

Characterization of wheezing phenotypes in the first 10 years of life

R. J. Kurukulaaratchy*, M. H. Fenn*, L. M. Waterhouse*, S. M. Matthews*, S. T. Holgate† and S. H. Arshad*†

*The David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport, Isle of Wight and †Respiratory Cell and Molecular Biology, School of Medicine, Southampton General Hospital, Southampton, UK

Summary

Background Childhood wheezing illnesses are characterized into different phenotypes. However, severity of the disease associated with these phenotypes has not been extensively studied.

Objectives To determine characteristics of childhood wheezing phenotypes in the first decade of life using health outcomes plus measurements of atopy, lung function and bronchial hyper-responsiveness.

Methods A whole population birth cohort ($n=1456$) was prospectively studied to examine the natural history of childhood wheezing. Children were seen at 1, 2, 4 and 10 years for questionnaire completion and prospectively collected data used to define wheezing phenotypes. Assessment was made of adverse health outcomes plus spirometry, bronchial hyper-responsiveness, serum IgE measurement at 10 years and skin test sensitization at both 4 and 10 years for wheezing phenotypes.

Results Phenotypic analysis identified that 37% early life wheezers (symptom onset by age 4 years) still wheezed at 10 years. These persistent wheezers showed significantly more physician-diagnosed asthma in early life ($P < 0.005$ at 2 years) than early transient wheezers (wheezing transiently with onset by age 4 years). Overall they experienced greater multiple hospital admissions ($P=0.024$), specialist referral ($P=0.009$) and use of inhaled ($P < 0.001$) and oral steroids ($P < 0.001$) than early transient wheezers. They also demonstrated enhanced bronchial hyper-responsiveness compared with early transient wheezers ($P < 0.001$). However, both groups of early life wheezers showed impairment of baseline lung function at 10 years in comparison with non-wheezers: FEV₁ ($P < 0.029$) and FEV₁/FVC ratio ($P < 0.001$) with persistent wheeze and PEF ($P=0.036$) with early transient wheeze. Late-onset wheezers (onset from 5 years onwards) had similar BHR to persistent wheezers but maintained normal lung function at age 10 and had lower cumulative prevalence of adverse health outcomes than persistent wheezers.

Conclusions Persistent wheezing with early childhood onset is associated with substantial morbidity in the first decade of life in association with high levels of atopy, bronchial hyper-responsiveness and impaired lung function at 10 years of age. Late-onset wheezing in the first decade of life could harbour potential for similarly significant disease subsequently.

Keywords atopy, bronchial hyper-responsiveness, childhood asthma, morbidity, wheezing phenotypes

Submitted 18 July 2002; revised 20 January 2003; accepted 5 February 2003

Introduction

Childhood wheezing illnesses emerged as commonplace during the final decades of the 20th century [1–6], placing a considerable burden upon global healthcare resources. Both increasing primary care consultations [7] and hospital admissions [8–11] due to asthma and wheezing have been identified in this context, although trends appear to have stabilized in recent years [12]. Mortality rates in many countries have shown similar patterns [13]. Indirect effects upon other aspects of life, including absence from schooling and impact upon education, have also been described [14].

Concurrently an enhanced understanding of the nature of childhood wheezing has evolved [15]. In the Tucson Children's

Respiratory Cohort Study Martinez and coworkers demonstrated that distinct wheezing phenotypes exist during the first 6 years of life [16, 17]. Whilst confirming that most early life wheezing is a transient entity, this landmark work identified a substantial burden of persistent wheezing throughout the first 6 years of life, typically associated with atopy, measurable bronchial hyper-responsiveness and reduced lung function. Despite such knowledge parents still commonly hold on to the more comforting notion of the 'happy infant wheezer' [18] who will suffer little of any long-term consequence. This may explain parents' reluctance to accept anti-inflammatory treatment for their child even in moderate to severe asthma [19]. Confirmation of the characteristics of childhood wheezing phenotypes in other populations could help reinforce awareness of their significance. Furthermore, whilst many characteristics of childhood wheezing phenotypes have been clarified using laboratory-based methods, 'clinical' features associated with these states, such as disease morbidity traits, remain unclear. Here

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

we have employed a similar phenotypic approach to Martinez et al. to examine the characteristics of childhood wheezing from birth to age 10 years in our unselected British cohort using both clinical and laboratory-based measures.

