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Factors relating to the severity of symptoms at 5 yrs in children with severe wheeze in the first 2 yrs of life

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Factors relating to the severity of symptoms at 5 yrs in children with severe wheeze in the first 2 yrs of life. N.M. Wilson, C.J. Doré, M. Silverman. ©ERS Journals Ltd 1997.
ABSTRACT: Wheezing in early childhood covers a wide spectrum of morbidity. Since little is known about the factors determining either the pattern or the severity of this range of symptoms, 51 children, admitted to hospital with acute wheeze in the first 2 yrs of life, were monitored prospectively between the ages of 4.5–5.5 yrs. Our hypothesis was that the predictors of severe episodes and of interval symptoms in 5 year olds would differ.

Symptom diaries were kept, from which the symptom pattern and severity was assessed. The frequency and severity of acute episodes were analysed separately from day-to-day (interval) symptoms. A physiological assessment was made at 5 yrs.

During the 12 month study period, 11 children were symptom-free, 15 were reported to wheeze only in response to viral infections, and 25 wheezed from multiple triggers. Bronchial responsiveness was significantly increased in those with a family history of asthma but was unrelated to any index of atopy. In a multiple logistic regression analysis, a family history of asthma and a personal history of allergy (but not results of skin-prick testing or serum immunoglobulin E (IgE)) significantly predicted both attack severity and interval symptoms. An additive effect of two factors (atopy plus a family history of asthma or bronchial responsiveness) on symptom severity was suggested, without any evidence of an interaction.

It is concluded that in this population of 5 year olds, with an early history of severe wheezing, familial bronchial responsiveness and atopy of operated independently to determine both interval symptoms and attack severity.
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Several epidemiological studies have emphasized the high prevalence of wheeze in the first few years of life [1, 2]. Overall prevalence statistics hide a wide spectrum of morbidity, ranging from a single mild episode to continuous disabling symptoms. Although the factors associated with the persistence of symptoms into early school years are becoming clearer [1], little is known of the factors that are associated with the severity of symptoms in the preschool age group. This is important, since the impact of wheezing disorders is clearly related to severity. There is an inherent problem of quantifying severity, since some children experience infrequent but severe attacks, whilst in others symptoms are milder but more frequent or persistent. It seems reasonable, therefore, to distinguish acute attacks, often related to viral infections [3], from other symptoms and to consider their frequency and severity separately. Since, in the population, episodic wheeze in the first few years is unrelated to atopy [4–6], in contrast to the situation in asthma in older children [7, 8], it is likely that within the spectrum of early wheezing disorders that are different causes, risk factors and outcomes.

The purpose of this study was to determine the risk factors for severity and pattern of wheeze between the ages of 4.5 and 5.5 yrs, in a group of children who had been followed-up prospectively since referral to hospital with acute severe wheeze in the first 2 yrs of life. Our hypothesis was that the predictors of (severe) episodes and of interval symptoms would be different. This precise age span was chosen as it represented the 6 month period preceding and following each child's clinical and physiological assessment at 5 yrs of age. By choosing an exact 12 month period in children of the same age, seasonal and age-related bias were avoided. The severity and frequency of acute episodes and the severity of day-to-day symptoms were evaluated independently. The results were related to measures of lung function, bronchial responsiveness and atopic sensitization, as well as to family history, and aspects of the home environment. To our knowledge, factors associated with wheeze severity assessed prospectively over a 12 month period in 5 year olds, have not previously been reported.

Methods

Subjects

Children who had been hospitalized with an acute episode of wheeze in the first 2 yrs of life were selected from the hospital records at the age of 3 yrs. Notes

of all children with a computer coding of bronchiolitis, asthma or wheeze were inspected, and the first 50 with their third birthday within the study period, in whom wheezing had been confirmed by a physician and whose parents agreed to participate, were included. The results of an initial assessment of this cohort at 3 yrs of age have been reported previously [6]. Of the original 50 children, one emigrated and four declined to continue in the study. A further five children, fulfilling the original criteria, were enrolled, along with an additional child whose parents had initially declined entry to the study, making a total of 51 children.

