

## Original article

## Predictors of response to bronchial allergen challenge in 5- to 6-year-old atopic children

**Background:** The relationship between atopy and bronchial allergy in young children is not completely understood.

**Objective:** To examine the association between response to bronchial allergen challenge, immune markers of atopy and other clinical characteristics in 5- to 6-year-old children.

**Methods:** Children with positive skin test (SPT) to aeroallergen, together with a proportion of SPT negative children (as controls), were recruited from a birth cohort of 198 children at high risk of developing atopic disease and underwent allergen challenge.

**Results:** Thirty-seven children (26 atopic and 11 SPT negative), median age 74.5 months, were challenged: 31 with house dust mite and six with grass allergen. Only atopic children responded to challenge:  $n = 12/26$  (46%). Wheal size [odds ratio (OR) 2.5 (1.2–5.3),  $P = 0.01$ ], allergen-specific immunoglobulin E (IgE) [OR 3.4 (1.23–9.61),  $P = 0.02$ ], total IgE [OR 8.6 (1.1–68.7),  $P = 0.04$ ], current wheeze [OR 12 (1.7–81.7),  $P = 0.006$ ] and persistent eczema [OR 11.0 (1.7–68.3),  $P = 0.006$ ] emerged as the strongest independent predictors of response to allergen challenge. Prediction of response to allergen challenge was significantly improved when immune markers of atopy, and in particular wheal size, were combined with clinical characteristics.

**Conclusion:** The relationship between atopy and bronchial allergy is quantitative at this age. There may be potential to create more powerful indicators of the presence of respiratory allergy in young children when immunological markers of atopy are considered quantitatively and when combined with clinical history of coexistent allergic disease.

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Key words: allergens; asthma; atopy; bronchial allergen challenge; childhood eczema; immunologic tests; paediatric; wheeze.

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Bronchial allergen challenge is predominantly a research tool used to examine the patho-physiological events associated with allergen exposure in the airways (1–5) and which may be rarely employed to confirm bronchial sensitization to a specific allergen in symptomatic individuals with a suggestive clinical history (6). A positive response to bronchial allergen challenge, defined by a fall in forced expiratory volume in one second (FEV<sub>1</sub>), is considered indicative of the presence of 'bronchial allergy' in the individual.

It is well recognized that response to bronchial allergen challenge in adults and older children with asthma may be predicted to varying extent by the degree of sensi-

zation expressed as wheal size or circulating immunoglobulin E (IgE) levels (6–13).

However, the relationship between bronchial allergy and atopy in young children remains poorly understood. In particular, there are currently no studies that explore the relationship between bronchial allergy and immune markers of atopy or clinical characteristics in young children in whom the diagnosis of atopic asthma has not been established, and whose wheeze prognosis is uncertain.

The aim of this study was to examine the relationship between response to bronchial allergen challenge, intensity of atopic sensitization and presence of other clinical characteristics traditionally associated with allergic disease in a group of 5- to 6-year-old atopic children deemed at high risk of developing asthma and allergy.

## Methods

### Subjects

Subjects for the present study were recruited from a highly characterized birth cohort of 198 children at high risk of developing

**Abbreviations:** AR, allergic rhino-conjunctivitis; CI, confidence interval; Der P 1, dermatophagoides pteronyssinus antigen; EAR, early asthmatic response; FEV<sub>1</sub>, forced expiratory volume in one second; HDM, house dust mite; IgE, immunoglobulin E; LAR, late asthmatic response; OR, odds ratio; PC<sub>20</sub>FEV<sub>1</sub>, provocation concentration of allergen causing a 20% fall in FEV<sub>1</sub>; SD, standard deviation; SPT, skin prick test.

