

Serum IgE levels, atopy, and asthma in young adults: results from a longitudinal cohort study

Peat JK, Toelle BG, Dermand J, van den Berg R, Britton WJ, Woolcock AJ. Serum IgE levels, atopy, and asthma in young adults: results from a longitudinal cohort study.

Allergy 1996; 51: 804–810. © Munksgaard 1996.

**J. K. Peat, B. G. Toelle,
J. Dermand, R. van den Berg,
W. J. Britton, A. J. Woolcock**

Respiratory Medicine, Department of Medicine,
University of Sydney, Sydney, Australia

To explore the natural history of asthma and its relation to allergic responses, we examined the relation between total serum IgE in early adulthood and a history of respiratory symptoms, airway hyperresponsiveness (AHR), and atopy during childhood. We studied 180 subjects aged 18–20 years who had been studied since the age of 8–10 years. We measured wheeze in the previous year by questionnaire, AHR by histamine inhalation test, atopy by skin prick tests, and serum IgE levels by immunoassay. Subjects with AHR in early adulthood had higher IgE levels (mean 257.0 IU/ml) than subjects with past AHR (mean 93.3 IU/ml) or with lifelong normal responsiveness (mean 67.6 IU/ml) ($P < 0.001$). Subjects who had symptoms had higher IgE levels (mean 125.9 IU/ml) than those who were lifelong asymptomatic (mean 63.1 IU/ml) ($P < 0.001$). Recent wheeze, AHR, and allergic sensitization all had a positive relation to serum IgE, but IgE was not more predictive of AHR than skin prick tests. The finding that young adults who are sensitized to common allergens are highly likely to have AHR even in the absence of symptoms is further evidence of the fundamental role of IgE-mediated responses in the natural history of AHR throughout childhood and into adulthood.

Key words: adults; airway; asthma; atopy; children; IgE.

Dr Jennifer K. Peat
c/o Professor Ann J. Woolcock
Institute of Respiratory Medicine
Royal Prince Alfred Hospital
Camperdown
Sydney NSW 2050
Australia

Accepted for publication 16 May 1996

For almost two decades, it has been recognized that the antibody immunoglobulin E (IgE) is responsible for allergic responses and that most asthmatic patients have raised serum IgE levels (1). Thus, serum IgE levels are considered to be a marker of the immune response to allergens that results in the development of airway hyperresponsiveness (AHR) (2). Although no relationship between serum IgE levels and AHR was found in early studies (3, 4), a significant dose-response relationship has been demonstrated in recent studies (5, 6). A close relation between atopy as measured by positive skin prick tests, respiratory symptoms, and AHR has been established in several epidemiologic studies (7–11), and it is thought that acquisition of allergy in early life before the immune system has fully developed has a much closer association with asthma continuing in later life than does allergy acquired at a later age (12–14). Most asthmatics

appear to be sensitized to recognized allergens (15–18), and the finding of a small proportion of asthmatics with low IgE levels may occur because some asthma is genuinely of nonallergic aetiology. The finding of some asthmatics with negative skin prick tests but high IgE levels may also occur because a limited number of allergens are used to measure sensitization or because factors other than common allergens, and which are not associated with asthma, can raise IgE levels.

In this paper, we examine the relation between sensitization to common allergens, respiratory symptoms, and AHR in childhood and levels of total serum IgE in a cohort of young adults aged 18–19 years who had been studied up to five times at 2-year intervals during their childhood. We also examine the extent to which serum IgE relates to skin prick test reactions and current respiratory health in early adulthood.

Material and methods

Subjects

In 1982, a large random sample of children aged 8–11 years who lived in Belmont, which is a coastal region south of the city of Newcastle, Australia, was studied (14). All children in school grades 3 and 4 at eight of the 10 primary schools in Belmont were asked to participate; the two schools omitted had fewer than 30 children in the appropriate grades. At this initial study, the consent rate was 88%, and 718 children were studied. Each second year thereafter until 1992, every effort was made to contact and study each subject. All studies were conducted in the winter months of June and July. Ethical approval for the studies was obtained from the New South Wales Department of Education and the Human Ethics Committee of the University of Sydney.