Methods

A whole population birth cohort was established on the Isle of Wight in 1989 to study the natural history of asthma and allergic disorders. 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. Enrolment took place at birth and children were followed at the ages of 1 ($n = 1167$), 2 ($n = 1174$), 4 ($n = 1218$) and 10 years ($n = 1373$). Results of cohort follow-up (1, 2, 4 and 10 years) have been reported previously [20–23]. At every follow-up, detailed questionnaires were completed with the parents for each child regarding asthma and allergy prevalence. At 10 years, International Study of Asthma and Allergy in Childhood (ISAAC [24]) written questionnaires were also used assessing respiratory, nasal and dermatological symptoms. Further additional information was collected at 10 years about disease morbidity. Consultations with a hospital asthma specialist ('specialist referral') were recorded along with hospital admissions or casualty attendances 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, leukotrienes antagonists or anti-histamines) 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' (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). Asthma-related definitions used at 10 years were of 'wheezing ever', 'current wheezing' (wheezing in the last 12 months) and 'diagnosed asthma ever' (physician diagnosis of asthma ever).

Baseline lung function was recorded in the majority of 10-year-olds seen ($n = 981$). At 10 years non-specific bronchial hyper-responsiveness (methacholine bronchial challenge) was also assessed in children with past or current wheezing ($n = 484$) and 300 children who had never wheezed (controls). Details of spirometry and bronchial challenge methodology used have been described previously [23].

At 4 and 10 years, skin prick testing (SPT) was performed in all children who attended the Centre to a standard battery of common allergens (ALK, Denmark). Positive (histamine dihydrochloride, 10 mg/mL) and negative controls (physiological saline) were included. Details of the individual allergens tested have been reported elsewhere [22, 23]. Mean wheal diameter 3 mm greater than the negative control was regarded as a positive test for any given allergen. Presence of at least one such reaction defined the subject as atopic. At 10 years, whole blood was also taken for measurement of total serum IgE and an inhalant screen (qualitative) for IgE antibody to common inhalant allergens (Phadiatop, Pharmacia, Uppsala, Sweden). Details of the inhalant screen allergens have been reported previously [23].

Analysis

Data were double entered onto SPSS (v10.0; SPSS Inc, Chicago, USA). Children were categorized at 10 years into four groups by presence of 'current wheeze' at each follow-up: non-wheezers (children who never wheezed in the first decade of life), early transient wheezers (wheezing onset in the first 4 years of life which ceased and was not present within 12 months of assessment at 10 years), persistent wheezers (children with wheezing onset in the first 4 years of life who still wheezed at 10) and late-onset wheezers (children with wheezing onset from 5 years onwards who still wheezed at 10).

Means for continuous variables were analysed (with transformation where necessary) using one-way ANOVA followed by the 'Bonferroni multiple comparisons test'. Differences in proportions between groups were tested using chi-square analysis with correction for multiple comparisons using a Bonferroni technique. For contingency tables with cells possessing expected counts of less than five subjects Fisher's exact test was used. Bronchial hyper-responsiveness (BHR) was categorized by PC_{20} FEV₁ as 'Normal' (> 16 mg/mL), 'Borderline' (4–16 mg/mL), 'Mild/Positive' (1–4 mg/mL) and 'Moderate-Severe' (< 1 mg/mL), following American Thoracic Society guidelines [25]. In our population, including non-wheezing children, many subjects might not be expected to possess a measurable PC_{20} . Therefore, a continuous measure of BHR (least-square dose-response slope) was also estimated by least-square regression of percentage change in FEV₁ upon methacholine dose for each child [26]. Inverse transformation, $1/(10\text{-slope})$, was used to satisfy normality and homoscedasticity. Thus low values for $1/(10\text{-slope})$ extrapolate to high BHR.

