ASTHMA

Characterisation of atopic and non-atopic wheeze in 10 year old children

R J Kurukulaaratchy, M Fenn, S Matthews, S H Arshad

Thorax 2004;59:563–568. doi: 10.1136/thx.2003.010462

See end of article for authors' affiliations

Correspondence to:
Dr S H Arshad, The David
Hide Asthma and Allergy
Research Centre, St Mary's
Hospital, Newport, Isle of
Wight PO30 5TG, UK;
sha@soton.ac.uk

Received 16 May 2003
Accepted 7 February 2004

Background: Wheezing occurs in both atopic and non-atopic children. The characteristics of atopic and non-atopic wheeze in children at 10 years of age were assessed and attempts made to identify whether different mechanisms underlie these states.

Methods: Children were seen at birth and at 1, 2, 4 and 10 years of age in a whole population birth cohort study (n = 1456; 1373 seen at 10 years). Information was collected prospectively on inherited and early life environmental risk factors for wheezing. Skin prick testing, spirometry, and methacholine bronchial challenge were conducted at 10 years. Wheezing at 10 years of age was considered atopic or non-atopic depending on the results of the skin prick test. Independent significant risk factors for atopic and non-atopic wheeze were determined by logistic regression.

Results: Atopic (10.9%) and non-atopic (9.7%) wheeze were equally common at 10 years of age. Greater bronchial hyperresponsiveness ($p < 0.001$) and airways obstruction ($p = 0.011$) occurred in children with atopic wheeze than in those with non-atopic wheeze at 10 years. Children with atopic wheeze more often received treatment ($p < 0.001$) or an asthma diagnosis for their disorder, although current morbidity at 10 years differed little for these states. Maternal asthma and recurrent chest infections at 2 years were independently significant factors for developing non-atopic wheeze. For atopic wheeze, sibling asthma, eczema at 1 year, rhinitis at 4 years, and male sex were independently significant.

Conclusions: Non-atopic wheeze is as common as atopic wheeze in children aged 10 years, but treatment is more frequent in those with atopic wheeze. Different risk factor profiles appear relevant to the presence of atopic and non-atopic wheeze at 10 years of age.

Much attention has focused on the strong association between atopic tendency and childhood wheezing. Causal roles for atopic sensitisation^{1,2} in the pathogenesis of wheezing and asthma have been postulated as a result of numerous studies showing a higher frequency of asthmatic symptoms in atopic children than in non-atopic children.^{3–6} Consequently, interventional strategies to prevent atopic sensitisation by allergen avoidance in early life have been applied in an attempt to modify the development of childhood allergy, wheeze, and asthma.^{7–9} However, these measures have met with mixed results and have not shown definitive lasting benefit.^{2,7–9} Given such evidence, Pearce *et al*¹⁰ recently questioned the role of atopy as a causative factor in asthma. Indeed, as amply shown by Martinez *et al*,¹¹ there is growing evidence for the existence of several distinct wheezing phenotypes in childhood, not all of which are closely linked to atopy. Some forms of non-atopic wheeze such as early life transient wheeze have been well characterised,¹¹ with associations with impaired lung function in infancy and maternal smoking. The nature of non-atopic wheeze in later childhood, however, remains unclear. In particular, the significance of such disease in terms of associated morbidity and the similarities or differences of its characteristics with atopic wheezing need confirmation. An understanding of whether different risk factors underlie atopic and non-atopic wheeze in later childhood could also provide fresh insight into the mechanisms underlying childhood wheezing and asthma. Here we describe findings that characterise non-atopic wheeze at 10 years of age and assess whether this differs in risk factor profile from atopic disease. The results were derived from our unselected whole population birth cohort which has been prospectively followed for the first decade of life.

METHODS

A whole population birth cohort was established on the Isle of Wight in 1989 to study prospectively the natural history of childhood wheezing and to identify risk factors relevant to the development of childhood wheezing states. Approval for the study was obtained from the local research ethics committee.

Of 1536 children born between 1 January 1989 and 28 February 1990, informed consent was obtained for 1456 subjects to be enrolled. Enrolment took place at birth and information on family history of allergy (parental or sibling), household pets, parental smoking, social class (Registrar General's classification), and birth weight were recorded. Children were followed at the ages of 1 (n = 1167; 80.2%), 2 (n = 1174; 80.6%), 4 (n = 1218; 83.7%) and 10 years (n = 1373; 94.3%). The results of cohort follow up at 1, 2, 4, and 10 years of age have been reported previously.^{12–15} At each follow up detailed questionnaires were completed with the parents for each child regarding the prevalence of asthma and allergy. "Current wheeze" was recorded as having occurred on at least one occasion in the previous 12 months. Exposure to relevant environmental factors (domestic pets and tobacco smoke) was noted. The method of feeding was recorded at 1 and 2 years. A history of recurrent chest infections (more than one in the past year) was assessed at 1 and 2 years of age. Investigators' diagnoses of eczema (chronic or chronically relapsing, itchy dermatitis lasting more than 6 weeks with characteristic morphology and distribution), recurrent nasal symptoms/rhinitis (recurrent nasal discharge or blockage with attacks of sneezing and itchy eyes), and food allergy (history of vomiting, diarrhoea, colic or rash within 4 hours of ingestion of a particular food on at least two occasions) were made each time. Further