Respiratory symptoms and interviews

From 1982 to 1988, a self-administered questionnaire to parents was used to measure symptom history. In 1990 and in 1992, the questionnaire was self-administered. Standard items in all studies asked whether the subject had ever had wheeze, exercise wheeze, or night cough; had ever used any medication for asthma; or had ever had asthma diagnosed by a doctor. Further questions asked whether the symptoms or medication use had occurred in the previous 12 months. Symptoms of wheeze or exercise wheeze in the 12 months before the study were defined as "recent wheeze".

Lung function and airway responsiveness

A histamine inhalation challenge test was administered by the rapid method (19). In 1990 and 1992, lung function was recorded by Mijnhardt rolling seal spirometers (Mijnhardt BV, Bunnik, The Netherlands) connected to IBM-PC computers running scientific and medical software for immediate data acquisition. From 1982 to 1988, Vitalograph spirometers (Vitalograph Ltd, Buckingham, UK) were used and tracings read manually. Forced expiratory manoeuvres were repeated until two readings of forced expiratory volume in 1 s (FEV₁) and forced vital capacity (FVC) within 100 ml were obtained, of which the largest value was used in analyses. Subjects who had taken a β -agonist within 6 h of presenting were asked to withhold medication before returning for later testing. Histamine was administered by De Vilbiss hand-held nebulizers in doses ranging from 0.03 to 7.8 μ mol histamine at all studies except in 1992 when the final dose was 3.9 μ mol. The test was stopped if the FEV₁ fell by

20% or more or if all dose steps had been administered. If the FEV₁ fell by 10% or more, 200 mg salbutamol aerosol was given to aid recovery. Percent fall in FEV₁ was plotted against the logarithm of the dose administered, and, for subjects whose FEV₁ fell by 20% or more, the dose of histamine that caused a 20% fall (PD₂₀FEV₁) was estimated.

Subjects with a PD₂₀FEV₁ of less than 3.9 μ mol were classified as having AHR. Subjects with both recent wheeze and AHR (or abnormal resting lung function and a positive bronchodilator response) were classified as having "current asthma" because this label identifies the group with the most severe impairment in terms of physiologic characteristics (20). In 1992, the dose-response ratio (DRR) was calculated for all subjects as the percent fall in FEV₁ at the last dose, divided by the total dose administered (21). A constant of 3 was added to all DRR values in order to obtain a positive, normally distributed value for logarithmic conversion (22) so that values are indicated by units:

$$\% \text{fall FEV}_1 / \mu\text{mol} + 3$$

Atopy and serum IgE levels

Skin prick test reactions on the forearm to eight common allergens were measured (23). The allergens tested were *Dermatophagoides farinae* and *D. pteronyssinus*, house dust, cat dander, cockroach, ryegrass, plantain, and *Alternaria tenuis* (Hollister-Stier). Histamine and glycerol were used as positive and negative controls. Wheal size was recorded as the long axis and its perpendicular; mean wheal size was used in analyses. A wheal of 3 mm or greater was regarded as positive for the studies in 1982 and 1984. In the studies from 1986 to 1992, a wheal of 4 mm was used as the criterion for positivity in accordance with the current practice of using different cutoff points at different ages. Subjects were considered atopic if they had a positive reaction to any of the tested allergens.

Total serum IgE

Total serum IgE was measured by a noncompetitive, two-site radioimmunoassay, the Quanticlone IgE method being used according to the manufacturer's instructions (24).

Statistical methods

Data were analysed by the statistical package SAS (SAS Institute, Inc., Cary, NC, USA). Geometric mean values are reported for serum IgE and DRR values, which were converted to base 10 logarithms

before analyses. For all analyses, *P* values greater than 0.05 were regarded as nonsignificant (NS). Prevalence rates and mean values are reported with 95% confidence intervals (95% CI). Chi-square tests were used to determine the significance of differences in categorical variables.

Results

A total of 407 of 718 subjects who attended the initial study in 1982 were also subjects at the final study in 1992. Of these 407 subjects, 180 volunteered to have blood taken so that total serum IgE level could be measured. These 180 subjects represented 44% of the sample in the final study in 1992 and 25% of the sample in the initial study in 1982. The subjects were aged 8–10 years when first studied in 1982 and 18–20 years when studied in 1992. The percentage of the 180 study subjects who had atopy, AHR, and respiratory symptoms in each study is shown in Table 1. As expected, the number of subjects with atopy and with indicators of asthma increased over the 10-year period as the subjects grew out of childhood into adulthood.