Study design

The children were followed-up by means of monthly symptom diaries from the age of 3 yrs until the age of 6 yrs. Their symptoms recorded between the ages of 4.5 to 5.5 yrs precisely, form the basis of this report. Half way through this period, within two months of their fifth birthday, each child attended the laboratory for completion of a detailed questionnaire and physiological assessment.

Monthly diaries

A diary was sent to all parents at the start of each calendar month; space was provided for recording the presence and severity of symptoms on each day. From this diary, parents compiled a summary at the end of each month, which was returned in the stamped addressed envelope provided. This monthly parental summary recorded: 1) the presence of any fever, cold, sore throat or ear infection, suggesting a virus infection; 2) the presence of any attack (onset or increase of symptoms of chesty cough or wheezing lasting more than 24 h); a severity score was given (1 mild=sleep/activities not disturbed, 2 moderate=slight disturbance; 3 severe=marked disturbance despite bronchodilator therapy, hospital attendance or oral corticosteroids), and the number of affected days were recorded; 3) whether or not the attack was related to a cold or infection; 4) the presence of any cough or wheeze (lasting less than 24 h) in the absence of an infection or cold, related to exercise, nighttime, excitement, smoky atmosphere, *etc*.; a severity score was given according to the frequency of these symptoms in the preceding month (0=none; 1=once or twice; 2=approximately once a week; 3=more than once a week) and the perceived cause of the symptoms was recorded; 5) all medication used, including bronchodilator, preventive asthma medication, oral corticosteroids or antibiotics.

If parents failed to return the diary, they were contacted by phone or letter. From the 12 monthly diaries, the following were calculated for each child over the 12 month period: 1) attack frequency (the number of attacks and the proportion considered to be associated with respiratory infections); 2) attack severity (the mean score for all attacks); 3) maximum attack severity (the maximum score for any attack during the 12 month period); 4) interval score (the mean monthly score for symptoms between attacks); 5) total severity score calculated by multiplying the attack number by the mean attack severity score and adding the interval symptom scores for each of the 12 months).

Laboratory visit at 5 yrs

Questionnaire. A questionnaire was completed recording the child's personal history and that of all first degree relatives; criteria for diagnosing allergy and asthma are presented in table 1. Wheezing with and without colds, parental smoking, presence of household pets and the number of siblings were also noted.

Lung function. Respiratory resistance was measured with the forced oscillation technique at 6Hz (R_{rs6}), as described previously [9]. The child sat with nose-clipped and cheeks supported by the operator during quiet breathing. Only values with a coherence (signal:noise ratio) of ≥95% were accepted. To calculate the within-subject coefficient of variation (COV), the measurement was repeated at 5 min intervals in 30 children. Transcutaneous oxygen tension (P_{tc,O_2}) was measured using an electrode (Kontron Instruments Ltd, Switzerland) at 44°C, attached to the anterior chest wall.

Methacholine challenge. Baseline lung function values were taken as the mean of six measurements for R_{rs6}. The mean of eight readings, made at 1 min intervals, was calculated for P_{tc,O_2}. Methacholine sulphate (Sigma Chemicals, USA) was administered *via* a Wright nebulizer, using tidal breathing through a mouthpiece with the nose-clipped. The inhalations were repeated using quadrupling concentrations (0.5–32 $g \cdot L^{-1}$) until the P_{tc,O_2} had fallen by 10%, when doubling steps were used. The inhalations continued until the P_{tc,O_2} had fallen by at least 15%, the child was dyspnoeic or the maximum concentration had been inhaled, whichever was the soonest. The response to challenge was assessed 3 min after each inhalation both by P_{tc,O_2} and R_{rs6}, as described previously [10]. Since R_{rs6} was found to be unreliable during induced bronchoconstriction, only the P_{tc,O_2} was used [11]. The concentration of methacholine causing a 15% fall in P_{tc,O_2} (PC_{15}) was calculated from log-dose response curves by interpolation.