atopic disease based on the presence of positive skin prick test (SPT) and history of atopic disease in one or both parents. Characteristics of this cohort have been published elsewhere (14). Briefly, these children were followed prospectively for 5 years with atopic status, infectious and clinical history assessed annually. Skin prick tests and serum IgE levels to a panel of allergens were performed at 6 months, 2 and 5 years. Lung function was measured at 5 years with spirometry. Those children with positive SPTs to a panel of environmental aeroallergens at 5 years of age were invited to undergo bronchial allergen challenge. A control group of children with negative SPTs to the panel of aeroallergens was randomly recruited from the birth cohort to undergo challenge and ensure positive reactions to challenge were attributable to atopic expression in the airways and not to nonspecific bronchial reactions. Exclusion criteria included: poorly controlled or severe asthma; asthma exacerbation requiring oral prednisolone within the past 6 months; a history of anaphylaxis on allergen exposure; immunodeficiency; inability to cooperate with the study; inability to perform acceptable and reproducible spirometry approaching American Thoracic Society (ATS) standards (15).

### Study design

A home visit was conducted prior to challenge to train each child in spirometry and assess eligibility for entry into the study based on ability to produce acceptable and reproducible spirometry approaching ATS standards (15). Skin prick testing to a panel of aeroallergens was repeated and wheal sizes recorded. Children underwent bronchial challenge with the allergen that produced the largest wheal size. All SPT negative (control) children were challenged with house dust mite (HDM). All challenges were performed at Princess Margaret Hospital for Children, Perth under the supervision of an experienced paediatrician with facilities for resuscitation and overnight admission. Children were free from respiratory tract infection for 6 weeks prior to challenge and all grass challenges were performed out of the pollen season (September–December). Medications likely to affect the results of the challenge test were withheld as follows: short-acting  $\beta_2$  agonist 12 h; long-acting  $\beta_2$  agonist 24 h; short-acting antihistamines 48 h; long-acting antihistamines 96 h; leukotriene receptor antagonist 2 weeks. Steroid inhalers were not withheld. All challenges commenced between 08:30 and 09:00 hours and children were supervised with serial lung function measurements for up to 8 h after completion of challenge. Following 8 h of observation postallergen challenge children were discharged home providing the child was asymptomatic and lung function was  $>85\%$  of baseline measurements. Parents received detailed instruction (as required) regarding the use of inhaled bronchodilator therapy in the event of nocturnal symptoms and the research doctor was available on call overnight. Each child was visited the following morning 24-h postchallenge for clinical review and measurement of lung function. The Human Research Ethics Committee of Princess Margaret Hospital for Children approved the study protocol and parents gave written consent for the study.

### Allergen extracts and skin prick testing

Commercial preparations (Hollister Stier Laboratories LLC, Toronto, ON, Canada) of the following allergens in 5% glycerine were used for skin testing: Dermatophagoides pteronyssinus (Der p 1) 30 000 BAU/ml; Cat pelt 10 000 Au/ml; Grass mix #7 10 000 Au/ml; Bermuda 10 000 Au/ml; Johnson grass 1 : 20 w/v; Perennial rye 10 000 Au/ml. The grasses were chosen to reflect local flora. The skin was gently perforated to the epidermis using a 1-mm stylus and

wheal size measured at 15 min. Mean wheal size was calculated using the longest diameter of wheal and its perpendicular diameter. Histamine phosphate 10 mg/ml and diluent were used as positive and negative controls, respectively. A mean wheal diameter of  $\geq 3$  mm was taken as a positive reaction. The allergen resulting in the largest wheal size was chosen for bronchial allergen challenge. House dust mite was chosen as the allergen for challenge in the nonatopic control group with the rationale that the Perth climate ensures almost universal exposure.

### Determination of total IgE and allergen-specific IgE levels

Blood samples obtained at age 5 years were analysed. Total IgE and allergen-specific IgE (HDM and Grass where appropriate) were assayed by fluoroenzyme immunoassay on a Pharmacia UniCAP 100 instrument (Pharmacia Biotech, Uppsala, Sweden) as per manufacturer's instructions.