Serum IgE level reflected allergic history. There were 75 subjects who were atopic when first studied at age 8–10 years (early atopy), 35 who were first recorded as being atopic in a later study (late atopy), and 69 with negative skin tests throughout (nonatopic). One subject with an IgE level of 45 900 IU/ml was omitted from analyses although this result was checked and was repeated. The mean IgE level in the group with early atopy was 138.0 IU/ml (95% CI 96.8, 197.0), which was not significantly different from the group with late atopy in whom the mean IgE level was 113.8 IU/ml (95% CI 70.0, 185.5). The nonatopic group had a mean serum IgE level of 45.9 IU/ml (95% CI 33.0, 64.0), which was significantly lower than in the other two atopic groups. This difference between groups was significant at the $P < 0.001$ level ($F = 10.5$; $df = 2, 177$). In all three groups, many

subjects had IgE levels above 300 IU/ml, which is considered to be in the high range (5, 6). The five subjects with IgE levels above 1000 IU/ml were all atopic at the age of 8–10 years.

There were 28 subjects who had AHR in the final study in 1992, 18 subjects with normal responsiveness in 1992 but who had AHR in a previous study, and 133 subjects with normal airway responsiveness in all studies. Analysis of variance showed a significant difference in mean IgE levels between these three groups ($F = 9.53$; $df = 2, 177$, $P < 0.001$). The mean IgE level in the group with AHR in 1992 was 257.0 IU/ml (95% CI 109.8, 602.0) compared to 93.3 IU/ml (95% CI 48.8, 178.6) in the group with AHR at an earlier study and 67.6 IU/ml (95% CI 53.0, 86.2) in the group who had never had AHR.

Fig. 1 shows that the prevalence of AHR increased with increasing serum IgE level ($P < 0.001$). The prevalence of AHR was highest in subjects with serum levels above 320 IU/ml. When subjects with AHR or with a serum IgE level above 320 IU/ml were stratified by sex, no significant differences were found. In the final study, 20.5% of males had a serum IgE level above 320 IU/ml compared with 19% of females. Although there was a difference in the prevalence of AHR between sexes in the final study (23.8% of males compared to 12.0% of females), this was not statistically significant. In the initial study, 12.0% of males had AHR compared to 11.1% of females.

There was a close relation between skin prick test reactions and AHR. The proportion with AHR was 4.6% of those with 3–4-mm wheals to any allergen, 19.4% of those with 5–6-mm wheals, 34.8% of those with 7–8-mm wheals, and 47.1% of those with wheals larger than 8 mm (trend significant at $P < 0.001$). Logistic regression showed that atopy was a significant risk factor for AHR with

Table 1. Age of cohort and percentage (%) of subjects with (%) of atopy, airway hyperresponsiveness, diagnosed asthma, and recent wheeze at initial and final studies. 95% confidence intervals are shown in parentheses

	Initial study in 1982	Final study in 1992
Age	8–10 years	18–20 years
Atopy	41.7 (34.5, 48.9)	52.8 (45.5, 60.1)
Atopic to house-dust mites	22.8 (16.7, 28.9)	42.8 (35.6, 50.0)
Atopic to ryegrass	6.7 (3.1, 10.4)	18.3 (12.7, 24.0)
Atopic to <i>Alternaria</i>	2.8 (0.4, 5.2)	6.7 (3.1, 10.4)
Airway hyperresponsiveness	12.2 (7.4, 17.0)	16.1 (10.7, 21.5)
Diagnosed asthma	12.2 (7.4, 17.0)	21.7 (15.7, 27.7)
Recent wheeze	20.6 (14.7, 26.5)	30.6 (24.3, 37.9)