additional information was collected at 10 years about disease morbidity. Consultations with a hospital asthma specialist ("specialist referral") were therefore recorded along with hospital admissions for wheezing episodes. Details of asthma treatment "ever used" such as bronchodilators, inhaled corticosteroids, other prophylactic medications (long acting β_2 agonists, sodium cromoglycate, theophyllines, leukotriene antagonists or antihistamines), and oral corticosteroid therapy were also obtained. Several measures of "current wheezing morbidity" (within the preceding 12 months) were recorded at 10 years. These included "wheeze frequency" (number of wheezing episodes), "sleep disturbance from wheezing" (occurring more or less than once per week), "exercise induced wheezing", "limitation of speech by wheezing" (severe enough to limit speech to one or two words between breaths), and "nocturnal cough" (dry cough at night not associated with cold or flu). At 10 years the parents were also asked to report suspected triggers (ever) for their child's wheezing episodes.

At 10 years of age the questionnaire information was updated in 1373 children.¹⁵ Of these, 1043 individuals attended for further tests including skin prick testing (n = 1036), serum IgE measurement (n = 953), baseline spirometry (n = 981), and methacholine bronchial challenge (n = 784).

Skin prick testing was performed to a panel of common inhaled and food allergens (ALK, Denmark) which comprised house dust mite (*Dermatophagoides pteronyssinus*), grass pollen mix, tree pollen mix, cat and dog epithelia, *Alternaria alternata*, *Cladosporium herbarum*, milk, hen's egg, soya, cod and peanut plus histamine and physiological saline which acted as positive and negative controls, respectively. An allergen skin test reaction with a mean wheal diameter of at least 3 mm more than the negative control was regarded as positive and the subject defined as atopic. Serum was analysed for total IgE and a qualitative inhalant screen (Phadiatop; Pharmacia Diagnostics, Uppsala, Sweden). The inhalant screen tested for common inhalant allergens: house dust mite (*D pteronyssinus* and *D farinae*), cat dander, dog dander, horse dander, timothy grass, *Cladosporium*, silver birch, olive, mugwort, and nettle. All children with past or current wheezing were invited to perform a methacholine bronchial challenge at 10 years to assess bronchial hyperresponsiveness (BHR) using a Koko dosimeter (Pds Instrumentation, Louisville, USA) with compressed air source at 8 l/min and nebuliser output of 0.8 l/min. Initial inhalation of 0.9% saline was followed 1 minute later by spirometric recordings to obtain a baseline value. Incremental concentrations from 0.0625 mg/ml to 16 mg/ml methacholine were then serially administered. The concentration causing a stable fall in forced expiratory volume in 1 second (FEV₁) from the post-saline value of 20% was interpolated and expressed as PC₂₀ FEV₁. The intention was to perform bronchial challenge whenever possible in all children with wheezing histories plus a control group (n = 300) of children who had never wheezed.

Analysis of data

Data were double entered onto SPSS version 10.0 (SPSS Inc, Chicago, USA). Children were categorised at 10 years of age into the following four groups by the presence of "current wheeze" and atopic status at the 10 year skin prick test: (1) non-atopic non-wheeze; (2) non-atopic wheeze; (3) atopic non-wheeze; and (4) atopic wheeze.

Comparison of continuous variables for atopic and non-atopic wheeze was made (with transformation where necessary) using independent samples *t* testing. A continuous measure of BHR was estimated as the least square dose-response slope using least square regression of percentage change in FEV₁ on methacholine concentration administered for each child. Inverse transformation of the resulting dose-response slope (inverse slope) was used to satisfy normality and homoscedasticity with low values of $1/(10 - \text{slope})$ extrapolating to high BHR. Interval data were analysed using non-parametric tests (Mann-Whitney U test).