### Bronchial allergen challenge

A standardized protocol (4, 16) was modified to accommodate a paediatric cohort. The allergen extract chosen was serially diluted in phosphate buffered saline (PBS) to create doubling concentrations of allergen solutions from  $1 \times 10^6$  dilution to a maximum concentration of  $1 \times 10^2$  (16). The starting concentration of inhaled allergen was determined by skin testing with the allergen dilutions and choosing the next doubling concentration below that which caused a 3-mm wheal (4). Allergen solutions were delivered via a Pari LC Plus (Hudson RCI, Temecula, CA, USA) jet nebulizer and inhaled through a disposable inhalation circuit with unidirectional valves and expiratory aerosol filter. The mean nebulizer output was calculated as 0.26 ml/min with a mean particle size of 6.56  $\mu$ m using 4 l/min oxygen. All spirometry for the study was performed using a handheld Welch Allyn Pneumocheck (WA Inc., Rydalmere, Australia). Baseline spirometry was performed on the morning of the challenge. Prior to allergen challenge each child inhaled a control solution of PBS to exclude the possibility of airway reactivity to the diluent. Allergens were delivered as 2-ml solutions inhaled during tidal breathing through a mouthpiece with nose clip *in situ*, and spirometry performed at 15-min postinhalation. The cycle was repeated with incremental doubling concentrations of allergen until reaction to challenge or maximum concentration reached. A positive early asthmatic response (EAR) was defined as a fall in FEV<sub>1</sub> of 20% from baseline immediately, or within the first 2 h, postchallenge and a late asthmatic response (LAR) defined as a fall in FEV<sub>1</sub> of 20% between 3 and 12-h postchallenge (4). Spirometry was performed at 30 min, 1 h and hourly for 7–8 h and at 24 h following challenge. Any early or late reactions to challenge were treated with Salbutamol.

### Statistical analysis

Individual results for the bronchial allergen challenges were classified as a positive or negative response. Associations between baseline characteristics and response to allergen challenge were analysed using chi-squared tests for independence for categorical variables and the Mann–Whitney *U*-test for numeric variables. Associations between clinical characteristics, immune markers of atopy (wheal size, total and specific IgE levels) and response to allergen challenge were respectively determined by logistic and linear regression for binary and quantitative responses. Results were expressed as unadjusted odds ratios, 95% confidence intervals (CI) and squared Pearson's correlation coefficients. Immune markers significantly

associated with response to allergen challenge were assessed for their potential as diagnostic indicators. Receiver operating characteristic (ROC) curves were used to characterize the sensitivity and specificity of continuous immune markers with cut points chosen to maximize the sum of sensitivity and specificity. To determine whether immune markers could improve the prediction of response to challenge achievable from clinical characteristics, we compared logistic regression models with a clinical characteristic and immune marker as predictor variables to a model with the clinical characteristic as the sole predictor variable. Models were compared using the likelihood ratio chi-squared test. Data analyses were performed using Statistical Package for the Social Sciences (SPSS version 11.5; SPSS Inc., Chicago, IL, USA) and STATA (8.2; Stata Corp., TX, USA). *P*-values  $\leq 0.05$  were considered statistically significant.

## Results

There were 69/198 (34.8%) children from the original longitudinal birth cohort who had positive skin tests to aeroallergen at age 5 years. The parents of 33 atopic children together with 15 parents of skin test negative children gave verbal consent for their child to participate in the study. A total of 37 children (26 atopics and 11 SPT negative controls) were able to produce technically acceptable spirometry and underwent allergen challenge.

Thirty-one children were challenged with HDM (Der P 1) and six with grass (Bermuda *n* = 3, Rye grass *n* = 3). The starting concentration of Der P 1 for inhalation (determined by skin test titration) was 12 Au/ml in six subjects and 60 Au/ml in 13 subjects. One sensitive individual commenced challenge at 1.2 Au/ml. The starting concentrations of the grass challenges were 20 Au/ml in four subjects and 4 Au/ml in the remaining two subjects. All children in the SPT negative group commenced inhalational challenge with Der P 1 at a concentration of 60 Au/ml.