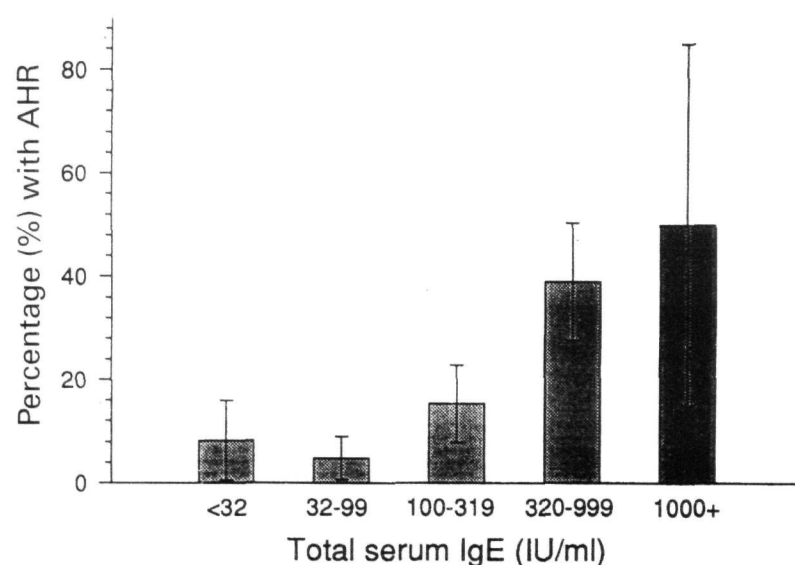


Fig. 1. Prevalence of AHR in subjects divided into groups according to their total serum IgE level in 1992.

an odds ratio of 5.2 (95% CI 1.9, 14.1) and that a serum IgE level above 200 IU/ml was equally predictive of AHR with an odds ratio of 5.4 (95% CI 2.3, 12.6).

There were 94 subjects who were lifelong asymptomatic and 85 subjects who had a report of cumulative wheeze, recent wheeze, or diagnosed asthma in any study. Subjects who were lifelong asymptomatic had lower serum IgE levels (mean 63.1 IU/ml, 95% CI 47.4, 84.0) than ever symptomatic subjects (mean 125.9 IU/ml, 95% CI 88.7, 178.6) ($P < 0.01$). Fig. 2 shows that AHR increased in subjects with a serum IgE level above 320 IU/ml irrespective of symptomatic history. In both symptom-history groups, there was a significant dose-response relation between the prevalence of AHR and the level of serum IgE; that is, $P < 0.0001$ in the asymptomatic group and $P < 0.01$ in the symptomatic group.

Fig. 3 shows serum IgE levels plotted against skin wheal size to *D. pteronyssinus* allergen, to which 82% of atopic subjects were sensitized. The regression through the plot was significant for both the subjects with AHR ($R = 0.65$, $P < 0.001$) and with no AHR ($R = 0.30$, $P < 0.001$). Many subjects with small skin test reactions of less than 4 mm had high IgE levels, but few subjects with reactions of 6 mm or larger had low IgE levels. At all sizes of skin wheal, the subjects with AHR tended to be those with higher IgE levels.

The relation between serum IgE and dose-response ratio in 1992 is shown in Fig. 4. A dose-response ratio above 9.2% fall $FEV_{1/\mu\text{mol}+3}$ is considered abnormal (22). Most subjects with a low

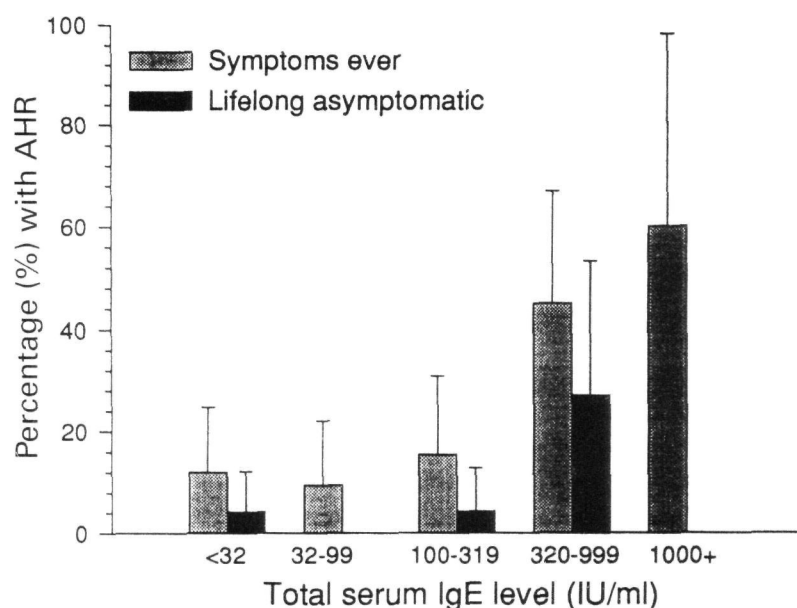


Fig. 2. Prevalence of AHR in subjects divided into groups by respiratory symptom history and into categories according to their total serum IgE level in 1992. Subjects were classified as lifelong asymptomatic if they had no reported history of wheeze or of asthma, and as having symptoms ever if they had report of wheeze or diagnosed asthma at some time in their lives.