Results

To improve accuracy and minimize recall bias our phenotypic analysis is restricted to 1034 (71%) of the original 1456 cohort recruits who were seen prospectively with information available from all study visits; 1 or 2 years, 4 and 10 years. Amongst this subgroup, baseline lung function and bronchial challenge results were available for 859 (82%) and 647 (63%) at 10 years. Skin prick data were available for 875 (85%) at 4 years and 861 (83%) at 10 years, whilst serum IgE measurements were present for 798 (77%) of this subgroup at 10 years. These 1034 children did not differ demographically or in major disease parameters from 339 children seen at 10 years but excluded from phenotypic analysis because of missing prior follow-up (Table 1).

Table 1. Demographic/disease characteristics of children included and excluded from the analysis

	Included (seen at all visits)	Excluded (seen at 10 years but not at other visits)
Number	1034	339
Male (%)	50.8%	50.4%
Birth weight (kg)	3.44	3.38
Social class I–III at birth (%)	47.2%	43.5%
Parental atopy at birth (%)	51.0%	50.1%
Wheeze ever		
(retrospective; 10 years) (%)	46.7%	41.9%
Current wheeze at 10 years (%)	19.9%	15.6%

By 10 years, the cumulative prevalence of prospectively determined 'wheeze ever' was 40.3% (417 children). Of these, 50.6% (211) were early transient wheezers, 30.0% (125) were persistent wheezers, and 19.4% (81) were late-onset wheezers. The remaining 617 children were categorized non-wheezers. Mean duration of wheezing (from symptom onset to last reported episode) was 8.80 years (95% confidence interval 8.61, 8.99) for persistent wheezers, 3.81 (3.27, 4.35) for early transient wheezers, and 4.53 (3.93, 5.13) for late-onset wheezers.

Physician diagnosis of asthma may serve as a crude indicator of morbidity in a wheezing child. At age 1 year, 'diagnosed current asthma' was present equally amongst persistent and early transient wheezers (29.6% vs. 25.1%; $P=0.370$). By age 2 years, however, 'diagnosed current asthma' was significantly higher in persistent wheezers (46.5% vs. 30.7%; $P=0.005$). At 4 years of age this trend was even stronger, with 74.8% persistent wheezers having 'diagnosed current asthma' compared with 32.9% early transient wheezers ($P<0.001$). At 10 years amongst 'currently wheezing' children 'diagnosed asthma ever' was reported significantly more often for persistent (76.0%) than late-onset wheezers (51.9%, $P<0.001$).

Within our cohort 39.5% children had ever been seen by their general practitioner because of wheezing, whilst 7.4% children had been admitted to hospital with wheezing illnesses during the first decade of life. Children with persistent wheeze had the highest 'lifetime requirements' for all levels of medical care with regard to their wheezing illness as indicated at 10 years by reported general practitioner (GP) care, asthma specialist referral, hospital admission and casualty department attendance, whilst early transient and late-onset wheeze did not differ significantly (Table 2). Amongst the whole group, 32.2% had ever received pharmacological treatment for wheezing by 10 years, regular prophylactic medications were reportedly used at some point by 17.7% and oral corticosteroids by

7.8% children. 'Treatment ever' (Fig. 1) with respect to inhaled bronchodilators ($P\leq 0.001$), inhaled corticosteroids ($P\leq 0.001$) and oral corticosteroids ($P\leq 0.001$) was significantly commoner in persistent than early transient wheeze. Persistent wheezers also had significantly higher prevalence of inhaled corticosteroid usage ($P=0.024$), multiple prophylactic therapy ($P=0.036$) and oral corticosteroids ($P\leq 0.001$) than late-onset wheezers. Use of inhaled bronchodilators ($P\leq 0.001$) and corticosteroids ($P\leq 0.001$) was significantly commoner in late-onset than early transient wheeze. Multiple courses of oral corticosteroids were more frequent amongst persistent than early transient wheezers (64.0% vs. 21.1%; $P=0.003$). Measures of 'current wheezing morbidity' at 10 years tended to be greater in persistent than late-onset wheeze (Fig. 2). However, this was