Atopic status. Atopic status was determined by three methods. Firstly, skin-prick tests (SPT) to five allergens (house dust mite, grass, cat, milk, egg) and positive histamine and negative control, were carried out in a standardized procedure using the multiple lancet technique

Table 1. – Criteria used to make a diagnosis of asthma and allergy

Parents	
Asthma:	Doctor-diagnosed and treated ever
Allergy:	Hay fever
	Conjunctivitis or rhinitis to known allergen
	Skin rash to known ingested allergen
Children	
Allergy:	Hay fever
	Conjunctivitis or rhinitis to known allergen
	Skin rash to known allergen
	Eczema
	Wheeze to known allergen

(Phazets, Pharmacia Uppsala, Sweden) [12]. A positive response was taken as a weal size of >2 mm greater than the negative control for at least one allergen. Secondly, total immunoglobulin E (IgE) and house dust mite specific IgE (radioallergosorbent test (RAST); Pharmacia, UK) was measured in serum. Thirdly, a history of allergy was deemed positive if eczema had been diagnosed, or nasal, ocular or respiratory symptoms induced by a known allergen were reported (table 1).

From the above, the following indices of atopy were calculated: 1) SPT atopy (present or absent) from results of skin-prick tests; 2) personal history of allergy (present or absent); 3) total atopy, (present or absent) from either a positive skin-prick test or a personal history of allergy; 4) serum IgE level; 5) house dust mite sensitization (present or absent) from either a positive skin-prick test or a RAST score of ≥2.

Statistical analysis

The variables which were considered as possible predictors of the various severity outcomes are summarized in table 2. The relationships between the variables and outcomes were assessed initially by linear regression for continuous variables and by unpaired t-test or Kruskal-Wallis one-way analysis of variance (ANOVA) as appropriate, for ordinal variables. Differences in proportions were assessed by Chi-squared analysis or Fisher's exact test. All outcome variables were then investigated using a stepwise multiple regression (attack severity, attack number, total severity score), or a stepwise ordinal logistic regression analysis (symptom pattern and interval scores). Since the distribution of interval scores was markedly skewed, the scores were graded so that: 0=1, 0–2.5=2; >2.5=3.

These were then considered as ordered categorical rather that continuous variables. Using only those variables where p-values were less than or equal to 0.09, various models were explored, using both forward and backward variable selection. The final models used only variables significant at a p-value less than 0.05. Interactions between the variables selected in the final model were sought. Since some data were missing for log PC15, and log IgE, the model fitting was repeated with and without these two variables. To allow for the modulating effect of treatment on symptom severity (attack severity, attack number, total severity score and interval score) the modelling was repeated after multiplying each severity score by 2 in those on inhaled steroids; this was performed with and without the three children on cromoglycate. A factor of 2 was chosen, as approximately a halving of symptoms following inhaled steroid therapy has been demonstrated in children of this age [13, 14].

Table 2. – Variables used as predictors of outcome

Gender
Respiratory resistance (R_{rs6})
Skin-prick test (positive/negative)
House dust mite sensitization
Personal history of allergy
Serum IgE (log transformed)*
Total atopy
Family history of allergy
Family history of asthma
Pet ownership
Number of siblings
Maternal smoking

*: not used in stepwise logistic regression. R_{rs6}: resistance of respiratory system at 6 Hz; IgE: immunoglobulin E.

Results

Diary records, skin tests and questionnaire details were completed for all 51 children, and blood samples obtained for serum IgE measurement in 33. Technically satisfactory measurements of R_{rs6} were obtained in 44: the mean within-subject COV for R_{rs6} was 11% (SD 3%). PC15 methacholine was available in 44 children.