Separate univariate risk factor analysis was conducted to identify risk factors present in early life (the first 4 years) that were associated with either atopic or non-atopic wheeze at 10 years of age. χ^2 analysis (with Fisher's exact test where indicated by low expected cell counts) was used for this purpose, comparing factors between the respective wheezing state and that of a non-atopic non-wheeler (common control). To obtain the independent effect of risk factors showing trends for significance at univariate testing ($p < 0.2$), separate logistic regression models were created for atopic and non-atopic wheeze at 10 years. Stepwise backward (likelihood ratio) logistic regression was used for this purpose. Where more than one risk factor could explain a particular exposure of interest, only the most relevant was entered into the model.

RESULTS

At 10 years of age skin prick testing was performed in 1036 subjects (75.5% of 1373). Subjects attending for skin prick testing were more likely to have a personal or family history of allergy than those providing only questionnaire data at 10 years (table 1). The prevalence of atopy—as defined by at least one skin test allergen positive response—was 26.9% (279/1036). Among the atopic children 159 (57.0%) were male. In the 1036 subjects who underwent skin prick tests, current wheeze was present at 10 years in 20.7% (n = 214), atopic wheeze in 10.9% (n = 113), and non-atopic wheeze in 9.7% (n = 101). Among non-wheezers at 10 years, 79.8% (n = 656) were non-atopic and 20.2% (n = 166) were atopic.

The median age of onset did not differ between children with atopic and non-atopic wheeze at 10 years (median 2.0 years *v* 2.0 years; $p = 0.954$, Mann-Whitney U test). Immunological and lung function characteristics of children with atopic and non-atopic wheeze at 10 years are shown in table 2. Total IgE was significantly higher in the atopic children. Positive IgE inhalant screen was also significantly greater for children with atopic wheeze than for those with non-atopic wheeze (100% *v* 8.6%; $p < 0.001$). Children with

Table 1 Characteristics of children at 10 years of age

	Skin prick tested	Not skin prick tested	p value
Male	49.7% (515/1036)	53.7% (181/337)	0.202
Social class I-III	47.8% (446/933)	56.0% (158/282)	0.015*
Current wheeze	20.7% (214/1036)	13.4% (45/337)	0.003*
Asthma ever	21.5% (223/1035)	15.5% (52/335)	0.017*
Eczema ever	43.4% (450/1030)	33.5% (113/337)	0.001*
Hay fever ever	20.5% (212/1036)	13.1% (44/337)	0.002*
Parental asthma	32.9% (323/982)	23.3% (78/335)	0.001*
Parental allergy	63.6% (625/983)	54.0% (181/335)	0.002*

*Statistically significant (χ^2 test).

Table 2 Mean (SE) characteristics of children with atopic and non-atopic wheeze at 10 years of age

	Atopic wheeze	Non-atopic wheeze	Mean difference (95% CI)	p value
Log ₁₀ total IgE	2.63 (0.049) (n = 106)	1.77 (0.078) (n = 92)	-0.859 (-1.035 to 0.683)	<0.001*
FEV ₁ (litres)	1.96 (0.026) (n = 112)	2.03 (0.031) (n = 100)	0.066 (-0.013 to 0.015)	0.099
FVC (litres)	2.28 (0.026) (n = 112)	2.30 (0.035) (n = 100)	0.020 (-0.061 to 0.106)	0.646
FEV ₁ /FVC	0.86 (0.006) (n = 112)	0.88 (0.006) (n = 100)	0.023 (0.005 to 0.041)	0.011*
PEF (l/s)	4.14 (0.070) (n = 112)	4.11 (0.085) (n = 100)	-0.031 (-0.246 to 0.185)	0.779
Inverse slope	0.0199 (0.002) (n = 110)	0.0472 (0.003) (n = 91)	0.027 (0.019 to 0.035)	<0.001*

FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; PEF = peak expiratory flow.

*p<0.05 (independent samples t tests).

atopic wheeze did not show significantly more impairment of baseline spirometric parameters (FEV₁, FVC, or PEF) but they did have significantly more evidence of airways obstruction (FEV₁/FVC), lower inverse slope measure of BHR, and a higher prevalence of greater BHR (PC₂₀ FEV₁<4.0 mg/ml) than those with non-atopic wheeze (64.5% v 23.1%; p<0.001, OR 6.07 (95% CI 3.25 to 11.34)). These findings did not vary with sex stratification (results not shown).