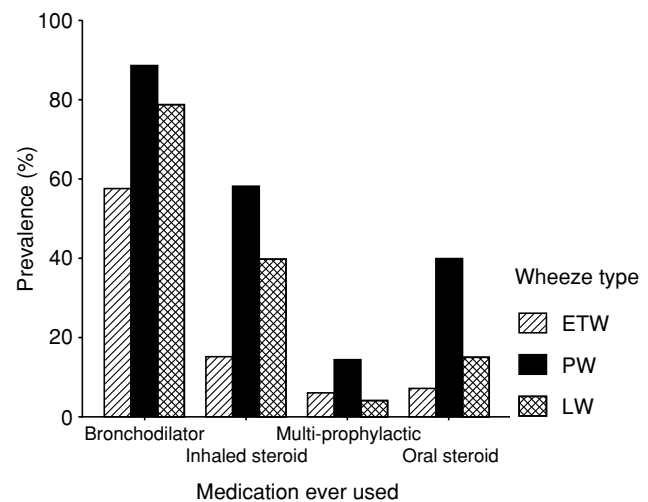


Fig. 1. Medication 'ever used' by wheezing phenotypes (see text for statistical comparisons).

Table 2. Use of healthcare resources by wheezing phenotypes

	Wheezing phenotype		
	Early transient wheezer	Persistent wheezer	Late-onset wheezer
GP treatment (%)	82.7%	93.5%†	91.4%
(number)	(115/139)	(116/124)	(74/81)
Specialist care (%)	8.6%	21.8%*¶	7.4%¶
(number)	(12/139)	(27/124)	(6/81)
Ever admitted to hospital (%)	16.1%	27.4%§	11.1%
(number)	(22/137)	(34/124)	(9/81)
Ever attended at casualty (%)	2.9%	11.4%†	4.9%
(number)	(4/134)	(14/123)	(4/81)
Multiple hospital admissions (%)	2.9%	11.3%‡	3.7%
(number)	(4/133)	(14/124)	(3/78)
Multiple casualty attendances (%)	0.7%	3.3%	0.0%
(number)	(1/138)	(4/123)	(0/81)

Chi-square analysis with Bonferroni correction approach was used. Statistical significance compared with early transient wheezer; * $P=0.009$; † $P=0.021$; ‡ $P=0.024$. Statistical significance compared with late-onset wheezer; § $P=0.015$; ¶ $P=0.018$.

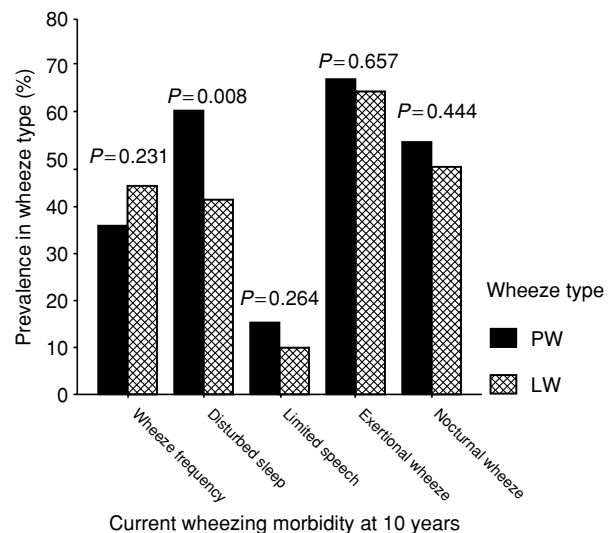


Fig. 2. Current wheezing morbidity at 10 years by wheeze phenotype. P-values denote comparison between persistent and late-onset wheezers by chi-square analysis (without Bonferroni correction). Wheeze frequency: four or more episodes in the last year. Disturbed sleep: any nocturnal disturbance by wheezing in the last year. Limited speech: limitation of speech to one or two words at a time by wheeze in the last year. Exertional wheeze: wheezing with exercise in the last year. Nocturnal wheeze: dry cough at night in the last year (not associated with cold or flu).