Sex differences

For the group as a whole, R_{rs6} was significantly lower in girls than boys (mean (SD), 94 (20) and 109 (22) % predicted, respectively; p=0.03) but there was no significant difference in the level of bronchial responsiveness between girls and boys (log PC15 (SD) 0.90 (0.47) and 0.99 (0.6), respectively; p=0.6).

Relationships between dependent variables

The variables considered as predictors of outcomes are summarized in table 2. All indices of atopy were highly correlated with each other (p<0.001), but only a personal history of allergy was used in the final multiple logistic regression analyses as it was the only significant predictor of outcome. PC15 was significantly lower in those with a family history of asthma (table 3). Therefore, to avoid using related variables in the final regression model, a family history of asthma and not PC15 was chosen, since data were missing for the latter in seven subjects. For significant outcome predictions, the two were interchangeable in the statistical models, unless otherwise stated. No significant interaction was found between a family history of asthma and a personal history of allergy, or any other index of atopy, in any of the multiple regression models (p>0.64).

Symptom pattern

Eleven children experienced no lower respiratory symptoms ("asymptomatic"), 15 reported wheeze only in response to virus infections ("viral wheeze") and 25 children wheezed in response to a number of environmental allergens ("multiple wheeze") (table 4). There was no overall significant difference in lung function, methacholine responsiveness, or the proportion with a family history of asthma between the three symptom pattern groups (table 4). The only difference in any index of atopy between the three groups was found in a personal history of allergy (Chi-squared=6.96; p=0.03) (table 4). In the ordinal logistic regression model, both

Table 3. – Comparison of severity outcomes

Outcome	Atopy						Family history			
	Skin-prick test		Personal history		House dust mite		Asthma		Maternal smoking	
	No (n=24)	Yes (n=27)	No (n=29)	Yes (n=22)	No (n=32)	Yes (n=19)	No (n=29)	Yes (n=22)	No (n=31)	Yes (n=20)
Attack severity score	1.38 (1.03)	1.69 (0.92)	1.24 (1.02)	1.94 (0.77)	1.41 (1.03)	1.76 (0.86)	1.22 (0.87)	1.96 (0.97)	1.64 (0.94)	1.40 (1.04)
	p=0.3		p=0.01		p=0.2		p=0.006		p=0.4	
Attack number per year	2.7 (2.4)	3.6 (2.6)	2.7 (2.5)	3.9 (2.5)	2.7 (2.3)	4.0 (2.7)	2.7 (2.5)	3.8 (2.5)	3.5 (2.5)	2.8 (2.5)
	p=0.2		p=0.09		p=0.07		p=0.11		p=0.3	
Interval score	1.25 (1.6)	1.33 (1.3)	1.03 (1.5)	1.04 (1.4)	1.16 (1.6)	1.53 (1.3)	0.86 (1.4)	1.86 (1.4)	1.26 (1.3)	1.35 (1.7)
	p=0.8		p=0.15		p=0.4		p=0.01		p=0.8	
Log PC_{15}	0.85 (0.4)	1.04 (0.6)	0.91 (0.5)	1.0 (0.7)	0.99 (0.5)	0.87 (0.5)	1.1 (0.5)	0.72 (0.6)	0.93 (0.6)	0.98 (0.4)
	p=0.2		p=0.6		p=0.5		p=0.02		p=0.8	

Values are presented as mean, and SD in parenthesis. p-values are from two sample t-tests. PC_{15}: provocative concentration of methacholine causing a 15% fall in transcutaneous oxygen tension. p-values of less than 0.05 are statistically significant.