Measures of current morbidity at 10 years of age were largely similar for children with atopic and non-atopic wheeze except for sleep disturbance from wheeze (table 3). Similarly, measures that could be regarded as indices of severity—such as hospitalisation for wheezing illness or specialist referral—did not differ significantly between atopic and non-atopic wheeze. Children with atopic wheeze were more likely to have been diagnosed as asthmatic by a physician, treated with regular medications for wheezing, and to have received oral corticosteroids. However, when stratified into social classes, children in higher social classes at 10 years (I–IIIm) who had atopic wheeze were no more likely than those with non-atopic wheeze to be diagnosed as asthmatic (31.3% v 45.2%; p = 0.172; OR 0.55; (95% CI 0.23 to 1.30)) or to have used inhaled corticosteroids (52.1% v 48.8%; p = 0.756; OR 1.14 (95% CI 0.50 to 2.63)). Other patterns of morbidity did not differ by social class and there was also little variation in morbidity/disease severity with sex stratified analysis (results not shown). Boys with atopic wheeze had a higher wheeze frequency than those with non-atopic wheeze (50.7% v 29.2%; p = 0.020; OR 2.50 (95% CI 1.15 to 5.46)) but they had less exercise induced wheeze than non-atopic children (27.8% v 49.0%; OR 0.40 (95% CI 0.19 to 0.85)). Other patterns of morbidity in boys and girls were similar to the overall trends shown in table 3.

Figure 1 shows parental reporting of suspected triggers (ever) for their child's wheezing. Infections, exercise, and stress did not differ significantly in frequency between children with atopic wheeze and those with non-atopic wheeze.

Univariate analysis showed a significant association between non-atopic wheeze and parental (particularly

Figure 1 Wheezing triggers ever reported; p values denote comparison between children with non-atopic and atopic wheeze (χ^2 test). Only significant p values are given.

Table 3 Morbidity and treatment of children with atopic and non-atopic wheeze at 10 years of age

	Atopic wheeze	Non-atopic wheeze	OR	95% CI	p value
Limitation of speech by wheeze in last year	16.4% (18/110)	10.1% (10/99)	1.74	0.76 to 3.98	0.184
Sleep disturbance by wheeze more than once per week in last year	12.6% (14/111)	4.0% (4/99)	3.43	1.09 to 10.79	0.027*
Wheeze frequency in last year (4 or more episodes in last year)	46.4% (51/110)	33.3% (32/96)	1.73	0.98 to 3.05	0.057
Nocturnal cough in last year	50.4% (57/113)	51.5% (52/101)	0.96	0.56 to 1.64	0.879
Exercise induced wheeze in last year	69.0% (78/113)	58.4% (59/101)	1.59	0.91 to 2.78	0.106
Physician diagnosed asthma ever	80.5% (91/113)	51.5% (52/101)	3.90	2.12 to 7.16	<0.001*
Inhaled steroids ever	61.1% (69/113)	37.4% (37/99)	2.63	1.51 to 4.58	<0.001*
Inhaled bronchodilators ever	93.8% (106/113)	72.7% (72/99)	5.68	2.35 to 13.74	<0.001*
Oral steroids ever	41.6% (47/113)	14.0% (14/100)	4.37	2.22 to 8.61	<0.001*
Specialist referral ever	18.6% (21/113)	15.0% (15/100)	1.29	0.63 to 2.67	0.486
Hospitalisation ever	25.7% (29/113)	16.0% (16/100)	1.81	0.92 to 3.58	0.085

*p<0.05 (χ^2 test).

maternal) allergic history, sibling asthma, personal allergy in the first year of life (eczema and food allergy) plus rhinitis at 2 years (table 4). Similarly, significant effects were observed for parental smoking throughout early life and recurrent chest infections in infancy. Exclusive formula feeding in the first 3 months of life also conferred a significant increased risk of having non-atopic wheeze, while exclusive breastfeeding in the first 3 months of life provided a significant reduction in risk.

Univariate analysis examining risk factors for atopic wheeze at 10 years showed significant associations with parental and sibling allergic histories (especially asthma and rhinitis), personal histories of eczema and food allergy throughout early life plus rhinitis and urticaria at 4 years (table 5). There was also a positive association with male sex. Early life environmental factors showed minimal effect on the development of atopic wheeze. Only recurrent chest infections at 2 years showed univariate significance, with social class at birth, method of infant feeding, pet exposure and parental smoking not having a statistically significant influence on the presence of atopic wheeze at 10 years of age.

Many of the factors showing significant effects by univariate analysis for these wheezing states at 10 years may have been linked. To determine independently significant variables associated with atopic and non-atopic wheeze, multivariate logistic regression analysis was used (table 6). For non-atopic wheeze at 10 years only maternal asthma and recurrent chest infections at 2 years were found to be independently significant factors while, for atopic wheeze, independent significance was found for male sex, diagnosed eczema at 1 year, diagnosed rhinitis at 4 years, and sibling asthma.