No child reacted to the placebo PBS solution inhalation. No child in the SPT negative control group responded to allergen challenge. All challenges were well tolerated with only mild symptoms experienced by participants during the period of in-hospital observation and at home overnight. Early asthmatic responses

responded promptly to inhaled bronchodilator with complete resolution of lung function deficits and symptoms. Satisfactory symptom control was achieved with inhaled bronchodilator during the LARs, although in many the lung function deficits were not completely corrected and mild symptoms tended to recur. No adverse events or overnight hospital admissions occurred.

The median age of children in the atopic group was 68.8 months (interquartile range 64.2–77.9) and was slightly younger than the skin test negative group [median 77.9 (76.6–82.4) months]. Males represented just over half of the cohort (57%). Fourteen children (*n* = 12 atopic and *n* = 2 SPT negative) had used inhaled bronchodilator therapy for wheezing during the 12 months prior to bronchial challenge and two children in the atopic group had used inhaled corticosteroids ever.

Positive response to bronchial challenge was observed in 12/26 (46%) atopic children (Der P 1 = 10, Grass = 2). Both early and late responses were observed in all 12 positive responders. Three (25%) children who responded also experienced exacerbation of eczema within 72-h postchallenge. Positive and negative responders did not differ significantly on any of the measured demographic characteristics (Table 1). In contrast, certain clinical characteristics and immune markers of atopy were significantly associated with response to challenge (Table 2). Positive responders had larger mean skin wheal size and higher log serum total IgE and allergen-specific IgE levels than the nonresponders.

Table 1. Characteristics of positive responders to challenge compared with non-responders amongst the atopic group only *n* = 26

|              | Response to challenge  |                        | <i>P</i> -value |
|--------------|------------------------|------------------------|-----------------|
|              | Positive <i>n</i> = 12 | Negative <i>n</i> = 14 |                 |
| Age (months) | 68.3 (64.2–76.2)       | 68.8 (64.2–79.3)       | 0.9             |
| Males (%)    | 8 (67)                 | 6 (43)                 | 0.27            |
| Height (cm)  | 114.1 (113–121.6)      | 118.9 (113–122.7)      | 0.4             |
| Weight (kg)  | 20.9 (18.5–24.1)       | 22.4 (20.3–25.9)       | 0.3             |

Data are expressed as median and (interquartile range) unless otherwise stated.

Table 2. Unadjusted OR for characteristics predicting a positive response to bronchial allergen challenge in the atopic group *n* = 26

|                                  | Response to challenge      |                            | OR (95% CI)     | <i>P</i> -value |
|----------------------------------|----------------------------|----------------------------|-----------------|-----------------|
|                                  | Positive <i>n</i> = 12 (%) | Negative <i>n</i> = 14 (%) |                 |                 |
| Atopy at 2 years                 | 7 (58)                     | 2 (14)                     | 0.9 (0.18–4.56) | 0.9             |
| Mean wheal size mm (SD)          | 6.0 (2.3)                  | 3.4 (1.1)                  | 2.5 (1.2–5.3)   | 0.01            |
| Log serum IgE*                   | 2.3 (1.8–3.2)              | 1.8 (1.2–2.1)              | 8.6 (1.1–68.7)  | 0.04            |
| Log serum allergen-specific IgE* | 1.3 (0.9–1.7)              | –0.2 (–0.7–0.4)            | 3.4 (1.23–9.61) | 0.02            |
| % Predicted FEV <sub>1</sub>     | 97.3 (85.9–103.5)          | 104.1 (88.2–122.3)         | 0.9 (0.9–1.0)   | 0.06            |
| Current wheeze                   | 8 (62)                     | 2 (14)                     | 12 (1.7–81.7)   | 0.006           |
| AR                               | 9 (64)                     | 5 (36)                     | 5.4 (0.9–29.7)  | 0.04            |
| Persistent eczema                | 9 (75)                     | 3 (21)                     | 11 (1.7–68.3)   | 0.006           |
| Transient eczema                 | 2 (17)                     | 6 (43)                     | 0.3 (0.04–1.7)  | 0.2             |

OR, odds ratio; CI, confidence interval; FEV<sub>1</sub>, forced expiratory volume in one second; IgE, immunoglobulin E; SD, standard deviation; AR, allergic rhino-conjunctivitis.