Table 3. Lung function and BHR ('inverse slope') by wheeze type

	Wheezing phenotype			
	Non-wheezers	Early transient wheezer	Persistent wheezer	Late-onset wheezer
FVC (litres)	2.31	2.26	2.28	2.28
(95% CI)	(2.28–2.34)	(2.21–2.31)	(2.22–2.35)	(2.22–2.34)
(number)	(495)	(178)	(111)	(76)
FEV ₁ (litres)	2.06	2.00	1.97†	1.99
(95% CI)	(2.03–2.08)	(1.95–2.04)	(1.91–2.03)	(1.94–2.05)
(number)	(494)	(178)	(111)	(76)
FEV ₁ : FVC	0.89	0.89	0.86*¶	0.87
(95% CI)	(0.89–0.90)	(0.88–0.90)	(0.85–0.88)	(0.86–0.89)
(number)	(494)	(178)	(111)	(76)
PEF (litres/s)	4.21	4.02‡	4.02	4.22
(95% CI)	(4.14–4.28)	(3.91–4.13)	(3.86–4.17)	(4.05–4.39)
(number)	(495)	(178)	(111)	(76)
1/(10 – slope)	0.058	0.057	0.030*§	0.033*§
(95% CI)	(0.054–0.062)	(0.051–0.062)	(0.025–0.036)	(0.025–0.041)
(number)	(318)	(152)	(101)	(75)

Values quoted are means with 95% confidence intervals (95% CI) for the means. Analysis was by one-way anova followed by Bonferroni multiple comparisons testing. Statistical significance compared with non-wheezers, * $P < 0.001$; † $P = 0.029$; ‡ $P = 0.036$. Statistical significance compared with early transient wheezer, § $P < 0.001$; ¶ $P = 0.008$.

statistically significant only for 'sleep disturbance by wheeze in the last year'.

Persistent wheezers had significantly lower forced expiratory volume in 1 s (FEV₁) than non-wheezers and FEV₁/FVC (forced vital capacity) ratio than both non-wheezers and early transient wheezers (Table 3). Conversely late-onset wheezers showed preservation of lung function. Early transient wheezers showed significantly lower peak expiratory flow (PEF) at 10 years than non-wheezers, a finding that continued amongst those transient wheezers with symptoms confined purely to the first 4 years (PEF: 4.21 vs. 4.00; $P = 0.048$; 95% CI for difference: 0.001, 0.418).

Assessment of BHR by American Thoracic Society classification (Fig. 3) and inverse slope (Table 3) revealed greater BHR at 10 years amongst late-onset and persistent wheezers than early transient or non-wheezers. 'Definite BHR' (American Thoracic Society categories, mild and moderate to severe) was significantly more prevalent in persistent wheezers (42.6%) and late-onset wheezers (53.3%) than non-wheezers (10.7%, $P < 0.001$) or early transient wheezers (15.1%, $P < 0.001$).

Further analysis revealed that persistent wheezers who had ever required oral corticosteroid for disease control demonstrated higher prevalence of 'definite BHR' (55.0% vs. 34.8%, $P = 0.041$). Similarly, persistent wheezers who had ever required hospital admission also had more 'definite BHR' (64.3% vs. 34.2%, $P = 0.006$). Amongst late-onset wheezers, having ever needed oral corticosteroid treatment was also associated with greater prevalence of 'definite BHR' (91.7% vs. 46.0%; $P = 0.004$). Furthermore, late onset wheezers needing oral corticosteroid additionally showed significantly lower FEV₁ (1.84 vs. 2.02; $P = 0.023$) and FEV₁/FVC (0.84 vs 0.88; $P = 0.040$) than those not requiring such medication. This finding was not observed amongst persistent wheezers.

Prevalence of atopy at both 4 and 10 years, defined by positive skin prick test (SPT) to one or more common allergens, was significantly higher amongst persistent or late-onset wheezers