DISCUSSION

This study shows that non-atopic wheezing is as frequent as atopic wheezing in an unselected cohort of 10 year old British children. Current morbidity for atopic and non-atopic wheezing at 10 years of age was also not dissimilar. However, BHR, all levels of treatment, and being diagnosed as asthmatic were significantly more frequent in children with atopic wheeze. Characterisation of early life risk factor profiles for these two states revealed different patterns. Male sex, heredity, and allergic traits were independently significant for atopic wheezing while the environmental factors

examined had little effect of their own on this state. Heredity in the form of maternal asthma also had a significant effect on the presence of non-atopic wheeze. In contrast to atopic wheeze, recurrent chest infections at 2 years of age were found to have a significant independent association with non-atopic wheeze.

A higher prevalence of wheeze and asthma in atopic children has previously been shown.³⁻⁶ It has recently been reported that 32% of subjects with wheeze aged 11 years and over are non-atopic as defined by serum IgE criteria.¹⁶ Defining atopy by skin test positivity, we found that half the children with wheeze at 10 years of age did not have an atopic tendency. In support of this definition of atopy, we found good concordance between atopy by skin prick testing and a positive IgE inhalant screen. However, it is possible that our definition of wheeze—at least one episode of wheezing in the last year regardless of duration—could have led to a high estimation of non-atopic wheeze. Some might consider that our figures for non-atopic wheeze include “insignificant” single episodes of viral induced wheeze which conventionally may not be considered to have the same importance as that associated with persistent atopic wheeze. However, it is worth reflecting that both atopic and non-atopic wheeze in our 10 year old children had their origins in infancy and were therefore “persistent” states. It is also noteworthy that chest infections were not reported more frequently as wheezing triggers by parents of the non-atopic children in our study. This is different from previous findings from Tucson which suggest that non-atopic childhood asthma is largely associated with early life chest infections and remits after the age of 6 years.¹⁷ This discrepancy could plausibly reflect the different environment encountered by our population.

Is the disease state in our unexpectedly large group of children with non-atopic wheeze as significant as in those with atopic wheeze? Clough *et al*¹⁸ showed that atopic children aged 7–8 years with cough and wheeze had lower FEV₁, greater BHR, and greater peak flow variability as well as increased symptom severity than non-atopic children. Ponsonby *et al*¹⁹ also found greater wheeze frequency and hospital attendance in 8–10 year old children with atopic wheeze than in those with non-atopic wheeze. In some respects our findings support suggestions of worse disease among those with atopic wheeze. Our study confirms greater

Table 4 Univariate analysis of early life risk factors for non-atopic wheeze in children at 10 years of age ($p < 0.05$)

	Non-atopic wheeze	Non-atopic non-wheeze	OR	95% CI	p value
Maternal asthma	31.3% (30/96)	16.1% (100/622)	2.37	1.47 to 3.84	<0.001
Maternal food allergy	11.5% (11/96)	3.7% (23/599)	3.37	1.59 to 7.16	0.003*
Parental food allergy	14.6% (14/96)	4.8% (30/622)	3.87	1.72 to 6.62	<0.001
Sibling asthma	41.7% (40/96)	28.5% (177/622)	1.80	1.16 to 2.79	0.009
Exclusively breastfed first 3 months	24.4% (22/90)	36.8% (215/584)	0.56	0.33 to 0.92	0.022
Exclusively formula fed first 3 months	50.0% (47/94)	37.1% (223/601)	1.70	1.10 to 2.62	0.017
Eczema at 1 year	13.4% (13/97)	6.1% (38/622)	2.38	1.22 to 4.65	0.009
Food allergy at 1 year	10.3% (10/97)	4.7% (29/622)	2.35	1.11 to 4.99	0.022
Rhinitis at 2 years	22.1% (19/86)	12.0% (70/581)	2.07	1.17 to 3.65	0.011
Recurrent chest infections at 2 years	30.2% (26/86)	11.7% (68/581)	3.27	1.93 to 5.53	<0.001
Parental smoking at 4 years	53.3% (48/90)	35.0% (206/589)	2.13	1.36 to 3.32	0.001

χ^2 testing was used with *Fisher's exact test where indicated by low expected cell counts.

Factors showing statistical significance at univariate analysis ($p < 0.05$) are shown. The strongest significance was found for parental smoking at 4 years with lesser statistical significance for smoking at birth, 1 and 2 years (not shown). Similarly, there was a higher significance for recurrent chest infections at 2 years than at 1 year (not shown).

Factors showing trends for significance ($p < 0.2$ but > 0.05) were maternal urticaria, paternal food allergy, cat ownership at birth, dog ownership at birth, and social class I–III at birth. Factors not showing trends for significance ($p > 0.2$) were paternal asthma, maternal/paternal eczema, maternal/paternal rhinitis, paternal urticaria, sibling eczema, sibling rhinitis, sibling urticaria, sibling food allergy, cat ownership at 1, 2, and 4 years, dog ownership at 1, 2, and 4 years, early weaning (within first 3 months), low birth weight (< 2.5 kg), rhinitis at 1 and 4 years, eczema at 2 and 4 years, food allergy at 2 and 4 years, and urticaria at 4 years.