\*Median (interquartile range).

Clinical characteristics that independently predicted a positive response to challenge were current wheeze (wheezing episodes within the previous 12 months), allergic rhino-conjunctivitis (AR) and a history of persistent eczema (present in at least three out of 5 years of the study). There was also a trend towards lower baseline spirometry for positive compared with negative responders.

Areas under the ROC curve for detecting positive response to challenge were large for mean wheal size [ROC area 0.85; 95% CI (0.65–0.96)], total IgE [ROC area 0.77 (0.53–0.90)] and allergen-specific IgE [ROC area 0.79 (0.58–0.93)]. Cut-points that maximized the sum of sensitivity and specificity were a mean wheal size of  $\geq 4.5$  mm [sensitivity 0.75, 95% CI (0.58–0.92); specificity 0.86 (0.72–0.99)] and an allergen-specific IgE level of  $\geq 5.1$  KU/l [sensitivity 0.82 (0.66–0.97); specificity 0.85 (0.70–0.99)]. Positive and negative predictive values for wheal size were, respectively, 0.82 (95% CI 0.67–0.97) and 0.80 (0.65–0.95). Corresponding values for allergen-specific IgE were 0.82 (0.66–0.97) and 0.85 (0.70–0.99). It was not possible to identify a cut off value for total IgE. For the three clinical characteristics significantly associated with response to challenge (persistent eczema, current wheeze, allergic rhinitis), each immune marker (continuous versions; log transformed total and allergen-specific IgE) was separately added to a logistic regression model with the clinical characteristic to determine whether any of the immune markers could enhance prediction of response to challenge. All three immune markers significantly improved prediction of response to challenge from persistent eczema (all  $P \leq 0.02$ ), current wheeze (all  $P \leq 0.01$ ), and allergic rhinitis (all  $P \leq 0.005$ ). For each clinical characteristic, the value of the likelihood ratio chi-squared test was larger for models with wheal size as the immune marker, indicating that this marker improved prediction at least somewhat more than total or allergen-specific IgE.

Amongst the group of 12 positive responders to challenge response to bronchial allergen challenge was also considered quantitatively in terms of the degree of airway responsiveness [expressed as the provocation concentration of allergen causing a 20% fall in FEV<sub>1</sub> (PC<sub>20</sub>FEV<sub>1</sub>)] and the magnitude of the EAR and LAR. The magnitude of the EAR was defined as the maximum % fall in FEV<sub>1</sub> within the first 2-h postchallenge, and the magnitude of the LAR defined as the maximum fall in FEV<sub>1</sub> during the 8 h of serial lung function measurement.

The PC<sub>20</sub>FEV<sub>1</sub> was determined by linear interpolation of the last two points of the concentration-response curve. The median (25–75th centile) PC<sub>20</sub>FEV<sub>1</sub> was 102.9 Au/ml (69.7–347.1), range 5.9–490.7 Au/ml. The PC<sub>20</sub>FEV<sub>1</sub> predicted the magnitude of the EAR ( $r^2 = 0.40$ ,  $P = 0.03$ ), but not the magnitude of the LAR ( $r^2 = 0.002$ ). Whilst wheal size weakly predicted the PC<sub>20</sub>FEV<sub>1</sub> ( $r^2 = 0.20$ ) none of the remaining clinical or

immune variables predicted the PC<sub>20</sub>FEV<sub>1</sub> amongst the responders (all  $r^2 < 0.09$ ).

Allergen-specific IgE levels predicted the magnitude of the EAR ( $r^2 = 0.6$ ,  $P = 0.007$ ), and mean wheal size ( $r^2 = 0.20$ ,  $P = 0.02$ ) and persistent eczema ( $r^2 = 0.15$ ,  $P = 0.05$ ) predicted the magnitude of the late response. For all other associations between clinical and immune variables and magnitude of the early and late responses,  $r^2 < 0.10$ . The magnitude of the LAR was not significantly associated with the magnitude of the EAR ( $P = 0.9$ ).

