma (10,13,15,17–19). Recently Martinez (1999) suggested an algorithm for the identification of asthma risk among young children who have needed hospitalization or at least three out-patient contacts for wheezing (25). According to his model, those with atopic dermatitis or parental history of asthma, have a significantly increased risk of asthma. Our results strongly support this algorithm and add known food allergy to the child's risk characteristics.

Taken together, our results confirm the generally favorable prognosis of children under 3 years old who need emergency treatment for wheezing. Those who have a history of food allergy, itchy rash, or asthma occurrence in a sibling or parent are at highest risk for symptom persistence and might benefit from early anti-inflammatory therapy. Cessation of parental smoking should be also encouraged to minimize the risk of chronic asthma.

Table 5. Multivariate analysis: Adjusted odds ratios (OR) of independent risk factors for current asthma

Risk factor	OR	95% CI	p-value
Hospital treatment for wheezing when <3 years of age	4.5	3.1–6.5	0.000
Passive smoking when <3 years of age	2.1	1.2–3.7	0.008
Itchy rash	2.2	1.6–3.2	0.000
Family history of asthma	1.9	1.3–2.8	0.001
Food allergy	1.8	1.2–2.5	0.002

Final model from stepwise logistic regression analysis.

Variables excluded from the model: gender, birth weight, use of inhaled anti-inflammatory asthma medication before the age of 3 years, passive smoking in the past year.

95% CI, 95% confidence interval.

Acknowledgments

This study was supported by grants from the Medical Research Fund of Tampere University Hospital, the

Support Fund for the Department of Pediatrics, Tampere University Hospital, Emil Aaltonen Foundation, Foundation for Pediatric Research, Finland, Tuberculosis Foundation of Tampere, and the Finnish Allergy Research Foundation.

References

1. BARNES PJ, PEDERSEN S. Efficacy and safety of inhaled corticosteroids in asthma. *Am Rev Respir Dis* 1993; 148: 1–26.
2. British Thoracic Society, National Asthma Campaign, Royal College of Physicians of London, et al. The British guidelines on asthma management 1995: review and position statement. *Thorax* 1997; 52: S1–S21.
3. Guidelines for the Diagnosis and Management of Asthma. Expert Panel Report 2. National Heart, Lung, and Blood Institute, Public Health Service, National Institutes of Health NIH Publication no. 97–4051. Bethesda, MD, US Department of Health and Human Services, 1997.
4. CARLSEN KH, LEEGEGAARD J, LARSEN S, ORSTAVIK I. Nebulized beclomethasone dipropionate in recurrent obstructive episodes after acute bronchiolitis. *Arch Dis Child* 1988; 63: 1428–33.
5. HAAHTELA T, JÄRVINEN M, KAVA T, et al. Comparison of a β_2 -agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. *N Engl J Med* 1991; 325: 388–92.
6. AGERTOFT L, PEDERSEN S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994; 88: 373–81.
7. SCARFONE RJ, LOISELLE JM, WILEY JF, DECKER JM, HENRETIG FM, JOFFE MD. Nebulized dexamethasone versus oral prednisone in the emergency treatment of asthmatic children. *Ann Emerg Med* 1995; 26: 480–6.
8. WENNERGREN G, KRISTJÁNSSON S, STRANNEGÅRD I-L. Decrease in hospitalization for treatment of childhood asthma with increased use of antiinflammatory treatment, despite an increase in the prevalence of asthma. *J Allergy Clin Immunol* 1996; 97: 742–8.
9. RICHTER H, SEDDON P. Early nebulized budesonide in the treatment of bronchiolitis and the prevention of postbronchiolitic wheezing. *J Pediatr* 1998; 132: 849–53.
10. FOUCARD T, SJÖBERG O. A prospective 12-year follow-up study of children with wheezy bronchitis. *Acta Paediatr Scand* 1984; 73: 577–83.
11. KORPPI M, KUIKKA L, REIJONEN T, REMES K, JUNTUNEN-BACKMAN K, LAUNIALA K. Bronchial asthma and hyperreactivity after early childhood bronchiolitis or pneumonia. An 8-year follow-up study. *Arch Pediatr Adolesc Med* 1994; 148: 1079–84.
12. STRACHAN DP, BUTLAND BK, ANDERSON HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. *BMJ* 1996; 312: 1195–9.
13. ROONEY JC, WILLIAMS MD. The relationship between proved viral bronchiolitis and subsequent wheezing. *J Pediatr* 1971; 79: 744–7.
14. BUSSE WW. Respiratory infections: their role in airway responsiveness and the pathogenesis of asthma. *J Allergy Clin Immunol* 1990; 85: 671–83.
15. MARTINEZ FD, WRIGHT AL, TAUSSIG LM, et al. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995; 332: 133–8.
16. DODGE R, MARTINEZ FD, CLINE MG, LEBOWITZ MD, BURROWS B. Early childhood respiratory symptoms and the subsequent diagnosis of asthma. *J Allergy Clin Immunol* 1996; 98: 48–54.
17. EISEN AH, BACAL HL. The relationship of acute bronchiolitis to bronchial asthma – a 4-to-14-year follow up. *Pediatrics* 1963; 31: 859–61.
18. SPORIK R, HOLGATE ST, COGSWELL JJ. Natural history of asthma in childhood – a birth cohort study. *Arch Dis Child* 1991; 66: 1050–3.
19. WENNERGREN G, HANSSON S, ENGSTRÖM I, et al. Characteristics and prognosis of hospital-treated obstructive bronchitis in children aged less than two years. *Acta Paediatr* 1992; 81: 40–5.
20. ANONYMOUS. Early childhood asthma: What are the questions? Proceedings of a Workshop. Salem, Massachusetts, May 18–20, 1994. *Am J Respir Crit Care Med* 1995; 151: S1–42.
21. ASHER MI, KEIL U, ANDERSON HR, et al. International study of asthma and allergies in childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; 8: 483–91.
22. PEKKANEN J, REMES ST, HUSMAN T, et al. Prevalence of asthma symptoms in video and written questionnaires among children in four regions of Finland. *Eur Respir J* 1997; 10: 1787–94.
23. REMES ST, KORPPI M, KAJOSAARI M, KOIVIKKO A, SOININEN L, PEKKANEN J. Prevalence of allergic rhinitis and atopic dermatitis among children in four regions of Finland. *Allergy* 1998; 53: 682–9.
24. REIJONEN T, KORPPI M, KUIKKA L, REMES K. Anti-inflammatory therapy reduces wheezing after bronchiolitis. *Arch Adolesc Med* 1996; 150: 512–7.
25. MARTINEZ FD. Recognizing early asthma. *Allergy* 1999; 54: 24–8.