serum IgE level had normal responsiveness and most subjects with increased responsiveness had high IgE levels. Subjects with recent wheeze tended to be those with higher IgE levels. There was a significant dose-response relationship between serum IgE and DRR in the symptomatic subjects ($R = 0.37$, $P < 0.001$) and in the asymptomatic subjects ($R = 0.24$, $P < 0.001$).

Discussion

We found that both serum IgE levels and atopy have an important dose-response relationship with AHR in young adults, even in the absence of

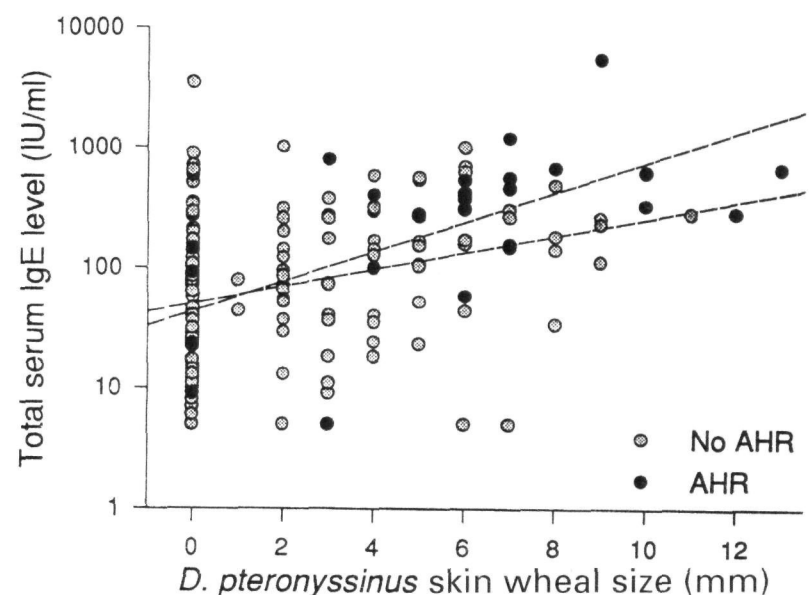


Fig. 3. Relation between total serum IgE level and size of skin wheal reaction to *D. pteronyssinus* in 1992. Dashed lines are regressions through plots of those with AHR when tested at age 18–20 years (upper line) and those with no AHR (lower line).

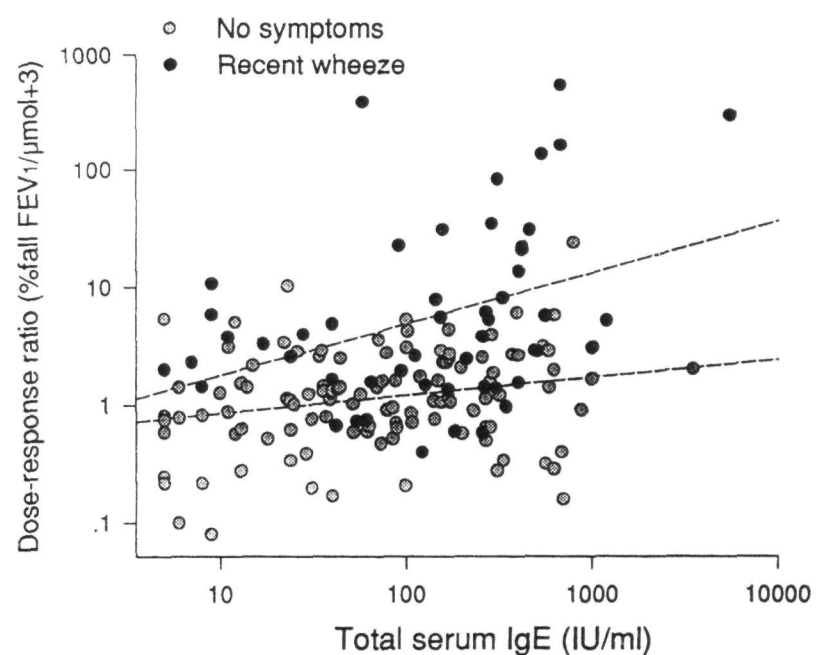


Fig. 4. Relation between serum IgE level and dose-response ratio in 1992. Dashed lines are regressions through plots of those with recent wheeze at age 18–20 years (upper line) and those with no recent wheeze (lower line).