## Discussion

This study explored the relationship between atopy and bronchial allergy (defined as response to bronchial allergen challenge to a single aeroallergen) in young atopic children potentially at high risk of developing asthma and clinical allergies. Additionally the values of clinical characteristics including wheeze, eczema and AR, as predictors of bronchial allergy in atopic children were investigated.

The results demonstrate that the relationship between atopy and bronchial allergy is quantitative at age 5–6 years. In this sample of children the odds of responding to bronchial allergen challenge were increased by 2.5 with every 1-mm increase in mean wheal size  $> 3$  mm. Median levels of allergen-specific IgE amongst positive responders to challenge were 30 times higher than atopic nonresponders. Current wheeze and persistent eczema emerged as the strongest independent predictors of response to challenge amongst the clinical characteristics examined.

Given that SPT negative children did not respond to challenge and the PBS diluent as placebo did not elicit bronchial reactivity in any child, one can assume that any positive reactions seen were attributable to airway sensitization to allergen and not nonspecific bronchial reactions.

We identified cut-off values of mean wheal size  $\geq 4.5$  mm and allergen specific IgE  $\geq 5.1$  KU/l above which positive response to challenge was highly likely in this cohort of children at high risk of developing asthma and allergy.

Prediction of response to allergen challenge improved when immune markers were combined with clinical history of current wheeze and persistent eczema. Given the small numbers, however, these results should be interpreted cautiously. Within these limitations, these data demonstrate potential for the development of more powerful indicators of bronchial allergy in individuals when immune markers of atopy (wheal size particularly) are considered quantitatively and when combined with particular clinical characteristics or history.

The proportion of children responding positively to allergen challenge (46%) is lower than reported in studies of older children (13, 17). This may reflect the different

cohort characteristics of this current study in which children were selected simply on the presence of atopy and genetic risk and not on the basis of chronic asthma or clinical suspicion of allergen induced respiratory symptoms, which characterize the cohorts in studies of older children. However, the prevalence of positive response to allergen challenge in atopic children may be influenced by increasing age. Ongoing follow up and repeated bronchial challenges in atopic individuals who did not respond to challenge at 5–6 years would investigate this further.

The results provide some insight into the relationship between eczema and bronchial allergy in early childhood. Children with transient eczema present in only the first 2 years of life were not likely to respond to bronchial allergen challenge at age five despite SPT positivity. Persistent eczema throughout the first 5 years of life, however, was strongly predictive of positive response to challenge and is possibly a clinical indicator of more intense atopy in young children. Three subjects, each with a history of persistent eczema, experienced exacerbation of eczema symptoms following allergen challenge in this study and to our knowledge this has not been reported before in young children. Therefore in children with persistent eczema both cutaneous and wheeze symptoms might be driven by aeroallergen.

The degree of airway responsiveness to allergen inhalation, expressed as the  $PC_{20}FEV_1$ , varied amongst the 12 positive responders to challenge and was weakly predicted by wheal size, but not allergen-specific IgE. In this cohort of young children 20% of the variation in  $PC_{20}FEV_1$  could be explained by wheal size and these observations are similar to reports in adult asthmatics (9, 18) and previous studies that have demonstrated the ability to partially predict the  $PC_{20}FEV_1$  on the basis of skin test sensitivity (8). The results suggest that, as observed in adult asthmatics (9), other factors such as nonspecific airway responsiveness may be stronger determinants of the  $PC_{20}FEV_1$  in atopic children at 5–6 years. Whilst it is possible that wheal size better predicts the  $PC_{20}FEV_1$  than does allergen-specific IgE in young atopic children, a larger study is required to obtain a more definitive answer to this question.

The  $PC_{20}FEV_1$  correlated reasonably strongly with the magnitude of the EAR in this group of children. Those responding to lower concentrations of allergen tended to have larger early responses and it is possible that these subjects have higher local concentrations of allergen-specific IgE in the airway (19).