Table 4. – Group characteristics

Group	Males	Log PC_{15}	R_{rs6} [15] % pred	Atopy		Family history asthma	Attack severity score	Attacks·yr^{-1}	Upper respiratory infections·yr^{-1}	Preventive therapy
				SPT positive	Personal history positive					
	n (%)	Mean (SD)	Mean(SD)	n (%)	n (%)	n (%)	Mean (SD)	Mean (SD)	Mean (SD)	n (%)
Remission (n=11)	7 (70)	1.2 (0.3)	104 (28)	4 (36)	1 (9)	3 (27)	–	–	2.7 (2.8)	0 (0)
Viral wheeze (n=15)	10 (63)	0.9 (0.5)	96 (17)	8 (53)	7 (47)	4 (27)	3.9 (2.4)	1.8 (0.6)	5.6 (2.6)	1 (7)
Multiple wheeze (n=25)	14 (56)	0.9 (0.6)	101 (21)	15 (60)	14 (56)	15 (60)	4.1 (2.0)	2.1 (0.6)	4.7 (2.1)	16 (64)
p-value equality	0.8	0.3	0.7	0.4	0.03	0.06	0.8	0.14	0.02	0.001
p-value trend	0.4	0.13	0.8	0.2	0.01	0.03	–	–	0.03	<0.001

SPT: skin-prick tests. For further definitions see legends to tables 2 and 3. For continuous variables, p-value for equality is from a one-way analysis of variance for equality of means, p-value for trend is testing for a linear trend in the means. For proportions, p-value for equality is testing for equality of the three proportions, p-values for trend tests for a linear trend in the three groups. p-values of less than 0.05 are statistically significant.

a family history of asthma and a personal history of allergy (but no other index of atopy) significantly predicted symptom pattern group (table 5).

Comparing symptomatic with asymptomatic children, there was a significant difference in log PC_{15} (mean (SD) 0.88 (0.56) and 1.2 (0.32), respectively; p=0.04) but not in R_{rs6} (97 (27) and 103 (27) % pred, respectively; p=0.55). Significantly fewer upper respiratory tract infections were reported in the asymptomatic group (p= 0.02) (table 3). In the ordinal logistic regression, the presence of any symptom was significantly predicted by a personal allergy (p=0.03), whereas within the two symptomatic groups, multiple wheeze, as opposed to viral wheeze, was significantly predicted by a family history of asthma (p=0.05).

Attack frequency

Eighty nine percent of attacks were reported as being associated with symptoms suggestive of a virus infection; however, all attacks were used in the analysis, including those with and without clinical suspicion of viral infection There was no difference in the number of attacks reported by the two symptomatic groups over the 12 month period (table 4). There was, however, a significant inverse relationship between attack frequency and PC_{15} (r=-0.33; p=0.03), and PC_{15} was the only significant predictor of the number of attacks in the multiple regression model (table 5). Maternal smoking (table 3), lung function, serum IgE, and number of siblings did not relate to attack frequency. Also, there was no correlation between attack severity and frequency (r=0.2; p=0.21).

Attack severity

There was no correlation between the attack severity score and maternal smoking (table 2) or lung function (r=-0.2; p=0.3), or serum IgE (r=0.02; p=0.9). The mean attack severity score was increased in those with

Table 5. – Best fit models for predicting outcome

Outcome	Significant variables	Coefficient (SE)	p-value
Attack severity score	Family history asthma	0.72 (0.24)	0.005
	Personal allergy	0.67 (0.24)	0.008
Attack number score	Log PC15	-1.55 (0.69)	0.03
	Personal allergy	1.36 (0.73)	0.07
Interval score	Family history of asthma	1.36 (0.57)	0.02
	Personal allergy	1.20 (0.56)	0.03
Interval symptom (yes/no)	Family history of asthma	1.63 (0.67)	0.02
	Personal allergy	1.63 (0.67)	0.05
Total severity	Family history of asthma	6.58 (2.2)	0.006
	Personal allergy	4.33 (2.3)	0.06
Symptom group	Family history of asthma	1.26 (0.59)	0.03
	Personal allergy	1.29 (0.58)	0.03
Log PC15	Family history of asthma	0.37 (0.15)	0.02
	Personal allergy	0.08 (0.16)	0.62

PC15: provocative concentration of methacholine causing a 15% fall in transcutaneous oxygen tension.

a family history of asthma (p=0.03) (table 3), as was the number with severe attacks (score 3) (p=0.007). Both of these scores were highly correlated with methacholine responsiveness (r=0.5; p=0.002 and r=0.77; p<0.001, respectively). The only index of atopy to show a significant relationship with attack severity, however expressed, was a personal history of allergy (table 3). In the multiple regression model, a personal history of allergy and a family history of asthma had an additive effect in predicting attack severity, with no interaction between the two (table 5 and fig. 1).