Table 5 Univariate analysis of early life risk factors for atopic wheeze at 10 years of age ($p < 0.05$)

	Atopic wheeze	Non-atopic non-wheeze	OR	95% CI	p value
Maternal asthma	28.6% (32/112)	16.1% (100/622)	2.09	1.32 to 3.32	0.002
Paternal asthma	26.8% (30/112)	12.4% (77/622)	2.59	1.60 to 4.19	<0.001
Paternal eczema	12.6% (14/111)	6.9% (43/622)	1.94	1.02 to 3.69	0.039
Paternal rhinitis	25.2% (28/111)	15.0% (93/622)	1.92	1.19 to 3.11	0.007
Male sex	63.7% (72/113)	46.5% (305/656)	2.02	1.34 to 3.05	0.001
Eczema at 1 year	30.5% (32/105)	6.1% (38/622)	6.73	3.97 to 11.44	<0.001
Food allergy at 1 year	10.5% (11/105)	4.7% (29/622)	2.40	1.16 to 4.95	0.016
Recurrent chest infections at 2 years	19.8% (20/101)	11.7% (68/581)	1.86	1.07 to 3.23	0.025
Rhinitis at 4 years	19.8% (21/106)	3.1% (18/59)	7.84	4.01 to 15.31	<0.001
Urticaria at 4 years	2.9% (3/102)	0.5% (3/586)	5.72	1.14 to 28.71	0.048

χ^2 testing was used with *Fisher's exact test where indicated by low expected cell counts.

Factors showing statistical significance at univariate analysis ($p < 0.05$) are shown. The strongest statistical significance was found for eczema at 1 year with a smaller but significant influence at 2 and 4 years. Similarly, food allergy had the strongest statistical significance at 1 year with a lesser but significant influence at 2 and 4 years.

Factors showing trends for significance ($p < 0.2$ but > 0.05) were maternal rhinitis, sibling asthma, sibling rhinitis, family (parental or sibling) history of urticaria, social class I-III at birth, cat ownership at 1 year, and recurrent chest infections at 1 year.

Factors tested but not showing trends for significance ($p > 0.2$) were maternal eczema, maternal/paternal urticaria, maternal/paternal/parental/family (parental or sibling) history of food allergy, sibling eczema, sibling urticaria, sibling food allergy, cat ownership at birth, 2 and 4 years, dog ownership at birth, 1, 2, and 4 years, early weaning (within first 3 months), exclusive breastfeeding in first 3 months, exclusive formula feeding in first 3 months, low birth weight (< 2.5 kg), parental smoking throughout early life, and rhinitis at 1 and 2 years.

BHR and obstructive patterns of airflow limitation among children with atopic wheeze. Disease severity as indicated by physician diagnosed asthma ever and receiving all levels of treatment for wheezing disorders might also appear to be greater for those with atopic wheeze in our study. However, we found that diagnosed asthma and inhaled steroid usage was no different between children with atopic and non-atopic wheeze in the highest three social classes. Furthermore, among the boys, current morbidity measures such as exercise induced wheeze were greater in non-atopic children. Overall, we found that most measures of current morbidity as well as hospitalisation and specialist referral for wheezing illness did not vary significantly by atopic status. There is therefore a discrepancy between morbidity and levels of treatment in our children with atopic and non-atopic wheeze. One explanation may be that children with atopic wheeze do indeed have more severe disease but that successful treatment prevents significantly more morbidity than in those with non-atopic wheeze. An alternative view might be that atopic wheeze is more recognisable (owing to family and personal history of allergy) and therefore is more readily treated, while non-atopic wheeze is not necessarily always milder but is being relatively overlooked and undertreated. In this context, a recent report from Australia suggests that the non-atopic

status may be associated with underdiagnosis of adult asthma.²⁰

Combinations of genetic and environmental influences are believed to underlie the development of wheezing and asthma. Court *et al*¹⁶ recently proposed that IgE and non-IgE mediated asthma might have distinctive aetiological mechanisms. We have confirmed different risk factor profiles for atopic and non-atopic wheeze in our children. Univariate analysis showed that parental smoking at all stages within early life, exclusive formula feeding in the first 3 months, and recurrent chest infections in infancy were significant factors for non-atopic but not for atopic wheeze. No effect of animal exposure or social class was observed for either state. Many significant factors may have been interlinked, and multivariate analysis found only recurrent chest infections at 2 years to have persisting independent significance for non-atopic wheeze. Whether this reflects a causal role for respiratory pathogens in non-atopic wheeze or merely increased susceptibility to infection because of intrinsic airway disease remains uncertain. Oddy *et al*²¹ identified wheezing lower respiratory illnesses as a significant risk factor for current asthma at 6 years of age in both atopic and non-atopic children. However, we did not find an independent association between such infections and development of