respiratory symptoms, and that subjects with a past history of atopy, AHR, or symptoms had the highest serum IgE levels. We measured serum IgE levels because we thought that they may have predicted AHR more precisely than skin prick tests. However, these measurements were not better predictors because there was a group of subjects with high IgE levels in the absence of atopy, AHR, or symptoms. Because the only five subjects who had AHR and negative skin prick reactions had serum IgE levels below 320 IU/ml, serum IgE levels contributed little extra information in terms of being able to classify correctly "allergic" subjects. From a practical viewpoint, skin prick tests are a more acceptable epidemiologic tool, especially for the study of young people.

Measurements of IgE and of skin prick tests were not always predictive of one another. The finding that not all subjects with high serum IgE levels had positive skin prick tests implies that IgE can be produced in response to an environmental factor other than a common allergen. However, the finding that high IgE levels in the absence of positive skin prick tests are not associated with increased levels of AHR has been reported by other research groups (6). In the current studies, eight allergens were used in the skin prick test panel because an earlier study had showed that addition of another five allergens identified only a further 2% of atopic subjects, a finding which suggests that most atopic subjects develop sensitization to a small number of common allergens (15). An elevated serum IgE level and skin prick test reactions may not develop concurrently. Although sensitization measured by skin prick tests continues to increase into adulthood (25–27), serum IgE levels are thought to peak between 6 and 15 years of age (28). Thus, the subjects in the current study were likely to have serum IgE levels close to their maximum but not to have attained their maximum response to skin prick tests. Serum IgE levels can change by at least twofold over a year depending on allergen exposure (29). Although we conducted our studies in the same season each year (winter), local exposures may have influenced individual serum IgE levels.

Every effort was made to contact all subjects and maintain standardized methods at each of the six studies. At the final study, we were able to test 57% of the original sample, but less than half (25% of the original sample) consented to have blood taken. Although this low consent rate precluded us from making any inferences about the prevalence of the outcome measurements, the sample size provided sufficient statistical power to test hypotheses about the relationships between symptoms, AHR, and allergic status, and there was no reason

to believe that sampling bias would have influenced the findings. Unfortunately, we did not study sufficient numbers for adequate statistical power to examine sex differences in the relationship between atopy and AHR. In 1990, we changed to the use of more modern spirometers to improve accuracy in recording measurements; however, this would not have had a systematic influence on the measurement of AHR, which is expressed as a percentage of baseline FEV₁. The changing of our definition of atopy from a minimum skin wheal of 3 mm in 1982 to 4 mm in 1992, when the cohort was 18–20 years of age, is in accordance with definitions normally used for adults. Despite this change, the definition in both years identified the portion of the sample who had the most severe allergic sensitization.

Only five subjects had AHR in the absence of a positive skin prick test or a raised IgE level, and could therefore be considered to have "intrinsic AHR". In the USA, patients who attend emergency rooms with acute asthma do not always have high IgE levels (2). However, Burrows et al. found that subjects in a large population sample who had low IgE levels did not have symptoms of asthma (6). The contrast in findings may relate to definitions. In Burrows et al.'s study, the definition of asthma as those with recent wheeze apart from colds and who "still had asthma" was likely to categorize a group with current and more severe respiratory illness than the group with AHR in our study who could have been asymptomatic. Nevertheless, both studies support the concept that asthma is almost always associated with some type of IgE response and that intrinsic asthma is a rare condition in children.