Interval symptoms

Like attack severity, interval symptoms scores were significantly greater in those with a family history of asthma (p=0.01), but interval symptoms were not greater in those with a personal history of allergy or any other atopic marker, or in those whose mothers smoked (table 3). A significant correlation was seen with PC15 (r=0.35; p=0.02), but not with lung function (r=0.04; p=0.8), or serum IgE (r=0.1; p=0.51). Again a family history of asthma and personal history of allergy both independently predicted interval symptom scores in the multiple regression (tables 3 and 5).

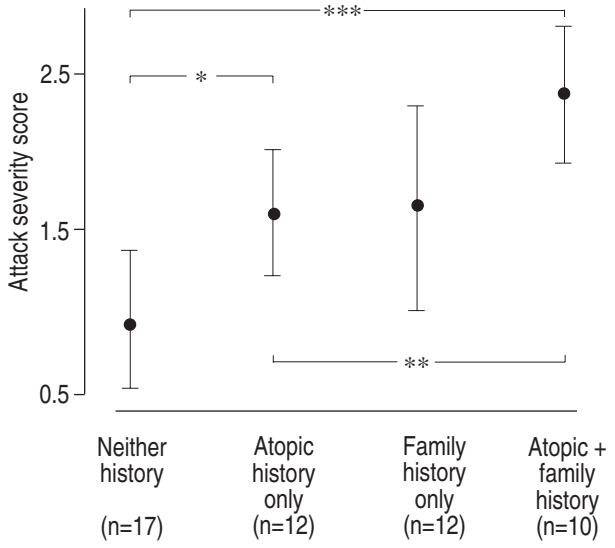

Fig. 1. – Mean attack severity score in those with and without a family history of asthma and personal history of atopy. Bars indicate 95% confidence limits. *: p=0.03; **: p=0.005; ***: p<0.001, for differences between groups.

Total severity score

When the severity outcomes were combined in a total severity score, a family history of asthma was the only significant predictor in the multiple regression model (p=0.006) (table 5). The total severity score was increased in those with a family history of asthma compared to those without (mean (SD) 13.53 (9.7) and 6.77 (7.1), respectively; p=0.01). The difference between those with and without a personal history of allergy, or any other index of atopy, failed to reach significance (p>0.05).

Asthma treatment

Seventeen of the children had been prescribed preventive therapy (table 4): 14 inhaled steroids and three cromoglycate. In the symptomatic children, there was no difference in any measure of symptom severity between those taking preventive medication and those who were not. Neither did the use of such medication relate to atopic status (Chi-squared=2.56; p=0.11). Multiplying each severity score by 2 in those on inhaled steroids failed to change the relationships in any of the multiple regression models; neither were these different if the three children on cromoglycate were included. When asymptomatic children were excluded and severity scores adjusted for use of preventive medication, the only predictor in the multiple regression model for attack severity and for total severity score was a family history of asthma (p=0.002 and p=0.01, respectively).

Methacholine PC15

The PC15 was significantly lower in those with a family history of asthma compared with those without (p=

0.02), but unaffected by any index of atopy including a personal history (table 3). When PC_{15}, was treated as an outcome in multiple regression modelling, a family history of asthma was the only significant predictor (table 5).