Both wheal size and allergen-specific IgE levels have been shown to predict the magnitude of the early and late response following allergen challenge in adults (9, 11, 20). The magnitude of the early and late asthmatic reaction amongst positive responders in this current cohort was associated with the intensity of atopy. Allergen-specific IgE levels were significantly associated with the magnitude of the early response but not the late response and *vice versa* for wheal size. Whilst markers of atopy may

have value as indicators of the likely magnitude of response to allergen challenge in young atopic children, this requires further investigation in a larger study. Consistent with previous reports in adult patients we did not observe an association between the magnitude of the EAR and magnitude of the subsequent LAR in young children (21).

In contrast to the immune markers of atopy there did not appear to be any significant associations between the presence of clinical characteristics and the magnitude of response to challenge in young children, other than persistent eczema which was only associated with the magnitude of the late response.

Early onset atopy and lung function did not emerge as significant predictors of bronchial allergy in this cohort. However, there were trends towards lower baseline  $FEV_1$  in those who responded to challenge. It is likely that the study was underpowered to detect these differences.

The relationship between response to bronchial allergen challenge and larger wheal size, or allergen-specific IgE levels, has been described in adults (7, 8, 11, 12) and older children with asthma (6, 10, 13). Cavanaugh et al. (6) observed more than 90% of positive responders to allergen challenge had wheal diameters  $\geq 5$  mm. Children in that study were older chronic asthmatics, skin testing was performed on the backs of participants and positive response to challenge was determined by changes in peak expiratory flow rate with only early responses investigated. None of these previous studies provides insight into the value of clinical characteristics or immune markers of atopy as markers of bronchial allergy in young atopic children in whom the diagnosis of atopic asthma is not established and whose wheeze prognosis is uncertain.

The quantitative relationship between wheal size or IgE level and bronchial allergy is paralleled in epidemiological studies of childhood asthma. Sears et al. (22) found a clear relationship between wheal size and risk of asthma in 13-year-old children, with asthma present in over 50% of those children with a wheal size  $> 8$  mm. Larger wheal size and more intense atopy has been associated with increasing severity of asthma in older children (23), persistence of asthma at puberty (24) and current asthma in atopic children at age 6 years (25).

Whilst it is acknowledged that bronchial allergen challenge may evoke immuno-physiological events similar to those observed in the airways of atopic asthmatics (1–3), and that up to 80% of asthmatic children respond to allergen challenge (13, 17), a positive response to challenge in this study cannot be considered diagnostic or predictive of atopic asthma. Therefore, although it is tempting to speculate that wheal size or allergen-specific IgE levels have potential in the search for simple predictors of atopic asthma, only further longitudinal study of this atopic cohort will determine if this is the case.

There are limitations of this study that need to be acknowledged. The results are based on small numbers of atopic children at high risk of developing allergy and asthma. A larger community study of young children is required to confirm these results and determine if these findings can be generalized. Children were defined as atopic based on response to skin testing with a panel of aeroallergens that was arguably not exhaustive, and these results may not be reproducible using other commercial allergen preparations of different potencies. Because of the demands of this current study in a young cohort we did not assess reproducibility of results in individuals, although reports in the literature confirm response to bronchial allergen challenge is reproducible in children and adults (26–28). The findings of this study may only apply to children at this age, and it is possible that the values of wheal size, allergen-specific IgE and clinical variables identified in this current study as indicators of bronchial allergy may differ at other ages during childhood.

## Conclusions

In atopic children aged 5–6 years sensitization of the airways to aeroallergen is established in a proportion that

have more intense atopy manifest by larger wheal sizes and higher total and allergen-specific IgE levels. It is possible that more powerful indicators of the presence of sensitization of the airway to allergen in young children may be created when immunological markers of atopy are considered quantitatively and combined with clinical history of coexistent allergic disease. Continued longitudinal follow up of this cohort will ultimately determine whether wheal size or levels of allergen-specific IgE in combination with clinical characteristics such as wheeze or persistent eczema have potential as simple predictors of atopic asthma in childhood.

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