Table 6 Multivariate analysis of early life risk factors for atopic and non-atopic wheeze at 10 years ($p < 0.2$)

	Risk factor	OR	95% CI	p value
Non-atopic wheeze	Maternal asthma	4.08	1.85 to 9.00	<0.001
	Recurrent chest infections at 2 years	3.99	1.78 to 8.92	0.001
Atopic wheeze	Sibling asthma	2.10	1.04 to 4.23	0.039
	Eczema at 1 year	2.80	1.01 to 7.80	0.048
	Rhinitis at 4 years	4.74	1.61 to 13.47	0.005
	Male sex	2.73	1.36 to 5.48	0.005

The regression models used the outcomes of each respective wheeze status compared with having non-atopic non-wheeze. Only factors which had a significant effect at the final step of each regression model are shown.

Factors entered into the regression model for non-atopic wheeze at 10 years were maternal asthma, maternal urticaria, parental food allergy, sibling asthma, cat ownership at birth, dog ownership at birth, social class I-III at birth, exclusive breastfeeding for first 3 months, parental smoking at 4 years, recurrent chest infections at 1 year, recurrent chest infections at 2 years, eczema at 1 year, food allergy at 1 year, and rhinitis at 2 years.

Factors entered into the regression model for atopic wheeze were maternal asthma, paternal asthma, paternal eczema, maternal rhinitis, paternal rhinitis, sibling asthma, sibling rhinitis, family history (parent or sibling) of urticaria, cat ownership at 1 year, social class I-III at birth, recurrent chest infections at 1 year, chest infections at 2 years, eczema at 1, 2, and 4 years, food allergy at 1 year, rhinitis at 4 years, urticaria at 4 years, and male sex.

atopic wheeze. This is consistent with findings reported by Von Mutius *et al*²² who found a higher risk of childhood asthma from repeated early childhood infections for non-atopic asthma. It also supports work from Tucson²³ showing no significant association between early life lower respiratory tract illness and allergic sensitisation at the ages of 6 or 11 years.

Work by Lowe *et al*²⁴ has suggested that there is a significant interaction between maternal asthma, the child's atopic status, and lung function in 3 year olds. Our findings illustrate an important role for asthmatic family history in the manifestation of wheeze, regardless of whether or not the subject is atopic. Thus, even in the absence of personal atopy, we have found that maternal asthma is independently associated with wheezing at 10 years of age. This agrees with the findings from Tucson associating maternal asthma with asthma in *Alternaria* negative (the predominant local aeroallergen) children.¹⁷ The mechanism behind such relationships remains obscure but, as Halonen *et al* suggest, it may involve in utero factors.¹⁷

Analysis by Pearce *et al*¹⁰ has shown that the population attributable risk for asthma in relation to atopy in a variety of studies is typically less than 50%. Our findings confirm that a substantial burden of non-atopic wheezing exists at 10 years of age and further question a predominant role for atopy in childhood wheezing. Whether a model of wheezing and asthma as a primary epithelial disorder that facilitates airway allergen sensitisation is a better explanation of the associations between atopy and wheeze is worth considering.²⁵ The high prevalence of non-atopic wheeze in our population and the risk factor profile associated with it might provide some clues as to the rising prevalence of wheeze and asthma in recent years. Whether the increasing prevalence of non-atopic wheeze is one explanation for this phenomenon needs to be considered. Certainly, our findings indicate that non-atopic wheeze should not be ignored as a disease entity in later childhood.

ACKNOWLEDGEMENTS

The authors acknowledge the cooperation of the children and parents who have participated in this ongoing study. The 10 year follow up was funded with the assistance of the National Asthma Campaign, UK (grant no 364). The authors also note the valued contributions of Linda Terry, Gail Poulton, Linda Waterhouse, Heidi Savory, Tessa Booth, Andrew Gallini, Cathy Wilby, Rosemary Lisseter and Roger Twiselton to the 10 year follow up of this study, and highlight the role of the late Dr David Hide in starting the study.