Discussion

In this group of children, who had been admitted to hospital with acute wheeze in the first 2 yrs of life, symptom severity between the ages of 4.5 and 5.5 yrs was consistently related both to a family history of asthma and a personal history of allergy. Since there was no statistical interaction between the two in multiple regression models, an additive effect on seventy is strongly suggested. A family history of asthma was significantly related to bronchial responsiveness in the child, and this also independently predicted symptom severity when a family history of asthma was omitted from the model. It is likely, therefore, that the influence of a family history of asthma on symptoms was mediated through enhanced bronchial responsiveness. The link between these two was independent of atopy, since PC_{15} was not related to any index of atopy, nor was it related to maternal smoking. In one study of infants, when bronchial responsiveness was measured soon after birth, it was also increased in those with a family history of asthma, even in those whose mothers did not smoke [16].

Two recent molecular genetic studies are relevant and shed light on the genetic basis of bronchial hyperresponsiveness, independent of atopy. Firstly, an Australian study showed significant linkage between increased bronchial responsiveness and the high affinity IgE receptor on chromosomes 11q13, even in the absence of an atopic phenotype [17]. Secondly, a Dutch study has shown evidence for co-inheritance on chromosome 5 of bronchial hyperresponsiveness and raised serum IgE, in the absence of a significant relationship between the two [18]. In the present study, a family history of allergy, when not associated with asthma, was unrelated to bronchial responsiveness or symptoms, a distinction which has been reported previously [19].

It is of interest that, as in the study of WENNERGREN *et al*. [20] who also measured total and specific IgE the only index of atopy to relate to symptoms in these 5 year old children was a personal history, the least objective measure and, therefore, the most open to bias. We calculated from the results of this study, that for a relationship between skin-prick test positivity (the most frequently used marker of atopy) and symptoms to become apparent with 80% power at the 5% level, a sample of more than 250 children including more than 200 symptomatic children would be needed. The possibility that a personal history of allergy was spuriously reported with greater frequency in those with a family history of asthma is not borne out by the independent influence of the two on symptoms. It would seem, therefore, that either symptomatic end organ allergen sensitization can precede systemic or simple objective evidence of atopy, or that allergic-type symptoms are not always IgE-related in this age group, This could have implications for epidemiological and clinical research in young children.

Previous studies looking at the risk factors in asthma have concentrated on prevalence [1, 2], rather than severity. The majority of young children have mild symptoms. We were concerned with troublesome disease, and therefore with the assessment of severity. A scale for measuring asthma severity, which included an assessment of the number and intensity of episodes, as well as frequency and severity of interval symptoms, has recently been recommended [21], Episodes were defined as symptoms which "were more troublesome than usual". An overall severity score was achieved by weighting the answers to a number of questions. This method, which has several features in common with the one used in the present study, has been validated in a population of Australian children [21]. That assessment, also over a 12 month period, was however, made retrospectively by parental questionnaire as opposed to being prospectively recorded, as in the present study.

In any assessment of severity, the modulating effect of preventive treatment on symptoms poses a problem. In contrast to the Australian study, which was concerned with "residual functional severity" [21], we were interested in the predictors of potential severity, and therefore had to provide some sort of weighting factor for those children on treatment. Multiplying the severity score by 2.0 in those receiving inhaled steroids, to allow for a possible beneficial effect, however, made no material difference to the results. Since, in carefully supervised placebo-controlled trials in this age group, the mean improvement in symptoms on inhaled steroids is approximately 30–60% [13, 14], this adjustment is probably reasonable.

Our original hypothesis was that the risk factors relating to the severity of attacks and interval symptoms were different. In fact, we found that a family history of asthma and a personal history of allergy consistently predicted both in a similar fashion in the regression models, although interval symptoms were not increased in those with evidence of atopy compared to those without.