We found a strong correlation between serum IgE levels and AHR. Other research groups have also found a close relationship between serum IgE level, AHR, and reduced lung function and that a decreased FEV₁/FVC ratio is only associated with increased AHR when levels of serum IgE are at least moderate (30). This implies that there is an interdependent relation between allergic sensitization, airway narrowing, and AHR. In a study of 562 subjects aged 11 years, Sears et al. concluded that IgE could have a major effect in determining lung function as a result of its relation with AHR (5). Although cause and effect cannot be determined by cross-sectional studies, it is thought that IgE-mediated inflammatory reactions in the airways of young children can lead to AHR and, directly or indirectly, to a reduction in baseline lung function (31). The finding of both this study and a study by Sears et al. (5) that a small number of lifelong asymptomatic subjects have both high IgE levels and AHR, indicating that AHR can be

related to serum IgE level even in the absence of symptoms, suggests that symptoms can be influenced by factors other than the presence of AHR.

Obviously, the airways of subjects with high serum IgE levels and normal airway responsiveness must be protected in some way from the inflammatory effects of IgE-mediated responses to common allergens. Although the relation between allergy and AHR is undoubtedly complex, the dose-response relationship between allergic sensitization, serum IgE levels, and AHR is further evidence that allergens are involved in the development of AHR, probably through IgE-mediated responses. It has been suggested that the ultimate goal of asthma therapy is to switch off the asthmatic process by suppressing IgE production or its effects (32). Because allergic history influences the presence of symptoms and AHR which continue into adulthood, further research is needed to determine the mechanisms which protect some sensitized children from developing AHR and to find ways of preventing susceptible children from developing sensitization and high serum IgE levels in response to the inhalation of common allergens.

Acknowledgments

We thank Allen & Hanburys, the National Health and Medical Research Council of Australia, the Asthma Foundation of New South Wales, and the Community Health and Anti-Tuberculosis Association for funding this project. In addition, we thank all of the subjects and staff who participated in the study; Ms Elena Belousova, who helped to organize the database; and staff of the Department of Clinical Immunology, Royal Prince Alfred Hospital, for performing the IgE assays.