Authors' affiliations

R J Kurukulaaratchy, M Fenn, S Matthews, S H Arshad, The David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport, Isle of Wight PO30 5TG, UK

REFERENCES

- Holt PG. Key factors in the development of asthma: atopy. *Am J Respir Crit Care Med* 2000;**161**:s172-5.
- Murray CS, Woodcock A, Custovic A. The role of indoor allergen exposure in the development of sensitisation and asthma. *Curr Opin Allergy Clin Immunol* 2001;**1**:407-12.
- Brooke AM, Lambert PC, Burton PR, *et al*. The natural history of respiratory symptoms in preschool children. *Am J Respir Crit Care Med* 1995;**152**:1872-8.
- Clifford RD, Radford M, Howell JB, *et al*. Prevalence of respiratory symptoms among 7 and 11 year old schoolchildren. *Arch Dis Child* 1989;**64**:1118-25.
- Mensinga TT, Schouten JP, Rijcken B, *et al*. The relationship of eosinophilia and positive skin test reactivity to respiratory symptom prevalence in a community-based population study. *J Allergy Clin Immunol* 1990;**86**:99-107.
- Sears MR, Herbison GP, Holdaway MD, *et al*. The relative risks of sensitivity to grass pollen, house dust mite and cat dander in the development of childhood asthma. *Clin Exp Allergy* 1989;**19**:419-24.
- Hide DW, Matthews S, Tariq S, *et al*. Allergen avoidance in infancy and allergy at 4 years of age. *Allergy* 1996;**51**:89-93.
- Koopman LP, van Strien RT, Kerkhof M, (PIAMA Study), *et al*. Placebo-controlled trial of house dust mite-impermeable mattress covers: effect on symptoms in early childhood. *Am J Respir Crit Care Med* 2002;**166**:307-13.
- Tauber E, Gartner C, Halmerbauer G, *et al*. Predictors of lung function in infants at high risk of atopy: effect of allergen avoidance. *Respir Med* 2002;**96**:230-5.
- Pearce N, Pekkanen J, Beasley R. How much asthma is really attributable to atopy? *Thorax* 1999;**54**:268-72.
- 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.
- Arshad SH, Hide DW. Effect of environmental factors on the development of allergic disorders in infancy. *J Allergy Clin Immunol* 1992;**90**:235-41.
- Arshad SH, Stevens M, Hide DW. The effect of genetic and environmental factors on the prevalence of allergic disorders at the age of two years. *Clin Exp Allergy* 1993;**23**:504-11.
- Tariq SM, Matthews SM, Hakim EA, *et al*. The prevalence of and risk factors for atopy in early childhood: a whole population birth cohort study. *J Allergy Clin Immunol* 1998;**101**:587-93.
- Kurukulaaratchy RJ, Fenn M, Twiselton R, *et al*. The prevalence of asthma and wheezing illnesses amongst 10-year old schoolchildren. *Respir Med* 2002;**96**:162-9.
- Court CS, Cook DG, Strachan DP. Comparative epidemiology of atopic and non-atopic wheeze and diagnosed asthma in national sample of English adults. *Thorax* 2002;**57**:951-7.
- Halonen M, Stern DA, Lohman C, *et al*. Two subphenotypes of childhood asthma that differ in maternal and paternal influences on asthma risk. *Am J Respir Crit Care Med* 1999;**160**:564-70.
- Clough JB, Williams JD, Holgate ST. Effect of atopy on the natural history of symptoms, peak expiratory flow, and bronchial responsiveness in 7- and 8-year-old children with cough and wheeze. A 12-month longitudinal study. *Am Rev Respir Dis* 1991;**143**:755-60.
- Ponsonby AL, Gatenby P, Glasgow N, *et al*. Which clinical groups within the spectrum of child asthma are attributable to atopy? *Chest* 2002;**121**:135-42.
- Adams RJ, Wilson DH, Appleton S, *et al*. Underdiagnosed asthma in South Australia. *Thorax* 2003;**58**:846-50.
- Oddy WH, de Klerk NH, Sly PD, *et al*. The effect of respiratory infections, atopy, and breastfeeding on childhood asthma. *Eur Respir J* 2002;**19**:899-905.
- Von Mutius E, Illi S, Hirsch T, *et al*. Frequency of infections and risk of asthma, atopy and airway hyperresponsiveness in children. *Eur Respir J* 1999;**14**:2-3.
- Stein RT, Sherrill D, Morgan WJ, *et al*. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999;**354**:541-5.
- Lowe L, Murray CS, Custovic A, *et al*. Specific airway resistance in 3-year old children: a prospective cohort study. *Lancet* 2002;**359**:1904-8.
- Holgate ST, Lackie P, Wilson S, *et al*. Bronchial epithelium as a key regulator of airway allergen sensitization and remodelling in asthma. *Am J Respir Crit Care Med* 2000;**162**:s113-7.