In both the previous report of this cohort and in another study of preschool children, an association was found between atopy and interval symptoms between colds [6, 22]. Both of these were retrospectively obtained, so that reporting bias is a possibility. Our evidence suggests that the continuing tendency to have any wheeze at 5 yrs of age was determined by atopic history, whereas the pattern of wheeze was related to a family history of asthma, in that those children who wheezed only in association with viral infections were less likely to have a positive family history of asthma. In the Tuscon study, persistence of any wheeze to 6 yrs of age related to maternal asthma and a raised serum IgE [1].

Although it may be useful to separate acute attacks from interval symptoms, at the present time no particular criteria for doing so have been validated [21, 23]. It is possible that our criterion for an acute episode of an increase in symptoms lasting more than 24 h may have been inadequate, and could have blurred the difference between attacks and interval symptoms. Since we were particularly interested in considering symptoms induced by viral infections separately from other triggers, another approach might have been to analyse separately

those attacks reported by parents to be associated with infections, although we did not have objective evidence of viral infection. On the other hand, viruses have been isolated during exacerbations of asthma in the absence of reported upper respiratory tract infections [3]. If this distinction is important, further work is needed on the objective definition of acute attacks.

The determinants of attack frequency and severity seem to be different, since there was no correlation between the two in symptomatic children, and attack severity unlike frequency was predicted by a family history of asthma and personal allergy. The finding of a significant relationship between bronchial responsiveness and attack frequency was unexpected, and it is not clear which is cause or effect. If acute attacks are clearly linked to viral infections, then the number of attacks would be expected to increase when the risk of viral infections was greatest [24, 25]. That we found no link with maternal smoking or the number of siblings, a known risk factor for increased infections, could be a reflection of the limited size of the study.

In population studies of school-aged children with asthma, the triad of reduced lung function, increased bronchial responsiveness and atopic sensitization is well-recognized [26]. Both a deficit in lung function and atopy have been linked to the increase in bronchial responsiveness in a population study of older children [27]. In this population of 5 year olds, respiratory resistance was not significantly increased in the symptomatic children compared to those in remission; nor was it related to bronchial responsiveness or symptom severity, although the previously reported greater level of resistance in young male children was detected [15], which suggests that our physiological technique was adequate. Furthermore, in contrast to the findings in populations of older children, no relationship was found between any marker of atopy, including serum IgE, and bronchial responsiveness or lung function. Although it could be argued that this was due to the small sample size, a strong association between bronchial responsiveness and a family history of asthma was demonstrated. This indicates that even at 5 yrs of age in this population, familial or possibly genetic factors other than atopy determine the level of bronchial responsiveness, as has been suggested in previous studies of 3 year old children and infants [6, 16].

Our findings do not exclude the later development of bronchial hyperresponsiveness related to atopy with increasing age in this group of children, since atopy in infancy has been shown to predict bronchial responsiveness in later childhood [28]; nor can it be assumed that in children of a similar age, with an onset of symptoms after 2 yrs of age, that the level of bronchial responsiveness is not linked to atopy. After allowing for its association with atopy, a familial history of asthma has been shown to be an independent significant predictor of recurrent wheeze in a population study of 7–12 year old children [29]. It is, therefore, possible that, along with environmental factors, a "familial nonatopic asthma" factor which we propose to be equivalent to (genetically determined) bronchial responsiveness, as well as atopy, plays its part in determining the age of onset, persistence and pattern and severity of childhood wheezing disorders. With increasing age through childhood, atopy seems to predominate, and an interaction between atopy and bronchial responsiveness may later emerge.

To our knowledge, no other study in young children has considered factors related to symptom severity, monitored prospectively over a 12 month period. The implications of our findings are that at the age of 5 yrs, in children with a history of severe wheeze in the first 2 years of life, two factors independently influence the severity both of acute episodes and interval symptoms: familial or genetic factors which influence the level of bronchial responsiveness and atopy. It should be remembered, however, that these conclusions are only applicable to this particular type of population, referred to hospital with acute wheeze in the first 2 yrs of life. The determinants of wheeze severity may differ at different ages and in children who present after the first few years of life.

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