References

- Johansson SGO, Berglund A, Kjellman N-IM. Comparison of IgE values as determined by different solid plate radio-immunoassay methods. *Clin Allergy* 1976;6:91-8.
- Platts-Mills TAE. Mechanisms of bronchial reactivity: the role of immunoglobulin E. *Am Rev Respir Dis* 1993;145:44S-7S.
- Lam S, Tan F, Chan H, Chan-Yeung M. Relationship between types of asthmatic reaction, nonspecific bronchial reactivity, and specific IgE antibodies in patients with red cedar asthma. *J Allergy Clin Immunol* 1983;72:134-9.
- Muranaka M, Suzuki S, Miyamoto T, Takeda K, Okumura H. Bronchial reactivities to acetylcholine and IgE levels in asthma subjects after long term remissions. *J Allergy Clin Immunol* 1974;54:32-40.
- Sears MR, Burrows B, Flannery EM, Herbison GP, Hewitt CJ, Holdaway MD. Relation between airway responsiveness and serum IgE in children with asthma and apparently normal children. *N Engl J Med* 1991;325:1067-71.
- Burrows B, Martinez FD, Halonen M, Barbee RA, Cline MG. Association of asthma with serum IgE levels and skin-test reactivity to allergens. *N Engl J Med* 1989;320:271-7.
- Sporik R, Holgate ST, Platts-Mills TAE, Cogswell JJ. Exposure to house-dust mite allergen (*Der p* I) and the development of asthma in childhood. *N Engl J Med* 1990;323:502-7.
- Charpin D, Kleisbauer J-P, Lanteaume A, et al. Asthma and allergy to house-dust mites in populations living in high altitudes. *Chest* 1988;93:758-61.
- Cookson WOCM, de Klerk NH, Ryan GR, James AL, Musk AW. Relative risks of bronchial hyper-responsiveness associated with skin-prick tests to common antigens in young adults. *Clin Exp Allergy* 1991;21:473-9.
- Pollart SM, Chapman MD, Fiocco GP, Rose G, Platts-Mills TAE. Epidemiology of acute asthma: IgE antibodies to common inhalant allergens as a risk factor for emergency room visits. *J Allergy Clin Immunol* 1989;83:875-82.
- Platts-Mills TAE, Chapman MD, Pollart S, Luczynska CM, Ward GW. Specific allergens evoking immune reactions in the lung: relationship to asthma. *Eur Respir J* 1991;4:68S-77S.
- Holt PG, McMenamin C, Helson D. Primary sensitisation to inhalant allergens during infancy. *Pediatr Allergy Immunol* 1990;1:3-13.
- Kelly WJW, Hudson I, Phelan PD, Pain MCF, Olinsky A. Childhood asthma in adult life: a further study at 28 years of age. *BMJ* 1987;294:1059-62.
- Britton WJ, Woolcock AJ, Peat JK, Sedgwick CJ, Lloyd DM, Leeder SR. Prevalence of bronchial hyper-responsiveness in children: the relationship between asthma and skin reactivity to allergens in two communities. *Int J Epidemiol* 1986;15:202-9.
- Peat JK, Woolcock AJ. Sensitivity to common allergens: relation to respiratory symptoms and bronchial hyper-responsiveness in children from three different climatic areas of Australia. *Clin Exp Allergy* 1991;21:573-81.
- Sears MR, Herbison GP, Holdaway MD, Hewitt CJ, Flannery EM, Silva PA. The relative risks of sensitivity to grass pollen, house dust mite and cat dander in the development of childhood asthma. *Clin Exp Allergy* 1989;19:419-29.
- Krillis S, Baldo BA, Basten A. Analysis of allergen-specific IgE responses in 341 allergic patients, associations between allergens and between allergen groups and clinical diagnoses. *Aust N Z J Med* 1985;15:421-6.
- Arruda K, Rizzo MC, Chapman MD, et al. Exposure and sensitization to dust mite allergens among asthmatic children in São Paulo, Brazil. *Clin Exp Allergy* 1991;21:433-9.
- Yan K, Salome CM, Woolcock AJ. Rapid method for measurement of bronchial responsiveness. *Thorax* 1983;38:760-5.
- Toelle BG, Peat JK, Salome CM, Mellis CM, Woolcock AJ. Toward a definition of asthma for epidemiology. *Am Rev Respir Dis* 1992;146:633-7.
- O'Connor G, Sparrow D, Taylor D, Segal M, Weiss S. Analysis of dose-response curves to methacholine. An approach suitable for population studies. *Am Rev Respir Dis* 1987;136:1412-17.
- Peat JK, Salome CM, Berry G, Woolcock AJ. Relation of dose response slope to respiratory symptoms in a population of Australian schoolchildren. *Am Rev Respir Dis* 1991;144:663-7.
- Pepys J. Skin testing. *Br J Hosp Med* 1975;14:412-17.
- Hamilton RG, Adkinson NF. Measurement of total serum IgE and allergen specific IgE antibody. In: Rose NR, de Mocio EC, Fahey JC, Friedman H, Renn GH, editors. *Manual of clinical laboratory immunology*. Washington, DC: American Society for Microbiology, 4th ed. 1992: 689-701.
- Barbee R, Lebowitz M, Thompson H, Burrows B. Longitudinal changes in allergen skin test reactivity in a community population sample. *Ann Intern Med* 1976;84:129-33.

26. Martin AJ, Landau LI, Phelan PD. Natural history of allergy in asthmatic children followed to adult life. *Med J Aust* 1981;2:470-4.
27. Burney PGJ, Britton JR, Chinn S, et al. Descriptive epidemiology of bronchial reactivity in an adult population: results from a community study. *Thorax* 1987;42:38-44.
28. Cline MG, Burrows B. Distribution of allergy in a population sample residing in Tucson, Arizona. *Thorax* 1989;44:425-31.
29. Hill DJ, Hosking CS, Shelton MJ, Turner MW. Childhood asthma: clinical and immunological changes over a decade. *Clin Exp Allergy* 1991;21:343-9.
30. Burrows B, Sears MR, Flannery EM, Herbison GP, Holdaway MD. Relationships of bronchial responsiveness assessed by methacholine to serum IgE, lung function, symptoms, and diagnoses in 11-year-old New Zealand children. *J Allergy Clin Immunol* 1992;90:376-85.
31. O'Connor GT, Sparrow D, Segal MR, Weiss ST. Smoking, atopy, and methacholine airway responsiveness among middle-aged and elderly men: the Normative Aging Study. *Am Rev Respir Dis* 1989;140:1520-6.
32. Barnes PJ. New concepts in the pathogenesis of bronchial hyperresponsiveness and asthma. *J Allergy Clin Immunol* 1989;83:1013-26.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.