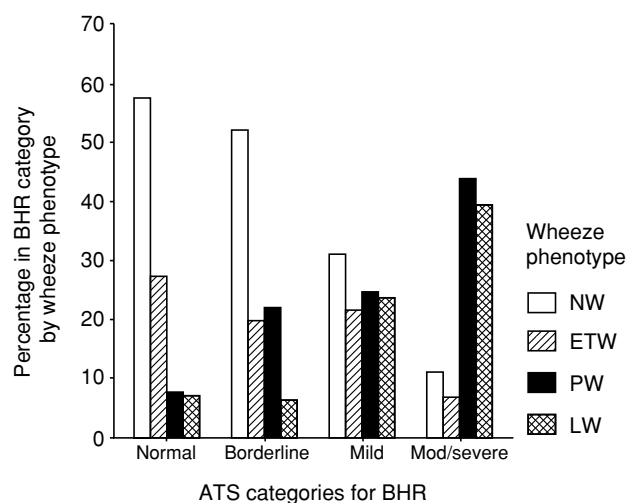


Fig. 3. Relationship between wheezing phenotype and BHR at 10 years. The proportions within each BHR category are shown according to their wheezing phenotype (see text for statistical comparisons). American Thoracic Society Categorization of BHR: normal BHR = PC₂₀ FEV₁ > 16 mg/mL; borderline = PC₂₀ FEV₁ = 4 to 16 mg/mL; mild/positive = PC₂₀ FEV₁ = 1 to 4 mg/mL; mod/severe = PC₂₀ FEV₁ < 1 mg/mL.

compared with non-wheezers and early transient wheezers. Similar trends were also noted for total serum IgE and positive IgE inhalant screen at 10 years (Table 4). Prospectively determined eczema, food allergy or hay fever ever were, however, significantly commoner for all wheezing phenotypes in comparison to non-wheezers.

Discussion

Our findings demonstrate that a phenotypic classification of childhood wheezing can provide valuable insights into its

Table 4. Atopy, allergic disease and wheeze phenotype

	Wheezing phenotype			
	Non-wheezers	Early transient wheezers	Persistent wheezers	Late-onset wheezers
Positive SPT 4 years (%)	14.6%	12.6%	46.8%*†	34.3%*†
(number)	(75/515)	(23/182)	(52/111)	(23/67)
Positive SPT 10 years (%)	19.3%	21.8%	54.5%*†	54.7%*†
(number)	(96/497)	(39/179)	(60/110)	(41/75)
Positive IgE inhalant (%)	25.2%	24.8%	60.4%*†	63.4%*†
screen 10 years				
(number)	(116/460)	(41/165)	(61/101)	(45/71)
Mean log ₁₀ total IgE 10 years	1.80	1.80	2.23*†	2.30*†
(95% CI)	(1.73–1.86)	(1.68–1.91)	(2.08–2.38)	(2.12–2.48)
(number)	(460)	(165)	(101)	(72)
Eczema ever (%)	21.3%‡	30.7%	40.3%*	40.7%*
(number)	(131/615)	(62/202)	(48/119)	(33/81)
Food allergy ever (%)	14.9%	28.5%*	40.3%*§	21.0%*
(number)	(92/617)	(57/200)	(48/119)	(17/81)
Hay fever ever (%)	26.2%	54.0%*	64.1%*	56.3%*
(number)	(161/614)	(112/205)	(75/117)	(45/80)

95% CI refers to 95% confidence interval for the mean. The Bonferroni correction approach has been applied to analyses. Eczema ever, food allergy ever and hay fever ever were determined from prospectively determined data concerning presence of each state at each study visit. Statistical significance compared with non-wheezers, * $P < 0.001$. Statistical significance compared with early transient wheezers, † $P < 0.001$; ‡ $P = 0.036$. Statistical significance compared with late-onset wheezers, § $P = 0.024$.

nature, particularly highlighting the severity of early life persistent wheezing. We can confirm the applicability of the approach adopted in the Tucson study [16, 17] towards childhood wheezing in our own different population, over a longer time period, some years later and with a high level of cohort retention.

It is acknowledged that most childhood wheezing arises in early childhood and that the majority of such disease is transient [15]. However, Martinez [16, 17] and Brooke [27] have demonstrated that a substantial minority of early life wheezing persists up to 6 years of age. Our findings of persistent wheeze to 10 years in 37% of early life wheezers are remarkably similar. Prior work [16, 17] has characterized such persistent wheezers as typically male, having coexistent atopy and allergic disorder plus lower lung function by 6 years of age and increased bronchial hyper-responsiveness by 11 years. We confirm that by 10 years of age persistent wheezers display significantly impaired baseline lung function compared with children who never wheeze as well as enhanced bronchial hyper-responsiveness compared with non-wheezers or early transient wheezers. Associated atopy throughout childhood plus high lifetime prevalence of clinical allergic states is a characteristic feature of this state in our population. High disease morbidity in terms of health-care utilization and pharmacological treatment demonstrates the clinical impact of such findings to the lives of persistent wheezers. The severity of persistent wheezing is emphasized by higher indices suggesting greatest disease severity, such as 'asthma specialist referral' and 'multiple hospital admissions'. In such terms our persistent wheezers constitute the typical childhood asthmatic. Physician-diagnosed asthma is a subjective indicator of this fact. Importantly, we found the prevalence of diagnosed asthma in early life to show an increasing trend amongst persistent wheezers from the age of 2 years onwards when compared with children with an ultimately transient wheezing outcome. This could be interpreted as suggesting

a picture of increasing morbidity amongst persistent wheezers as they continue to wheeze.

Findings from the CAMP study, USA [28], suggest that persistent wheezers possess the greatest scope for development of uninterrupted airway inflammation with consequent airway structural damage and BHR. This notion is further supported by Stevenson et al. [29], who demonstrated that ongoing 'persistent inflammation' may be detected in the airways of typically asthmatic children (such as our persistent wheezers) even when asymptomatic. This may explain our findings that by 10 years persistent wheezers display the lowest FEV₁ and FEV₁/FVC ratio, whilst late-onset wheezers showed relatively normal lung function.

The BTS guidelines for management of asthma propose a stepwise approach to treatment of this condition [30]. Using this approach, persistent wheezers showed highest prevalence of treatment indicating more serious disease like regular inhaled corticosteroids, multiple prophylactic medications and oral corticosteroids. Intermediary requirements for such therapy were noted in late-onset wheezers, with lowest levels in early transient wheezers. The increased reliance of persistent and late-onset wheezers on anti-inflammatory treatment suggests a similar inflammatory aetiology for these phenotypes. That both persistent and late-onset wheezers with higher levels of bronchial hyper-responsiveness had higher prevalence of needing oral corticosteroid for disease control tends to confirm this notion. Whilst many indicators of overall disease morbidity were significantly greater for persistent than late-onset wheezers this trend was not confirmed for indicators of current morbidity at 10 years (with the exception of nocturnal disturbance). This similarity in current morbidity between persistent and late-onset wheezers is consistent with the theory that wheezing duration has a bearing on morbidity; by 10 years many late-onset wheezers may have begun to develop clinically significant

long-term sequelae of persisting airways inflammation. The potential for future disease in such late-onset wheezers should therefore be a matter of concern.

It is the authors' experience that many parents and physicians still believe the infant wheezer ultimately outgrows their illness and experiences no long-term consequences of their disease. This belief may explain worrying observations from NHANES III 1988–94 [19] revealing low uptake of maintenance therapy in children with moderate to severe asthma. Our findings demonstrate that this perception of early life wheezing is a misnomer. By allowing such attitudes to persist are we missing an opportunity to reduce the morbidity of childhood wheezing? Could early identification and intervention in children destined to wheeze persistently from early life interrupt their disease propagation and substantially lower the considerable morbidity and burden on healthcare resources that we have identified in association with such disease? This may seem an attractive proposition but it is worth noting that by 10 years, the 37% of early life wheezers we identified to have persistent disease still possessed higher BHR and lower lung function than non-wheezers despite high usage of inhaled corticosteroids and other prophylactic measures. Thus whether currently available treatment truly influences the course of persistent wheezing or whether new alternative approaches are needed remains to be seen.

Acknowledgements

The authors gratefully 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). We also note the valued contributions of Linda Terry, Gail Poulton, Heidi Savory, Tessa Booth, Andrew Gallini, Cathy Wilby, Rosemary Lisseter and Roger Twiselton to the 10-year follow-up of this study. Finally we would like to highlight the role of the late Dr David Hide in conceiving this study.

References

- Smith JM, Harding LK, Cumming G. The changing prevalence of asthma in school children. *Clin Allergy* 1971; 1:57–61.
- Smith JM. The prevalence of asthma and wheezing in children. *Br J Dis Chest* 1976; 70:73–7.
- Park ES, Golding J, Carswell F, Stewart-Brown S. Preschool wheezing and prognosis at 10. *Arch Dis Child* 1986; 61:642–6.
- Lee DA, Winslow NR, Speight ANP, Hey EN. Prevalence and spectrum of asthma in childhood. *BMJ* 1983; 286:1256–8.
- Shamssain MH, Shamsian N. Prevalence and severity of asthma, rhinitis, and atopic eczema: the north east study. *Arch Dis Child* 1999; 81:313–7.
- Kaur B, Anderson HR, Austin J et al. Prevalence of asthma symptoms, diagnosis, and treatment in 12–14 year old children across Great Britain. (international study of asthma and allergies in childhood, ISAAC UK) *BMJ* 1998; 316:118–24.
- Fleming DM, Crombie DL. Prevalence of asthma and hayfever in England and Wales. *BMJ* 1987; 294:279–83.
- Anderson HR. Is the prevalence of asthma changing? *Arch Dis Child* 1989; 64:172–5.
- Burney PGJ, Chinn S, Rona RJ. Has the prevalence of asthma increased in children? Evidence from the national study of health and growth 1973–86. *BMJ* 1990; 300:1306–10.
- Anderson HR. Increase in hospital admissions for childhood asthma: trends in referral, severity, and readmissions from 1970 to 1985 in a health region of the United Kingdom. *Thorax* 1989; 44 (8):614–9.
- Jonasson G, Carlsen KH, Lodrup Carlsen KC, Mowinckel P, Leegard J, Halvorsen KS. Trends in hospital admissions for childhood asthma in Oslo, Norway, 1980–95. *Allergy* 2000; 55:232–9.
- Fleming DM, Sunderland R, Cross KW, Ross AM. Declining incidence of episodes of asthma: a study of trends in new episodes presenting to general practitioners in the period 1989–98. *Thorax* 2000; 55:657–61.
- Risk Factors. Global Initiative for Asthma; Global Strategy for Asthma Management and Prevention NHLBI/WHO Workshop Report. Publication number 95–3659. Bethesda: National Institutes of Health, 1995.
- Taylor WR, Newacheck PW. Impact of childhood asthma on health. *Pediatrics* 1992; 90:657–62.
- Martinez FD, Helms PJ. Types of asthma and wheezing. *Eur Respir J* 1998; 12 (Suppl. 27):3s–8s.
- Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995; 332:133–8.
- Stein RT, Holberg CJ, Morgan WJ et al. Peak flow variability, methacholine responsiveness and atopy as markers for detecting different wheezing phenotypes in childhood. *Thorax* 1997; 52:946–52.
- Grol MH, Gerritsen J, Postma DS. Asthma: from childhood to adulthood. *Allergy* 1996; 51:855–69.
- Halterman JS, Aligné CA, Auinger P, McBride JT, Szilagyi PG. Inadequate therapy for asthma among children in the United States. *Pediatrics* 2000; 105:272–6.
- 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, Stevens M, Arshad SH, Hide DW. 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, Matthews S, Arshad SH. The prevalence of asthma and wheezing illnesses amongst 10-year old schoolchildren. *Respiratory Med* 2002; 96:162–9.
- ISAAC. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema. *Lancet* 1998; 351:1225–32.
- ATS guidelines for exercise and methacholine challenge testing. *Am J Respir Crit Care Med* 2000; 161:309–29.
- Chinn S, Burney P, Sunyer J, Jarvis D, Luczynska C. Sensitization to individual allergens and bronchial responsiveness in the ECRHS. *Eur Respir J* 1999; 14:876–84.
- Brooke AM, Lambert PC, Burton PR, Clarke C, Luyt DK, Simpson H. The natural history of respiratory symptoms in preschool children. *Am J Respir Crit Care Med* 1995; 152:1872–8.
- Zeiger RS, Dawson C, Weiss S. Relationships between duration of asthma and asthma severity among children in the Childhood Asthma Management Program (CAMP). *J Allergy Clin Immunol* 1999; 103:376–87.
- Stevenson EC, Turner G, Heaney LG et al. Bronchoalveolar lavage findings suggest two different forms of childhood asthma. *Clin Exp Allergy* 1997; 27:1027–35.
- The British Thoracic Society. The British guidelines on asthma management: 1995 review and position statement. *Thorax* 1997; 52 (Suppl. 1):S1–2.